PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

DEXITHERA 4 µg/mL solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of solution for infusion contains dexmedetomidine hydrochloride equivalent to 4 micrograms dexmedetomidine.

Each 100 mL bag contains 400 micrograms of dexmedetomidine.

Excipients with known effect:

Contains sugar: Each 100 mL bag contains 5,5 g glucose monohydrate.

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear, colourless solution, pH 3,5 – 5,0.

Osmolality: 285 – 315 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DEXITHERA 4 µg/mL is an alpha-$_2$ adrenoreceptor agonist sedative with analgesic properties indicated for:

Intensive Care Unit Sedation:

Sedation of intubated and mechanically ventilated adult post-surgical patients during treatment in an intensive care setting.

Monitored anaesthesia care (MAC)/ Conscious sedation in a theatre or intensive care setting for:

- Minor surgical procedures under local anaesthesia
- Fibreoptic intubation

Efficacy and safety have not been studied in children under 18 years of age.

4.2 Posology and method of administration

NOTE: DEXITHERA 4 µg/mL should be administered only by health professionals skilled in the management of patients in the intensive care setting. Continuous monitoring of vital signs, in particular blood pressure, heart rate and oxygen saturation is mandatory during infusion of DEXITHERA 4 µg/mL.

In order to minimise undesirable pharmacologic side effects, bolus injections of DEXITHERA 4 µg/mL should not be used. Clinically significant events of bradycardia and sinus arrest

have been associated with dexmedetomidine hydrochloride administration in young healthy volunteers with high vagal tone, or with different routes of administration including rapid intravenous or bolus administration of dexmedetomidine hydrochloride.

DEXITHERA 4 µg/mL should be administered by continuous intravenous infusion not to exceed 24 hours.

Fluid supplementation should be administered prior to and during administration of DEXITHERA 4 µg/mL to ensure normovolaemia. DEXITHERA 4 µg/mL has been administered to patients requiring mechanical ventilation as well as to patients breathing spontaneously after extubation. There is no respiratory depression associated with the administration of DEXITHERA 4 µg/mL.

Patients receiving DEXITHERA 4 µg/mL have been observed to be arousable and alert when stimulated. This is an expected component of dexmedetomidine sedation and should not be considered as evidence of lack of efficacy in the absence of other clinical signs and symptoms. DEXITHERA 4 µg/mL has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post extubation. It is not necessary to discontinue dexmedetomidine prior to extubation.

Posology

Adults

ICU sedation

DEXITHERA 4 µg/mL dosage should be individualised and titrated to the desired clinical effect.

Initiation:

For adult patients, it is recommended to initiate DEXITHERA 4 µg/mL with a loading dose of 1,0 microgram/kg over ten minutes

Maintenance of ICU sedation:

Adult patients will generally require a maintenance infusion in the range of 0,2 to 0,7 microgram/kg/h. The rate of the maintenance infusion can be adjusted in order to achieve the desired clinical effect. Dosages as low as 0,05 micrograms/kg/h have been used in clinical studies.

A dose reduction for both the loading and maintenance infusions should be considered in patients with impaired hepatic or renal function and in patients over 65 years of age (see sections 4.3, 4.4 and 5.2).

Conscious sedation

Monitored anaesthesia care (MAC) with an adequate nerve block and awake fibreoptic intubation (AFI). DEXITHERA 4 µg/mL dosing should be individualised and titrated to the desired clinical effect.

Initiation

For adult patients, DEXITHERA 4 µg/mL is generally initiated with a loading infusion of 1 (one) microgram/kg over 10 minutes.

For patients over 65 years of age or those undergoing less invasive procedures such as ophthalmic surgery, a loading infusion of 0,5 micrograms/kg over 10 minutes may be suitable.

Maintenance of conscious sedation (MAC):

MAC - Following the load, maintenance dosing of DEXITHERA 4 µg/mL should generally be initiated at 0,6 micrograms/kg/h and titrated to achieve desired clinical effect with doses ranging from 0,2 to 1 micrograms/kg/h for all procedures.

The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation.

AFI - Following the load in awake fibreoptic intubation, a fixed maintenance dose of 0,7 micrograms/kg/h should be used.

Dosage adjustment

Due to possible pharmacodynamic interactions a reduction in dosage of DEXITHERA 4 µg/mL or other concomitant anaesthetics, sedatives, hypnotics or opioids may be required when co-administered (see section 4.5).

Impaired hepatic function

Dosage reductions may need to be considered for patients with hepatic impairment, as DEXITHERA 4 µg/mL is metabolised primarily in the liver.

Special population

Impaired renal function

Since the majority of metabolites are excreted in the urine, dosage reductions may need to be considered for patients with renal impairment.

Elderly population

Since the elderly are more sensitive to the effects of DEXITHERA 4 µg/mL dosage reductions may need to be considered.

Paediatric population

Safety and efficacy of DEXITHERA 4 µg/mL has not been studied in children and adolescents and is therefore not recommended for patients under 18 years of age.

Method of administration

For intravenous infusion

A controlled infusion device should be used to administer DEXITHERA 4 µg/mL. Parenteral products should be inspected visually for particulate matter and discolouration prior to administration.

DEXITHERA 4 µg/mL bags are intended for single patient use only.

4.3 Contraindications

DEXITHERA 4 µg/mL is contraindicated in:

- Hypersensitivity to dexmedetomidine or to any of the excipients listed in section 6.1.

- Patients with sepsis.
- Unstable trauma patients.
- Hypovolaemic patients.
- Heart block.
- Uncontrolled cardiac failure.
- Imminent hepatic failure.

4.4 Special warnings and precautions for use

Interference with daily activities may continue for up to 24 hours and no legal/contractual decisions should be entered into for 24 hours after receiving anaesthetic/conscious sedation. Alcohol use should also be avoided for the same time period.

Clinical events of bradycardia and sinus arrest have been associated with DEXITHERA 4 µg/mL administration in some young, healthy volunteers with high vagal tone, or with different routes of administration including rapid intravenous or bolus administration of DEXITHERA 4 µg/mL. Bolus injections of DEXITHERA 4 µg/mL should not be used, in order to minimise undesirable pharmacological side effects.

Monitoring

DEXITHERA 4 µg/mL is intended for use in an intensive care setting, operating room and during diagnostic procedures. The use in other environments is not recommended. DEXITHERA 4 µg/mL should only be administered by health care providers skilled in the management of patients in these settings and who have received complete training in the use of DEXITHERA 4 µg/mL in these environments.

During the infusion of DEXITHERA 4 µg/mL, all patients should receive continuous cardiac monitoring. Continuous electrocardiogram (ECG), blood pressure and oxygen saturation monitoring are mandatory during DEXITHERA 4 µg/mL infusion. Due to the risk of respiratory depression and in some cases apnoea (see section 4.8), respiration should be monitored in non-intubated patients.

The safety and efficacy of DEXITHERA 4 µg/mL in non-surgical intensive care patients have not been established.

The time to recovery after the use of DEXITHERA 4 µg/mL was reported to be approximately one hour. When used in an outpatient, setting close monitoring should continue for at least one hour (or longer based on the patient condition), with medical supervision continued for at least one further hour to ensure the safety of the patient.

General precautions

DEXITHERA 4 µg/mL should not be given as bolus dose and in the ICU a loading dose is not recommended. Users should be ready to use an alternative sedative for acute control of agitation, or during procedures, especially during the first few hours of treatment. During procedural sedation a small bolus of another sedative may be used if a rapid increase in sedation level is required.

Some patients receiving DEXITHERA 4 µg/mL have been observed to be arousable and alert when stimulated. This alone should not be considered as evidence of lack of efficacy in the absence of other clinical signs and symptoms.

Dexmedetomidine normally does not cause deep sedation and patients may be easily

roused (see section 4.2). DEXITHERA 4 µg/mL is therefore not suitable in patients who will not tolerate this profile of effects, for example those requiring continuous deep sedation.

DEXITHERA 4 µg/mL should not be used as a general anaesthetic induction medicine for intubation or to provide sedation during muscle relaxant use. DEXITHERA 4 µg/mL lacks the anticonvulsant action of some other sedatives and so will not suppress underlying seizure activity.

Care should be taken if combining DEXITHERA 4 µg/mL with other substances with sedative or cardiovascular actions as additive effects may occur. DEXITHERA 4 µg/mL is not recommended for patient controlled sedation due to a lack of adequate data.

When DEXITHERA 4 µg/mL is used in an outpatient setting patients should normally be discharged into the care of a suitable third party. Patients should be advised to refrain from driving or other hazardous tasks and where possible to avoid the use of other medicines or substances that may sedate (e.g, benzodiazepines, opioids, alcohol) for a suitable period of time (see section 4.7), based on observed effects of DEXITHERA 4 µg/mL, the procedure, concomitant medications, the age and the condition of the patient.

Cardiovascular effects and precautions

DEXITHERA 4 µg/mL reduces heart rate and blood pressure through central sympatholysis but at higher concentrations causes peripheral vasoconstriction leading to hypertension (see section 5.1). DEXITHERA 4 µg/mL is therefore not suitable in patients with severe cardiovascular instability.

Clinical events of bradycardia or hypotension may be potentiated when DEXITHERA 4

µg/mL is used concurrently with propofol or midazolam (see section 4.5).

Caution should be exercised when administering DEXITHERA 4 µg/mL to patients with pre-existing bradycardia disorders (i.e., advanced heart block). Data on the effects of DEXITHERA 4 µg/mL in patients with heart rate < 60 are very limited and particular care should be taken with such patients.

Bradycardia does not normally require treatment but has commonly responded to anti-cholinergic medicine or dose reduction where needed. In clinical trials, atropine and glycopyrrolate were found to be effective in the treatment of most episodes of DEXITHERA 4 µg/mL-induced bradycardia. More resuscitative measures were however required in some patients with significant cardiovascular dysfunction.

Patients with high physical fitness and slow resting heart rate may be particularly sensitive to bradycardic effects of alpha-$_2$ receptor agonists and cases of transient sinus arrest have been reported. Also, cases of cardiac arrest, often preceded by bradycardia or atrioventricular block, have been reported (see section 4.8).

The hypotensive effects of dexmedetomidine may be of greater significance in those patients with pre-existing hypotension (especially if not responsive to vasopressors), hypovolaemia, chronic hypotension or reduced functional reserve such as patients with severe ventricular dysfunction (e.g., ejection fraction < 30 %), including congestive heart failure and cardiac failure and the elderly. Hypotension does not normally require specific treatment but, where needed, users should be ready to intervene with dose reduction, fluids and/or vasoconstrictors.

Treatment may include dose reduction or discontinuation of DEXITHERA 4 µg/mL, elevation of the lower extremities, increasing the rate of IV fluid administration and/or administration of vasoconstrictors. DEXITHERA 4 µg/mL is contraindicated for use in patients with hypovolaemia (see section 4.3). Patients who are hypovolaemic may become hypotensive during DEXITHERA 4 µg/mL treatment. Normovolaemia must therefore be ensured prior to administration of DEXITHERA 4 µg/mL (see section 4.2).

Patients with impaired peripheral autonomic activity (e.g., due to spinal cord injury) may have more pronounced haemodynamic changes after starting DEXITHERA 4 µg/mL and so should be treated with care.

Transient hypertension has been observed primarily during the loading dose in association with the peripheral vasoconstrictive effects of dexmedetomidine. Treatment of hypertension has generally not been necessary but decreasing the continuous infusion rate may be advisable. Following the loading infusion, the central effects of DEXITHERA 4 µg/mL dominate and the blood pressure usually decreases.

The use of DEXITHERA 4 µg/mL may enhance the pharmacodynamic effect of vasodilators or negative chronotropic medicines when co-administered. In these cases, DEXITHERA 4 µg/mL should be administered with caution and careful titration is advised (see section 4.5).

Local vasoconstriction at higher concentration may be of greater significance in patients with ischaemic heart disease or severe cerebrovascular disease who should be monitored closely. Dose reduction or discontinuation should be considered in a patient developing signs of myocardial or cerebral ischaemia. Caution is advised when administering DEXITHERA 4 µg/mL together with spinal or epidural anaesthesia due to possible increased

risk of hypotension or bradycardia.

Patients with hepatic impairment

Care should be taken in severe hepatic impairment as excessive dosing may increase the risk of adverse reactions, over-sedation or prolonged effect as a result of reduced DEXITHERA 4 µg/mL clearance.

Patients with neurological disorders

Experience of dexmedetomidine in severe neurological disorders, such as head injury and after neurosurgery is limited and it should be used with caution here, especially if deep sedation is required. DEXITHERA 4 µg/mL may reduce cerebral blood flow and intracranial pressure, and this should be considered when selecting therapy.

Elderly patients

Caution should be exercised when administering DEXITHERA 4 µg/mL to elderly patients. Elderly patients over 65 years of age may be more prone to hypotension with the administration of DEXITHERA 4 µg/mL, including a loading dose, for procedures. Close cardiovascular monitoring is required in these patients and the dose of DEXITHERA 4 µg/mL must be carefully titrated until the desired effect is obtained. Elderly patients often require lower doses of DEXITHERA 4 µg/mL.

Other

Alpha-$_2$ agonists have rarely been associated with withdrawal reactions when stopped abruptly after prolonged use (in excess of 24 hours). This possibility should be considered if

the patient develops agitation and hypertension shortly after stopping DEXITHERA 4 µg/mL. Other symptoms of withdrawal may include headache, nervousness and elevated catecholamine concentrations in the plasma.

DEXITHERA 4 µg/mL may induce hyperthermia that may be resistant to traditional cooling methods. DEXITHERA 4 µg/mL treatment should be discontinued in the event of a sustained unexplained fever and is not recommended for use in malignant hyperthermia-sensitive patients.

Treatment with DEXITHERA 4 µg/mL may result in decreased lacrimation. To avoid corneal dryness, lubrication of the patient's eyes may be considered when administering DEXITHERA 4 µg/mL.

Glucose monohydrate

DEXITHERA 4 µg/mL contains 5,5 g glucose monohydrate per 100 mL bag. This should be taken into account in patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

Co-administration of DEXITHERA 4 µg/mL with anaesthetics, sedatives, hypnotics, and opioids is likely to lead to an enhancement of effects, including sedative, anaesthetic and cardiorespiratory effects. Specific studies have confirmed enhanced effects with isoflurane, propofol, alfentanil, and midazolam.

No pharmacokinetic interactions between dexmedetomidine and isoflurane, propofol, alfentanil and midazolam have been demonstrated. However, due to possible pharmacodynamic interactions, when co-administered with DEXITHERA 4 µg/mL, a reduction in dosage of DEXITHERA 4 µg/mL or the concomitant anaesthetic, sedative, hypnotic or opioid may be required.

Inhibition of cytochrome P (CYP) enzymes including CYP2B6 by dexmedetomidine has been studied in human liver microsome incubations. *In vitro* study suggests that interaction potential *in vivo* exists between DEXITHERA 4 µg/mL and substrates with dominant CYP2B6 metabolism.

Induction of dexmedetomidine *in vitro* was observed on CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP3A4, and induction *in vivo* cannot be excluded. The clinical significance is unknown. The possibility of enhanced hypotensive and bradycardic effects should be considered in patients receiving other medicines causing these effects, for example beta blockers, although additional effects in an interaction study with esmolol were modest.

Following the co-administration of DEXITHERA 4 µg/mL and rocuronium, no clinically meaningful increases in the extent of neuromuscular blockade and no pharmacokinetic interactions can be observed.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Pregnancy

Available data from published randomized controlled trials and case reports over several decades of use with intravenously administered dexmedetomidine during pregnancy have not identified a drug-associated risk of major birth defects and miscarriage; however, the reported exposures occurred after the first trimester. Most of the available data are based on studies with exposures that occurred at the time of caesarean section delivery, and these studies have not identified an adverse effect on maternal outcomes or infant Apgar scores. Available data indicate that dexmedetomidine crosses the placenta.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

Labour and delivery

The safety of DEXITHERA 4 µg/mL in labour and delivery has not been studied and it is therefore not recommended for obstetrics, including caesarean section deliveries.

Breastfeeding

Available published literature reports the presence of DEXITHERA 4 µg/mL in human milk following intravenous administration. There is no information regarding the effects of DEXITHERA 4 µg/mL on the breastfed infant or the effects on milk production. Advise women to monitor the breastfed infant for irritability. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DEXITHERA 4 µg/mL and any potential adverse effects on the breastfed infant from DEXITHERA 4 µg/mL or from the underlying condition.

In two published clinical studies, a total of 14 women were given intravenous dexmedetomidine 6 micrograms/kg/hour for 10 minutes after delivery followed by continuous infusion of 0,2 – 0,7 microgram/kg/hour. Breast milk and maternal blood samples were collected at 0, 6, 12, and 24 hours after discontinuation of dexmedetomidine. Plasma and milk dexmedetomidine concentrations were detectable up to 6 hours in most subjects, up to 12 hours in one subject and undetectable in all at 24 hours. The milk- to-plasma ratio from single paired maternal milk and plasma concentrations at each time point ranged from 0,53 to 0,95. The relative infant dose was estimated to range from 0,02 to 0,098 %.

Fertility

In the rat fertility study, dexmedetomidine had no effect on male or female fertility. No human data on fertility are available.

4.7 Effects on ability to drive and use machines

Dexmedetomidine has major impact on the ability to drive and use machines. Patients should be advised to refrain from driving, operating machines, undertaking any other hazardous tasks or make legal decisions for at least 24 hours after receiving DEXITHERA 4 µg/mL.

4.8 Undesirable effects

Summary of the safety profile

Sedation of adult ICU patients

In the ICU setting, the most frequent reported adverse reactions are hypotension, hypertension, bradycardia, nausea, dry mouth and hypoxia. Hypotension and bradycardia were the most frequent dexmedetomidine-related serious adverse reactions occurring in ICU patients.

Procedural/conscious sedation

The most frequent adverse events reported in procedural sedation are hypotension, respiratory depression, bradycardia and dry mouth. Most of the adverse reactions were assessed to be mild in severity.

The following undesirable effects have been reported during clinical trials in the ICU setting

Blood and lymphatic system disorders

Frequent: anaemia

Metabolism and nutrition disorders

Frequent: hyperglycaemia, hypoglycaemia, hypovolaemia

Less frequent: metabolic acidosis, hypoalbuminemia, hypocalcaemia

Psychiatric disorders

Frequent: agitation

Less frequent: hallucination

Cardiac disorders

Frequent: bradycardia[1, 2], myocardial ischaemia or infarction, tachycardia[2], atrial fibrillation

Less frequent: atrioventricular block[1], cardiac output decreased, cardiac arrest[1], sinus tachycardia, ventricular tachycardia

Vascular disorders

Frequent: hypotension[1, 2], hypertension[1, 2]

Respiratory, thoracic and mediastinal disorders

Frequent: respiratory depression[2], atelectasis, pleural effusion, hypoxia[3], bradypnoea[3]

Less frequent: dyspnoea, apnoea, pulmonary oedema, wheezing

Gastrointestinal disorders

Frequent: nausea[2], vomiting, dry mouth[2]

Less frequent: abdominal distention

Renal and urinary disorders

Frequency unknown: polyuria

General disorders and administration site conditions

Frequent: withdrawal syndrome, hyperthermia, pyrexia, chills

Less frequent: medicine ineffective, thirst, peripheral oedema

Investigations

Less frequent: urine output decreased

Injury, poisoning and procedural complications

Frequent: post-procedural haemorrhage

[1] See section on Description of selected adverse reactions.

[2] Adverse reaction observed also in procedural/conscious sedation studies.

[3] Adverse reaction only observed in procedural/conscious sedation studies.

Post-marketing Experience

Table 3 : Adverse Events Experienced During Post-approval Use of DEXITHERA 4 µg/mL

Body system (WHOART)	**Preferred term**
Body as a whole – general disorders	Allergic reaction, ascites, fever, hyperpyrexia, hypovolaemia, light anaesthesia, oedema, peripheral oedema, pain, syncope, withdrawal syndrome, rigors
Cardiovascular disorders, General	Blood pressure fluctuation, circulatory failure, cyanosis, abnormal ECG, heart disorder, hypertension, aggravated hypertension, pulmonary hypertension, hypotension, postural hypotension, pulmonary hypertension, myocardial infarction
Central and peripheral nervous system disorders	Convulsion, dizziness, headache, neuralgia, neuritis, neuropathy, paraesthesia, paralysis, paresis, speech disorder
Gastrointestinal system disorders	Abdominal pain, diarrhoea, eructation, mucosal ulceration, nausea, vomiting
Heart rate and rhythm disorders	Dysrhythmia, atrial dysrhythmia, atrial fibrillation, AV block, bradycardia, bundle branch block, cardiac arrest, extrasystoles, heart block, hypoxia, supraventricular tachycardia,T wave inversion, tachycardia, ventricular dysrhythmia, ventricular tachycardia
Liver and biliary system disorders	Increased AG ratio, increased GGT, abnormal hepatic function, hyperbilirubinaemia, increased aspartate transaminase (AST), increased alanine transaminase (ALT), jaundice

Metabolic and nutritional disorders	Acidosis, lactic acidosis, respiratory acidosis, diabetes mellitus, hyperglycaemia, hypoglycaemia, hypokalaemia, hyperkalaemia, hypoproteinaemia, increased alkaline phosphatase, increased non-protein nitrogen (NPN), thirst
Musculoskeletal system disorders	Muscle weakness
Myo-, endo-, pericardial & valve disorders	Angina pectoris, myocardial infarction, myocardial ischaemia
Platelet, bleeding & clotting disorders	Coagulation disorders, disseminated intravascular coagulation, haematoma, abnormal platelets, decreased prothrombin, thrombocytopenia
Psychiatric disorders	Agitation, anxiety, confusion, delirium, depression, hallucination, illusion, nervousness
Red blood cell disorders	Anaemia
Renal disorders	Increased blood urea, oliguria
Resistance mechanism disorders	Infection, fungal infection, sepsis
Respiratory system disorders	Adult respiratory distress syndrome, apnoea, bronchial obstruction, bronchospasm, coughing, dyspnoea, emphysema, haemoptysis, hypercapnia, hypoventilation, hypoxia, pharyngitis, pleurisy, pneumonia, pneumothorax, pulmonary congestion, pulmonary oedema, respiratory depression, respiratory disorder, respiratory insufficiency, increased sputum, stridor
Skin and appendages disorders	Rash erythematous, increased sweating
Urinary system disorders	Haematuria, acute renal failure, abnormal renal function, urinary retention

Vascular (extracardiac) disorders	Haemorrhage, cerebral haemorrhage, peripheral ischaemia, vascular disorder, vasodilation
Vision disorders	Diplopia, photopsia, abnormal vision
White cell & RES disorders	Leukocytosis

Description of selected adverse reactions

Clinically significant bradycardia or hypotension should be treated as described in section 4.4.

When treated with dexmedetomidine, bradycardia has occasionally led to sinus arrest or pause in relatively healthy, non-ICU subjects. A response in symptoms resulted from leg raising and the administration of anticholinergic medicine, such as atropine or glycopyrrolate. In patients with pre-existing bradycardia, isolated cases have been reported of bradycardia progressing to periods of asystole. Also, cases of cardiac arrest, often preceded by bradycardia or atrioventricular block, have been reported.

Hypertension has been associated with the use of a loading dose and this reaction can be reproduced by avoiding such a loading dose or reducing the infusion rate or size of the loading dose.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care

providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Abbott Laboratories South Africa Pharmacovigilance: pv.south-africa@abbott.com.

4.9 Overdose

Symptoms of overdose

First-degree AV block and second-degree heart block may occur.

Bradycardia, with or without hypotension, and cardiac arrest may occur.

Because DEXITHERA 4 µg/mL has the potential to augment bradycardia induced by vagal stimuli, clinicians should be prepared to intervene. In clinical trials, atropine and glycopyrrolate were effective in the treatment of DEXITHERA 4 µg/mL -induced bradycardia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.9 Other analgesics

Pharmacotherapeutic group: Psycholeptics, other hypnotics and sedatives

ATC code: N05CM18

Mechanism of action

Dexmedetomidine is an alpha$_2$-adrenoreceptor agonist.

The sedative actions of dexmedetomidine are believed to be mediated primarily by post-synaptic alpha$_2$- adrenoreceptors, which in turn act on inhibitory pertussis-toxin-sensitive G protein, thereby increasing conductance through potassium channels. The site of the sedative effects of dexmedetomidine has been attributed to the locus ceruleus. The analgesic actions are believed to be mediated by a similar mechanism of action at the brain and spinal cord level.

Alpha$_2$ selectivity is demonstrated following low and medium doses given slowly. Alpha$_2$ and alpha$_1$ activity is seen following rapid administration. Dexmedetomidine has no affinity for beta adrenergic, muscarinic, dopaminergic, or serotonin receptors.

5.2 Pharmacokinetic properties

Distribution

Following administration, dexmedetomidine exhibits the following pharmacokinetic characteristics: rapid distribution phase with a distribution half-life (t ½ α) of about six minutes; terminal elimination half-life (t ½) of approximately two hours; steady-state volume of distribution (Vss) of approximately 118 L. Clearance has an estimated value of about 39 L/h. The mean body weight associated with this clearance estimate was 72 kg.

Dexmedetomidine protein binding was assessed in the plasma of normal healthy male and female human subjects: the average binding was 94 % and constant across the different concentrations tested. Protein binding was similar in males and females. The fraction of

dexmedetomidine that was bound to plasma proteins was statistically significantly decreased in subjects with hepatic impairment compared with healthy subjects.

Dexmedetomidine is unlikely to cause clinically significant changes in the plasma protein binding of fentanyl, ketorolac, theophylline, digoxin, lidocaine, phenytoin, warfarin, ibuprofen and propranolol.

Elimination

Dexmedetomidine is eliminated almost exclusively by metabolism with 95 % of a radio-labelled dose being excreted in the urine and 4 % in the faeces. Approximately 34 % of the excreted metabolites are products of N-glucuronidation.

Special populations

Hepatic impairment

In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values were lower than in healthy subjects. The mean clearance values for subjects with mild, moderate, and severe hepatic impairment were 74 %, 64 % and 53 % respectively, of those observed in the normal healthy subjects. Mean clearances for free medicine were 59 %, 51 %, and 32 % respectively, of those observed in the normal healthy subjects.

Although dexmedetomidine is dosed to effect, it may be necessary to consider dose

reduction depending on the degree of hepatic impairment (see section 4.2 and section 4.4).

Renal impairment

Dexmedetomidine pharmacokinetics (Cmax, Tmax, AUC, t½, CL and Vss) were not different in subjects with severe renal impairment (Cr Cl: < 30 mL/min) compared with healthy subjects.

Gender

No difference in dexmedetomidine pharmacokinetics due to gender was observed.

Elderly population

The pharmacokinetic profile of dexmedetomidine was not altered by age. The elderly are more sensitive to the effects of dexmedetomidine. In clinical trials, there was a higher incidence of bradycardia and hypotension in elderly patients (> 65 years of age).

Paediatric population

The pharmacokinetic profile of dexmedetomidine has not been studied in subjects less than 18 years of age.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose monohydrate.

Water for injection.

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

Compatibility studies have demonstrated the potential for absorption of dexmedetomidine to some types of natural rubber. Although DEXITHERA 4 µg/mL is dosed to effect, it is advisable to use administration components made with synthetic or coated natural rubber gaskets.

6.3 Shelf life

24 months.

Stability when mixed with magnesium sulphate 40 mg/kg, dexamethasone 4 mg/mL or sufentanil 10 micrograms/mL:

Chemical and physical in-use stability have been demonstrated at 25 °C for 24 hours when DEXITHERA 4 µg/mL is mixed with magnesium sulphate 40 mg/kg, dexamethasone 4 mg/mL or sulfentanil 10 micrograms/mL.

From a microbiological perspective, DEXITHERA 4 µg/mL should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the administrator.

6.4 Special precautions for storage

Store at or below 25 °C.

For storage conditions after mixing, see section 6.3

6.5 Nature and contents of container

DEXITHERA 4 µg/mL polypropylene bags: 100 mL flexible Polypropylene bag with an aluminium overpouch.

DEXITHERA 4 µg/mL PVC-free polyolefin bags: 100 mL PVC-free polyolefin bag with an aluminium overpouch.

Pack sizes:

Polypropylene bag: 1 x 100 mL, 4 x 100 mL

PVC-free polyolefin bag: 1 x 100 mL, 4 x 100 mL

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

DEXITHERA 4 µg/mL bags are intended for single patient use only.

DEXITHERA 4 µg/mL should be inspected visually for particulate matter and discoloration prior to administration. The preparation of the infusion solution is alike for both the loading and the maintenance dose.

DEXITHERA 4 µg/mL does not need to be diluted prior to infusion.

Strict aseptic technique must always be maintained during handling of DEXITHERA 4 µg/mL infusion.

DEXITHERA 4 µg/mL has been shown to be compatible when administered with the following intravenous fluids and medicines:

Magnesium sulphate 10 mg/kg and 40 mg/kg, sufentanil 50 micrograms/mL and dexamethasone 4 mg/mL.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Abbott Laboratories S.A. (Pty) Ltd

Abbott place, 219 Glof Club Terrace

Constantia Kloof 1709

South Africa

8. REGISTRATION NUMBERS

56/2.9/0938

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 September 2025

10. DATE OF REVISION OF THE TEXT

N/A