Part VI: Summary of the risk management plan

Summary of risk management plan for Dzuveo (Sufentanil (as citrate))

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

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

This summary of the RMP for Dzuveo 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 Dzuveo's RMP.

I. The medicine and what it is used for

Dzuveo is authorised for the management of moderate-to-severe acute pain in adult patients (see SmPC for the full indication). It contains Sufentanil (as citrate) as the active substance and it is given as 30 mcg sublingual tablet.

Further information about the evaluation of Dzuveo's benefits can be found in Dzuveo's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/human/medicines/004335/human_med_002265.jsp&mid=WC0b01ac058001d124

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

Important risks of Dzuveo, together with measures to minimise such risks and the proposed studies for learning more about Dzuveo'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 (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Dzuveo, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

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 Dzuveo is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Dzuveo 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 Dzuveo. 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 Hypersensitivity
Important potential risks	Drug abuse and drug diversion Overdose Bradycardia Hypotension Paralytic ileus Spasm of sphincter of Oddi Use in patients with raised intracranial pressure Convulsion
Missing information	Use during pregnancy and lactation Use in patients with hepatic impairment Use in patients with renal impairment Use beyond 48 hours

II.B Summary of important risks

Respiratory depression (slow or shallow breathing)	
Evidence for linking the risk to the medicine	Sufentanil may cause respiratory depression, for which the degree/severity is dose related. The respiratory effects of sufentanil should be assessed by clinical monitoring, e.g. respiratory rate, sedation level and oxygen saturation. Respiratory depression caused by sufentanil can be reversed by opioid antagonists. Repeat antagonist administration may be required as the duration of

	respiratory depression may last longer than the duration of the effect of the antagonist.
Risk factors and risk groups	Patients at higher risk are those with respiratory impairment or reduced respiratory reserve. Respiratory depression is a particular concern in very elderly and debilitated patients and those with underlying pulmonary conditions such as chronic bronchitis, multiple sclerosis, chronic obstructive pulmonary disease or those who receive other CNS drugs that affect ventilation (Pergolizzi et al. 2008). CNS depressants such as benzodiazepines, barbiturates, antidepressants, phenothiazine derivatives, and alcohol increase the risk of respiratory depression if taken with any opioid analgesia (Dahan and Teppema 2003, Pergolizzi et al. 2008) this may progress to apnoea.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.2, 4.3, 4.4, 4.5, 4.8, 5.1* *SmPC section 4.4 where advice is given on monitoring the respiratory effects* *PL section 2, 4* *Prescription only medicine* *Minimum 1 hour dosing interval on the pouch and outer carton labels* Additional risk minimization measures *Healthcare Professional Guide*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Survey aiming at measuring the effectiveness of the risk minimisation measures (routine / additional) See section II.C of this summary for an overview of the post-authorisation development plan.
Hypersensitivity (allergic reactions)	
Evidence for linking the risk to the medicine	Hypersensitivity to the active substance or to any of the excipients of the medicinal product can occur.
Risk factors and risk groups	Risk factors for allergic reactions include heredity, gender, race and age, with heredity being by far the most significant. In addition, environmental factors can play a role including alterations in exposure to infectious diseases during early childhood, environmental pollution, allergen levels, and dietary changes. The risk of hypersensitivity and anaphylaxis will be increased in those known to be

	hypersensitive to sufentanil or to any of the excipients within medicinal product.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.3, 4.8* *PL section 2, 4* *Prescription only medicine*
Drug abuse and drug diversion	
Evidence for linking the risk to the medicine	Similar to all opioids, sufentanil is known to have a risk of abuse (misuse) and diversion (illegal use for recreational purposes). Dzuveo is administered by the HCP to the patient. However, it is known that due to the nature of the medicine some people may try to use sufentanil for illegal purposes. The product information warns about the potential risk of abuse and diversion with sufentanil.
Risk factors and risk groups	Patients with a high potential for abuse include those with a history of substance abuse or psychiatric issues.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4* *Prescription only medicine*
Overdose	
Evidence for linking the risk to the medicine	Patients with moderate to severe hepatic or severe renal impairment should be monitored carefully for symptoms of sufentanil overdose. Management of sufentanil overdose should be focused on treating symptoms of μ-opioid receptor agonism including administration of oxygen and opioid antagonists. Primary attention should be given to obstruction of airways and the necessity of assisted or controlled ventilation.
Risk factors and risk groups	Opioid overdose has been associated with a history of depression or substance abuse and is related to the dose prescribed. Elderly patients and patients with renal impairment are also at increased risk. Sufentanil should also be used with caution in patients with previous or pre-existing bradyarrhythmias as sufentanil in overdose is known to cause bradycardia. In hypovolemic patients sufentanil in overdose may cause hypotension and appropriate measures should be taken to maintain stable arterial pressure.
Risk minimisation measures	Routine risk minimisation measures

	SmPC section 4.4, 4.9 *SmPC section 4.9 where advice is given on management of overdose* *PL section 3* *PL section 3 where advice is given how to detect sign and symptoms of overdose* *Prescription only medicine* *Minimum 1 hour dosing interval on the pouch and outer carton labels* Additional risk minimization measures *Healthcare Professional Guide*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Survey aiming at measuring the effectiveness of the risk minimisation measures (routine / additional) See section II.C of this summary for an overview of the post-authorisation development plan.
Bradycardia (slow heart rate)	
Evidence for linking the risk to the medicine	Sufentanil may cause bradycardia. Therefore, it should be used with caution in patients with previous or pre-existing bradyarrhythmias. Low doses of intravenous sufentanil associated with likely vagal (cholinergic) activity cause mild bradycardia and mildly reduced systemic vascular resistance without significantly lowering blood pressure.
Risk factors and risk groups	The risk of bradycardia is increased by beta- blockers and anaesthetic drugs. Patients with arrhythmia or with a history of arrhythmia including bradycardia might be at greater risk of heart rhythm disturbances.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4, 4.5, 4.8, 5.1* *PL section 2, 4* *Prescription only medicine*
Hypotension (low blood pressure)	
Evidence for linking the risk to the medicine	Sufentanil may cause hypotension, especially in hypovolemic patients. Appropriate measures should be taken to maintain stable arterial pressure.
Risk factors and risk groups	Hypovolemic patients are at increased risk of hypotension.
Risk minimisation measures	Routine risk minimisation measures

	SmPC section 4.4, 4.8 *PL section 2, 4* *Prescription only medicine*
Paralytic ileus (paralysis of the gut)	
Evidence for linking the risk to the medicine	Opioids can slow and even stop movement within the gastrointestinal (GI) tract (gut) which affects normal function and may cause pain. Patients who have a higher risk of paralysis of the gut include those who already have a bowel disorder or who have recently undergone major stomach surgery.
Risk factors and risk groups	Patients with paralytic ileus, obstructive bowel disorder, prostatic hyperplasia and undergoing major abdominal operations are at increased risk of paralytic ileus. A greater risk is associated with abdominal and pelvic surgery, open laparotomy, longer surgery time, greater estimated blood loss, prolonged opioid use, and inhalational anaesthesia (Moss et al. 1986, Code and Schlegel 1974).
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4* *PL section 2* *Prescription only medicine*
Spasm of the sphincter of Oddi	
Evidence for linking the risk to the medicine	Opioids may produce spasm of the sphincter of Oddi. Therefore, sufentanil should be used in caution in patients with pancreatitis or gall bladder disease.
Risk factors and risk groups	Patients with biliary tract disease and acute pancreatitis are at increased risk.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4* *PL section 2* *Prescription only medicine*
Use in patients with raised intracranial pressure (Use in patients with increased pressure to the brain)	
Evidence for linking the risk to the medicine	Warning to use sufentanil with caution in patients who may be particularly susceptible to the cerebral effects of CO_2 and patients with brain tumours is included in SmPC.

Risk factors and risk groups	Patients who are particularly susceptible are those with impaired consciousness, head injuries or brain tumours.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4* *PL section 2* *Prescription only medicine*
Convulsion (seizures, fits)	
Evidence for linking the risk to the medicine	Compounds with μ-opioid receptor agonist activity in general are known to have excitatory effects on the CNS (Duthie and Nimmo 1987).
Risk factors and risk groups	For opioids with active metabolites, such as pethidine, codeine, morphine, and (to a lesser degree) hydromorphone, use of the opioid for a period greater than a few days may increase the risk of convulsions when the dose of the metabolite builds up (Gallagher 2007). Factors such as dehydration, infection, or adding drugs that depress the CNS can increase the risk of convulsions in the elderly.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.8* *PL section 4* *Prescription only medicine*
Use during pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.6* *PL section 2* *Prescription only medicine*
Use in patients with hepatic impairment (use in patients with liver problems)	
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.2, 4.4, 4.8, 5.2* *SmPC section 4.4 where advice is given on monitoring the liver function* *PL section 2* *Prescription only medicine*
Use in patients with renal impairment (use in patients with kidney problems)	

Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.2, 4.4, 4.8, 5.2* *SmPC section 4.4 where advice is given on monitoring the liver function* *PL section 2* *Prescription only medicine*
Use beyond 48 hours (use for longer than 48 hours)	
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.2, 5.1* *Prescription only medicine*