Approved Professional Information for Medicines for Human Use:

SEDODEX 200 µg/2 mL CONCENTRATE FOR SOLUTION FOR INFUSION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

SEDODEX 200 µg/2 mL CONCENTRATE FOR SOLUTION FOR INFUSION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of concentrate contains 118 µg dexmedetomidine hydrochloride equivalent to 100 micrograms dexmedetomidine.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for IV infusion (sterile concentrate).

Clear, colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SESODEX 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: SESODEX 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 SESODEX.

In order to minimise undesirable pharmacologic side effects, bolus injections of SESODEX 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.

SESODEX should be administered by continuous intravenous infusion not to exceed 24 hours.

Fluid supplementation should be administered prior to and during administration of SESODEX to ensure normovolaemia.

SESODEX 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 SESODEX.
Patients receiving SESODEX 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. SESODEX 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 extubtion.

Posology

Adults

ICU Sedation

SESODEX dosage should be individualised and titrated to the desired clinical effect.

Initiation

For adult patients, it is recommended to initiate SESODEX with a loading dose of 1,0 mcg/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 mcg/kg/hr. The rate of the maintenance infusion can be adjusted in order to achieve the desired clinical effect.

Dosages as low as 0,05 mcg/kg/hr 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 section 4.3, 4.4 and 5.2).

Conscious Sedation

Monitored anaesthesia care (MAC) with an adequate nerve block and awake fibreoptic intubation (AFI). SESODEX dosing should be individualised and titrated to the desires clinical effect.

Initiation:

For adult patients, SESODEX is generally initiated with a loading infusion of 1 (one) mcg/kg over 10 minutes.

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

Maintenance of Conscious Sedation:

MAC: Following the load, maintenance dosing of SESODEX should generally be initiated at 0,6 mcg/kg/hr and titrated to achieve desired clinical effect with doses ranging from 0,2 to 1 mcg/kg/hr 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 mcg/kg/hr should be used.

Dosage Adjustment

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

Special populations

Impaired Hepatic Function

Dosage reductions may need to be considered for patients with hepatic impairment, as SESODEX is metabolised primarily in the liver.

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

Since the elderly are more sensitive to the effects of SESODEX dosage reductions may need to be considered.

Paediatric population

Safety and efficacy of SESODEX has not been studied in children and adolescents and is therefore not recommended for patients under 18 years of age.

Method of administration

SESODEX must be administered only as a diluted intravenous infusion using a controlled infusion device.

4.3 Contraindications

SESODEX is contraindicated in

- patients with a known 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

Monitoring

SESODEX is intended for use in an intensive care setting, operating room and during diagnostic procedures. The use in other environments is not recommended. All patients should have continuous cardiac monitoring during SESODEX infusion.

Respiration should be monitored in non-intubated patients due to the risk of respiratory depression and in some case apnoea (see section 4.8).

The time to recovery after the use of dexmedetomidine 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

SESODEX should not be given as a bolus dose and in the ICU a loading dose is not recommended. Users should therefore 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 SESODEX 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. Dexmedetomidine is therefore not suitable in patients who will not tolerate this profile of effects, for example those requiring continuous deep sedation.

SESODEX should not be used as a general anaesthetic induction medicine for intubation or to provide sedation during muscle relaxant use.

Dexmedetomidine lacks the anticonvulsant action of some other sedatives and so will not suppress underlying seizure activity.

Care should be taken if combining dexmedetomidine with other substances with sedative or cardiovascular actions as additive effects may occur.

SESODEX is not recommended for patient controlled sedation. Adequate data is not available.

When SESODEX 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 agents that may sedate (e.g., benzodiazepines, opioids, alcohol) for a suitable period of time based on observed effects of dexmedetomidine, the procedure, concomitant medications, the age and the condition of the patient.

Caution should be exercised when administering dexmedetomidine to elderly patients. Elderly patients over 65 years of age may be more prone to hypotension with the administration of dexmedetomidine, including a loading dose, for procedures. A dose reduction should be considered. (see section 4.2).

Cardio-vascular effects and precautions

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

Caution should be exercised when administering dexmedetomidine to patients with pre-existing bradycardia. Data on the effects of SESODEX 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. 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 and the elderly and special care is warranted in these cases

(see section 4.3). Hypotension does not normally require specific treatment but, where needed, users should be ready to intervene with dose reduction, fluids and/or vasoconstrictors.

Patients with impaired peripheral autonomic activity (e.g. due to spinal cord injury) may have more pronounced haemodynamic changes after starting dexmedetomidine 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 and a loading dose is not recommended in ICU sedation. Treatment of hypertension has generally not been necessary but decreasing the continuous infusion rate may be advisable.

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 dexmedetomidine 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 dexmedetomidine 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. Dexmedetomidine may reduce cerebral blood flow and intracranial pressure and this should be considered when selecting therapy.

Other

Alpha-2 agonists have rarely been associated with withdrawal reactions when stopped abruptly after prolonged use. This possibility should be considered if the patient develops agitation and hypertension shortly after stopping dexmedetomidine.

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

SESODEX contains less than 1 mmol sodium (23 mg) per mL.

4.5 Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

Co-administration of dexmedetomidine 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 dexmedetomidine, a reduction in dosage of dexmedetomidine or the concomitant anaesthetic, sedative, hypnotic or

opioid may be required.

Inhibition of 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 dexmedetomidine 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 medicinal products causing these effects, for example beta blockers, although additional effects in an interaction study with esmolol were modest.

Neuromuscular blockers

No clinically meaningful increases in the magnitude of neuromuscular blockade and no pharmacokinetic interactions were observed with SESODEX and rocuronium administration.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

Breastfeeding

Safety in breastfeeding has not been established.

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

The patient should not drive or operate machinery or make legal decisions until 24 hours after recovery from surgical procedure in which SESODEX was used.

4.8 Undesirable effects

a) Summary of the safety profile (exclude heading if not NCE, unless included in EU innovator SmPC)

Sedation of adult ICU (Intensive Care Unit) patients

The most frequently reported adverse reactions with dexmedetomidine in ICU setting are hypotension, hypertension, bradycardia, nausea, dry mouth and hypoxia.

Hypotension and bradycardia were also the most frequent dexmedetomidine-related serious adverse reactions occurring in 1,7% and 0,9 % of randomised Intensive Care Unit (ICU) patients respectively.

Procedural/awake sedation

The most frequently reported adverse reactions with dexmedetomidine in procedural sedation are listed below (the protocols of phase III studies contained pre-defined thresholds for reporting changes in blood pressure, respiratory rate and heart rate as AEs).

- Hypotension (55 % in dexmedetomidine-group vs. 30 % in placebo-group receiving rescue midazolam and fentanyl)
- Respiratory depression (38 % in dexmedetomidine-group vs. 35 % in placebo-group receiving rescue midazolam and fentanyl)
- Bradycardia (14 % in dexmedetomidine-group vs. 4 % in placebo-group receiving rescue midazolam and fentanyl)

b) Tabulated list of adverse reactions (exclude heading if not NCE, unless included in EU innovator SmPC)

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with dexmedetomidine.

System Organ Class	Frequency		
	Frequent	**Less Frequent**	**Not known**
Metabolism and nutrition disorders	Hyperglycaemia, hypoglycaemia	Metabolic acidosis, hypoalbuminaemia	-
Psychiatric disorders	Agitation	Hallucination	-
Cardiac disorders	Bradycardia, myocardial ischaemia or infarction, tachycardia	Atrioventricular block, cardiac output decreased, cardiac arrest	-
Vascular disorders	Hypotension, hypertension	-	-
Respiratory, thoracic and mediastinal disorders	Respiratory depression	Dyspnoea, apnoea	-
Gastrointestinal disorders	Nausea, vomiting, dry mouth	Abdominal distension	-
Renal and urinary disorders	-	-	Polyuria
General disorders and administration site conditions	Withdrawal syndrome, hyperthermia	Drug ineffective, thirst	-

c. Description of selected adverse reactions

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

In relatively healthy non-ICU subjects treated with dexmedetomidine, bradycardia has occasionally led to sinus arrest or pause. The symptoms responded to leg raising and anticholinergics such as atropine or glycopyrrolate. In isolated cases bradycardia has progressed to periods of asystole in patients with pre-existing bradycardia. 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 reduced by avoiding such a loading dose or reducing the infusion rate or size of the loading dose.

d. Paediatric population

Children > 1 month post-natal, predominantly post-operative, have been evaluated for treatment up to 24 hours in the ICU and demonstrated a similar safety profile as in adults. Data in new-born infants (28 – 44 weeks gestation) is very limited and restricted to maintenance doses ≤ 0,2 mcg/kg/h. A single case of hypothermic bradycardia in a neonate has been reported in the literature.

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

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

Because SESODEX 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 SESODEX-induced bradycardia.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A2.9 Other Analgesics

Pharmacotherapeutic group: Psycholeptics, other hypnotics and sedatives

ATC Code: N05CM18

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 coeruleus. 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 ($t_{1/2\alpha}$) of about six minutes; terminal elimination

half-life ($t_{1/2}$) of approximately two hours; steady state volume of distribution (V_{ss}) of approximately 118 litres. Clearance has an estimated value of 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 protein 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.

Biotransformation and 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.

Pharmacokinetics in 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 drug 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 4.4).

Renal Impairment

Dexmedetomidine pharmacokinetics (C_{max}, T_{max}, AUC, $t_{1/2}$, CL and V_{ss}) 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

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

Sodium chloride

Water for injection

6.2 Incompatibilities

SESODEX must not be mixed with other medicines or diluents except those mentioned in section 6.6.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

SESODEX is filled in single-use Type I colourless glass vials with fluoropolymer coated bromobutyl rubber stoppers and sealed with aluminium seals with polypropylene flip-off caps. (Colourless glass vial with a rubber stopper and flip-off seal)

200 µg/2 mL vials. (Pack size 4's and 25's)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

A controlled infusion device should be used to administer SESODEX.

Parenteral medicines should be inspected visually for particulate matter and discolouration prior to administration. Ampoules/vials are intended for single patient use only.

Preparation of solution:

Strict aseptic technique must always be maintained during handling of SESODEX infusion.

Preparation of infusion solutions is the same, whether for the loading dose or for the maintenance dose.

To prepare the infusion, withdraw 2 mL of SESODEX concentrate and add to 48 mL of 0,9 % sodium chloride solution to total 50 mL. Shake gently to mix well.

After dilution, SESODEX is intended for immediate use and should be discarded after 24 hours.

Administration with other fluids:

SESODEX has been shown to be compatible when administered with the following intravenous fluids and medicines: Lactated Ringers, 5 % Dextrose in Water, 0,9 % Sodium Chloride in Water, 20 % Mannitol, thiopental sodium, etomidate, vecuronium bromide, pancuronium bromide, succinylcholine, atracurium besylate, mivacurium chloride, glycopyrrolate bromide, phenylephrine

HCl, atropine sulphate, midazolam, morphine sulphate, fentanyl citrate a plasma-substitute (i.e. Haemacel).

SESODEX must not be mixed with other medicinal products or diluents except those mentioned above.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

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10. DATE OF REVISION OF THE TEXT