Part VI: Summary of the risk management plan

Summary of risk management plan for *Dexmedetomidine hameln 4 micrograms/ml solution for infusion (dexmedetomidine hydrochloride)*

This is a summary of the risk management plan (RMP) for *Dexmedetomidine hameln 4 micrograms/ml solution for infusion*. The RMP details important risks of *Dexmedetomidine-hameln 4 micrograms/ml solution for infusion*, how these risks can be minimised, and how more information will be obtained about the products' risks and uncertainties (missing information).

The summary of product characteristics (SmPC) for *Dexmedetomidine hameln 4 micrograms/ml solution for infusion* and the associated package leaflet give essential information to healthcare professionals and patients on how these products should be used.

Important new concerns or changes to the current ones will be included in updates of the RMP for *Dexmedetomidine hameln 4 micrograms/ml solution for infusion*.

I. The medicine and what it is used for

Dexmedetomidine hameln 4 micrograms/ml solution for infusion is authorised for sedation of adult ICU (Intensive Care Unit) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3) and for sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural awake sedation (see SmPC for full indication). It contains dexmedetomidine hydrochloride as the active substance and it is given by intravenous infusion.

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

Important risks of *Dexmedetomidine hameln 4 micrograms/ml solution for infusion,* together with measures to minimise such risks and the proposed studies for learning more about the risks associated with treatment with *Dexmedetomidine hameln 4 micrograms/ml solution for infusion*, 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 a prescription) can help to minimise its risks.

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

In the case of *Dexmedetomidine hameln 4 micrograms/ml solution for infusion,* 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 dexmedetomidine is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of *Dexmedetomidine hameln 4 micrograms/ml solution for infusion* 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 *Dexmedetomidine hameln 4 micrograms/ml solution for infusion*. 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).

Summary of safety concerns	
Important identified risks	• Atrioventricular block • Cardiac arrest • Bradycardia • Hypotension • Hypertension • Hyperglycaemia • Withdrawal syndrome
Important potential risks	• Cortisol suppression • Convulsions • Hypothermia • Torsade de pointes/QT prolongation • Overdose • Off-label use • Rhabdomyolysis • Increased mortality in younger ICU patients
Missing information	• Pregnancy

II.B Summary of important risks

Important identified risk: Atrioventricular block	
Evidence for linking the risk to the medicine	The risk is based on theoretical mechanism of action and postmarketing data.

Risk factors and risk groups	Cardiovascularly compromised patients.
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.3, 4.4, 4.8* *PL sections 2,4* Contraindication of advanced heart block in section 4.3 Advice that all patients should have continuous cardiac monitoring during dexmedetomidine infusion included in section 4.4.
Important identified risk: Cardiac arrest	
Evidence for linking the risk to the medicine	The risk is based on postmarketing data.
Risk factors and risk groups	Patients with pre-existing bradycardia, especially in connection with high physical fitness (see Identified risk of bradycardia). Patients with medical history of cardiac conduction or structural disorders. Usage in paediatric population. Vagal stimulation. Usage of bolus/loading dose.
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.4, 4.8, 4.9* *PL section 2,4* Advice that all patients should have continuous cardiac monitoring during dexmedetomidine infusions and advice on the length of monitoring when used in an outpatient setting included in section 4.4.

Important identified risk: Bradycardia	
Evidence for linking the risk to the medicine	The risk is based on data from randomised clinical trials
Risk factors and risk groups	Patients with severe bradycardia or advanced block (Grade 2/3 AV Block unless paced) and patients with high physical fitness and slow resting heart rate may be at greater risk).
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.2, 4.4, 4.5, 4.8* *PL sections 2,3,4* As described in section 4.2 early signs of bradycardia should be monitored (indication 2). Advice that all patients should have continuous

	cardiac monitoring during dexmedetomidine infusion and advice on the length of monitoring when used in an outpatient setting included in section 4.4

Important identified risk: Hypotension	
Evidence for linking the risk to the medicine	The risk is based on data from randomised clinical trials
Risk factors and risk groups	Hypotension might be expected to be more common in patients with hypovolemia or chronic hypotension
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8* *PL sections 2,3,4* As described in section 4.2 early sings of hypotension should be monitored (indication 2). The use of a loading dose during procedural sedation may increase the risk for hypotension in the elderly. Contraindication of uncontrolled hypotension in section 4.3 Advice on the length of monitoring when used in an outpatient setting included in section 4.4.

Important identified risk: Hypertension	
Evidence for linking the risk to the medicine	The risk is based on data from randomised clinical trials
Risk factors and risk groups	Hypertension might be expected to be more common in patients with chronic hypertension or peripheral autonomic dysfunction.
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.2, 4.4, 4.8* *PL sections 3,4* As described in section 4.2 early sings of hypertension should be monitored (indication 2).

Important identified risk: Hyperglycaemia	
Evidence for linking the risk to the medicine	The risk is based on data from randomised clinical trials
Risk factors and risk groups	Patients with diabetes mellitus
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.8* *PL section 4*

Important identified risk: Withdrawal syndrome	
Evidence for linking the risk to the medicine	The risk is based on data from randomised clinical trials
Risk factors and risk groups	Patients treated with alpha-2 agonists for a long period of time have rarely been shown to develop withdrawal syndrome after the treatment has been stopped abruptly.
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.4, 4.8* *PL section 4*

Important potential risk: Cortisol suppression	
Evidence for linking the risk to the medicine	The risk is based on a potential imidazole class effect.
Risk factors and risk groups	Features that have been associated with cortisol suppression in the scientific literature include sepsis and/or shock, high lactate, hypoalbuminaemia, high percentage of eosinophils, low sodium and glucose, low platelets, severe underlying disease or organ failure, and use of antifungal agents.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 5.1*

Important potential risk: Convulsions	
Evidence for linking the risk to the medicine	The risk has been reported to be an adverse effect of clonidine, another alpha-2-adrenergic receptor agonist, when given in high doses.
Risk factors and risk groups	No specific groups known. However, dexmedetomidine lacks the anticonvulsant action of some other sedatives and so will not supress underlying seizure activity.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4*

Important potential risk: Hypothermia	
Evidence for linking the risk to the medicine	The risk has been reported to be an adverse effect of clonidine, another alpha-2-adrenergic receptor agonist, when given in high doses.
Risk factors and risk groups	Small reductions in body temperature are unlikely to be of clinical relevance however neonates may be at greater risk of developing significant hypothermia and associated bradyarrhythmia, and this is identified in the SmPC.
Risk minimisation measures	Routine risk minimisation measures: *Not included in the SmPC*

Important potential risk: Torsade de pointes/ QT prolongation	
Evidence for linking the risk to the medicine	The risk is based on postmarketing data.
Risk factors and risk groups	QTc prolongation is unlikely to occur due to dexmedetomidine based on the preclinical data and data from the clinical trials. Rate dependent ECG intervals including PR and uncorrected QT intervals may appear to increase during dexmedetomidine infusion in keeping with its known bradycardic effect. However, there is no evidence of increases in the corrected QT (QTc) on dexmedetomidine using either Bazett or Fridericia corrections, and neither was there clinical evidence of

	increase in relevant rhythm disturbances. No TdP was attributed to dexmedetomidine in the ICU controlled studies. TdP is a recognised hazard of concomitant medication used in the ICU such as haloperiodol; this risk is managed by continuous ECG monitoring and rapid treatment of TdP in the ICU.
Risk minimisation measures	Routine risk minimisation measures: *Not included in the SmPC*

Important potential risk: Overdose	
Evidence for linking the risk to the medicine	The risk is based on reported medication errors resulting in overdose.
Risk factors and risk groups	Lack of familiarity or standard procedure with a drug increases the risk of such errors.
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.2, 4.9, 6.6*

Important potential risk: Rhabdomyolysis	
Evidence for linking the risk to the medicine	The risk is based on postmarketing data.
Risk factors and risk groups	Features that have been associated with rhabdomyolysis in the scientific literature in general include e.g. direct muscle injury, prolonged compression during immobility (for example time-consuming surgery without adequate periodic patient mobilisation or self-induced intoxication), strenuous muscular activity, seizures, electrolyte imbalances, hyperthermia, neuroleptic malignant syndrome and numerous bacterial, viral, fungal and protozoal infections.
Risk minimisation measures	No risk minimisation measures

Important potential risk: Increased mortality in younger ICU patients	
Evidence for linking the risk to the medicine	The risk is based on data from the academy sponsored, randomised, controlled, open-label clinical trial SPICE III.
Risk factors and risk groups	The heterogeneity of effect on mortality from age was most prominent in cases with early use of dexmedetomidine in high dose to achieve deep sedation in patients admitted for other reasons than post-operative care and increased with increasing APACHE II scores.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where advice is given to weigh the findings of increased mortality in the age-group ≤ 65 years seen in the SPICE III trial against the expected clinical benefit of dexmedetomidine.* Additional risk minimisation measures: DHPC dissemination

Important potential risk: Off-label use	
Evidence for linking the risk to the medicine	The risk is based on recognised off-label use of dexmedetomidine, including off-label use in children.
Risk factors and risk groups	Paediatric patients, off-label routes of administration (e.g. intranasal administration or use as an adjunct with local anaesthetic in peripheral blocks).
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.1, 4.2, 4.4* *PL section 1,3* Indications and instructions for administration included in section 4.1 and 4.2, respectively. Use in only ICU, operating room and during diagnostic procedures emphasised in section 4.4.

Missing information: Pregnancy	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.6* *PL section 2* Advice that dexmedetomidine should not be used during pregnancy unless the clinical condition of the woman requires treatment with dexmedetomidine included in section 4.6.

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 a specific obligation for *Dexmedetomidine hameln 4 micrograms/ml solution for infusion*.

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

There are no studies required for *Dexmedetomidine hameln 4 micrograms/ml solution for infusion*.