

EU Risk Management Plan for DEXMEDETOMIDINA GALENICA SENESE (DEXMEDETOMIDINE)

Part VI: Summary of the risk management plan

Summary of risk management plan for DEXMEDETOMIDINA GALENICA SENESE (dexmedetomidine hydrochloride)

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

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

I. The medicine and what it is used for

DEXMEDETOMIDINA GALENICA SENESE is authorized:

1. 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.)
2. For sedation of non-intubated patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation.

It contains dexmedetomidine hydrochloride as the active substance and it is given by intravenous infusion.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of DEXMEDETOMIDINA GALENICA SENESE, together with measures to minimise such risks and the proposed studies for learning more about DEXMEDETOMIDINA GALENICA SENESE'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;
- 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 and missing information

Important risks of DEXMEDETOMIDINA GALENICA SENESE 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 DEXMEDETOMIDINA GALENICA SENESE. 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	<ul style="list-style-type: none"> • Atrioventricular block • Cardiac arrest • Bradycardia • Hypotension • Hypertension • Hyperglycaemia • Withdrawal syndrome
Important potential risks	<ul style="list-style-type: none"> • Cortisol suppression • Convulsions • Hypothermia • Torsade de pointes/QT prolongation • Overdose • Off-label use • Rhabdomyolysis • Increased mortality in younger ICU patients
Missing information	<ul style="list-style-type: none"> • Pregnancy

II.B Summary of important risks

Important identified risk: Atrioventricular block	
Evidence for linking the risk to the medicine	This risk is based on theoretical mechanism of action and postmarketing data.
Risk factors and risk groups	Cardiovascularly compromised patients.
Risk minimisation measures	<p>Routine risk minimisation measures: SmPC sections 4.3, 4.4, 4.8 PL sections 2, 4</p> <p>Contraindication of advanced heart block in section 4.3</p> <p>Advice that all patients should have continuous cardiac monitoring during DEXMEDETOMIDINA GALENICA SENESE infusion included in section 4.4.</p>

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	<p>Patients with pre-existing bradycardia, especially in connection with high physical fitness (see Identified risk Bradycardia).</p> <p>Patients with medical history of cardiac conduction or structural disorders. Usage in paediatric population. Vagal stimulation. Usage of bolus/loading dose.</p>
Risk minimisation measures	<p>Routine risk minimisation measures: SmPC sections 4.4, 4.8, 4.9 PL section 2, 4</p> <p>Advice that all patients should have continuous cardiac monitoring during DEXMEDETOMIDINA GALENICA SENESE infusion and advice on the length of monitoring when used in an outpatient setting included in section 4.4.</p>

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 heart 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	<p>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.)</p> <p>Advice that all patients should have continuous cardiac monitoring during DEXMEDETOMIDINA GALENICA SENESE infusion and advice on the length of monitoring when used in an outpatient setting included in section 4.4.</p>
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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 hypovolaemia or chronic hypotension.
Risk minimisation measures	<p>Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8. PL sections 2, 3, 4</p> <p>As described in section 4.2 early signs 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.</p> <p>Contraindication of uncontrolled hypotension in section 4.3</p> <p>Advice on the length of monitoring when used in an outpatient setting included in section 4.4.</p>

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	<p>Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8 PL sections 3, 4</p> <p>As described in section 4.2 early signs of hypertension should be monitored (indication 2.)</p>

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 suppress underlying seizure activity.

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4
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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 haloperidol; 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: 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 anesthetic 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 sections 4.1 and 4.2, respectively Use in only ICU, operating room and during diagnostic procedures emphasised in section 4.4

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 mobilization 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
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Evidence for linking the risk to the medicine	This 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	<p>Routine risk minimisation measures: SmPC section 1.4 where advice is given to weigh the findings of increased mortality in the age-group ≤ 65 years seen in the SPICE II trial against the expected clinical benefit of dexmedetomidine</p> <p>Additional risk minimisation measures: DHPC dissemination</p>

Missing information : Pregnancy	
Risk minimisation measures	<p>Routine risk minimisation measures: SmPC section 4.6 PL section 2</p> <p>Advice that DEXMEDETOMIDINA GALENICA SENESE should not be used during pregnancy unless the clinical condition of the woman requires treatment with dexmedetomidine included in section 4.6</p>