PROFESSIONAL INFORMATION

SEDMEDEX 100 µg/ml should not be used outside an Intensive Care Unit setting or surgical operating theatres. There should be continuous monitoring of vital parameters.

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

SEDMEDEX 100 µg/ml sterile solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of sterile solution for injection contains dexmedetomidine hydrochloride equivalent to 100 micrograms dexmedetomidine.

Each 2 ml vial contains 200 micrograms of dexmedetomidine.

Sugar free.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Sterile solution for injection

Clear, colourless solution, free from visible extraneous matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

SEDMEDEX 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 case 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

Posology

NOTE: SEDMEDEX should be administered only by health care 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 SEDMEDEX.

In order to minimise undesirable pharmacologic side effects, bolus injection of SEDMEDEX 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.

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

SEDMEDEX 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 SEDMEDEX. Patients receiving SEDMEDEX 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. SEDMEDEX has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post

extubation. It is not necessary to discontinue SEDMEDEX prior to extubation.

Adults

ICU sedation

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

Initiation

For adult patients, it is recommended to initiate SEDMEDEX 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 micrograms/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). SEDMEDEX dosing should be individualised and titrated to the desired clinical effect.

Initiation

For adult patients, SEDMEDEX 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 – Following the load, maintenance dosing of SEDMEDEX 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 pharmacodynamics interactions a reduction in dosage of SEDMEDEX 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 SEDMEDEX 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 SEDMEDEX dosage reductions may need to be considered.

Paediatric population

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

Method of administration

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

A controlled infusion device should be used to administer SEDMEDEX. Parenteral products should be inspected visually for particulate matter and discolouration prior to administration. Vials are intended for single patient use only.

For the preparation of the solution and administration with other fluids see section 6.6. For incompatibilities see section 6.2.

4.3 Contraindications

SEDMEDEX is contraindicated in:

- Patients with a known hypersensitivity to dexmedetomidine or to any of the excipients (see section 6.1)
- Patients with sepsis
- Unstable trauma patients
- Hypovolaemic patients
- Heart block
- Uncontrolled cardiac failure
- Imminent hepatic failure
- Uncontrolled hypotension
- Acute cerebrovascular conditions

4.4 Special warnings and precautions for use

SEDMEDEX should be administered only by health care professionals skilled in the management of patients in the intensive care setting and who have received complete training in the use of SEDMEDEX in the ICU setting.

Safety and efficacy of SEDMEDEX in non-surgical intensive care patients have not been

established. Continuous electrocardiogram (ECG), blood pressure and oxygen saturation monitoring are mandatory during infusion of SEDMEDEX.

Caution should be exercised in patients with pre-existing severe bradycardia disorders (i.e. advanced heart block), or patients with pre-existing severe ventricular dysfunction (e.g. ejection fraction < 30 %) including congestive heart failure and cardiac failure in whom sympathetic tone is critical for maintaining haemodynamic balance (see section 4.3).

Hypotension, bradycardia and sinus arrest

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

Decreased blood pressure and/or heart rate may occur with the administration of SEDMEDEX. Based on clinical experience with SEDMEDEX, if medical intervention is required, treatment may include decreasing or stopping the infusion of SEDMEDEX, increasing the rate of intravenous fluid administration, elevation of the lower extremities and use pressor medicines. Because SEDMEDEX has the potential to augment bradycardia induced by vagal stimuli, clinicians should be prepared to intervene. The intravenous administration of anticholinergic medicines should be considered to modify vagal tone. In clinical trials, atropine and glycopyrrolate were effective in the treatment of most episodes of dexmedetomidine-induced bradycardia. However, in some patients with significant cardiovascular dysfunction, more advanced resuscitative measures were required.

Dexmedetomidine decreases sympathetic nervous activity and therefore, these effects may be expected to be most pronounced in patients with desensitised autonomic nervous system control (i.e. elderly, diabetes, chronic hypertension, severe cardiac disease).

Prevention of hypotension and bradycardia should take into consideration the

haemodynamic stability of the patient and normovolaemia must be ensured prior to the administration of SEDMEDEX. Patients who are hypovolaemic may become hypotensive under SEDMEDEX therapy. Therefore, fluid supplementation should be administered prior to and during the administration of SEDMEDEX.

Additionally, in situations where the vasodilators or negative chronotropic medicines are administered, co-administration of SEDMEDEX could have an additive pharmacodynamics effect and should be administered with caution and careful titration (see section 4.5).

Clinical events of bradycardia or hypotension may be potentiated when SEDMEDEX is used concurrently with propofol or midazolam. Therefore, consider a dose reduction of propofol or midazolam (see section 4.3).

Transient hypertension

Transient hypertension has been observed primarily during the loading infusion, associated with initial peripheral vasoconstrictive effects of dexmedetomidine and relatively higher plasma concentrations achieved during the loading infusion. If intervention is necessary, reduction of the loading infusion rate may be considered. Following the loading infusion, the central effects of SEDMEDEX dominate and the blood pressure usually decreases.

SEDMEDEX may cause reduced lacrimation. Lubrication of the patient's eyes may be considered when administering dexmedetomidine to avoid corneal dryness.

Elderly

The elderly are more prone to cardiovascular adverse events e.g. hypotension and bradycardia and the dose must be carefully titrated to obtain the desired effect. Close CVS monitoring is required. Elderly patients (over 65 years) often require lower doses of dexmedetomidine.

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 less frequently 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 SEDMEDEX.

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

4.5 Interaction with other medicines and other forms of interaction

Co-administration of SEDMEDEX 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 SEDMEDEX 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 medicines 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 dexmedetomidine and rocuronium administration.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Pregnancy

There are no or limited amount of data from the use of dexmedetomidine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). SEDMEDEX should not be used during pregnancy.

Breastfeeding

Dexmedetomidine is excreted in human milk, however levels will be below the limit of

detection by 24 hours following treatment discontinuation. A risk to infants cannot be excluded. SEDMEDEX should not be used during breastfeeding.

Fertility

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

Labour and delivery

The safety of SEDMEDEX in labour and delivery has not been studied and it is therefore not recommended for obstetrics, including caesarean section deliveries.

4.7 Effects on ability to drive and use machines

Patients should be advised to refrain from driving or performing other hazardous tasks or make legal decisions for a suitable period of time after receiving SEDMEDEX for procedural sedation.

4.8 Undesirable effects

a. Summary of the safety profile

Sedation of adult ICU (Intensive Care Unit) patients

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

Procedural/awake sedation

The most frequently reported adverse reactions with dexmedetomidine in procedural sedation are hypotension, respiratory depression and bradycardia.

b. Tabulated summary of adverse reactions

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: Frequent, Less frequent and Frequency unknown.

MedDRA system organ class	Frequency	Adverse reactions
Infections and infestations	Less frequent	Infection, fungal infection, sepsis
Blood and lymphatic system disorders	Less frequent	Anaemia, leucocytosis, coagulation disorders, disseminated intravascular coagulation, haematoma, abnormal platelets, decreased prothrombin, thrombocytopenia
Immune system disorders	Less frequent	Allergic reactions
Metabolism and nutrition disorders	Frequent	Hyperglycaemia, hypoglycaemia
	Less frequent	Metabolic acidosis, hypoalbuminaemia, lactic acidosis, respiratory acidosis, diabetes mellitus, hypokalaemia, hyperkalaemia, hypoproteinaemia, increased alkaline phosphate, increased Non-protein nitrogen (NPN), thirst
Psychiatric disorders	Frequent	Agitation
	Less frequent	Hallucination, anxiety, confusion, delirium, depression, illusion, nervousness
Nervous system disorders	Less frequent	Convulsion, dizziness, headache, neuralgia, neuritis, neuropathy, paraesthesia, paralysis, paresis, speech disorder
Eye disorders	Less frequent	Diplopia, photopsia, abnormal vision

MedDRA system organ class	**Frequency**	**Adverse reactions**
Cardiac disorders	Frequent	Bradycardia, myocardial ischaemia, myocardial infarction, tachycardia
	Less frequent	Angina pectoris, dysrhythmia, atrial dysrhythmia, atrial fibrillation, bundle branch block, cardiac arrest, extrasystoles, heart block, hypoxia, supraventricular tachycardia, T-wave inversion, ventricular dysrhythmia, ventricular tachycardia, AV block, cardiac output decreased
Vascular disorders	Frequent	Hypotension, hypertension
	Less frequent	Haemorrhage, cerebral haemorrhage, peripheral ischaemia, vascular disorder, vasodilation
Respiratory, thoracic and mediastinal disorders	Frequent	Respiratory depression
	Less frequent	Adult respiratory distress syndrome, apnoea, dyspnoea, bronchial obstruction, bronchospasm, coughing, emphysema, haemoptysis, hypercapnia, pharyngitis, pleurisy, pneumonia, pneumothorax, pulmonary congestion, pulmonary oedema, respiratory disorder, respiratory insufficiency, increased sputum, stridor
Gastrointestinal disorders	Frequent	Nausea, vomiting, dry mouth
	Less frequent	Abdominal pain, diarrhoea, eructation, mucosal ulceration, abdominal distention

MedDRA system organ class	Frequency	Adverse reactions
Hepato-biliary disorders	Less frequent	Increased albumin to globulin (AG) ratio, increased gamma-glutamyl transpepsidase (GGT), abnormal hepatic function, hyperbilirubinaemia, increased aspartate transaminase (AST), increased alanine transaminase (ALT), jaundice
Skin and subcutaneous tissue disorders	Less frequent	Rash erythematous, increased sweating
Musculoskeletal and connective tissue disorders	Less frequent	Muscle weakness
Renal and urinary disorders	Less frequent	Increased blood urea, oliguria, haematuria, acute renal failure, abnormal renal function, urinary retention
General disorders and administration site conditions	Frequent	Withdrawal syndrome, hyperthermia
	Less frequent	Drug ineffective, ascites, fever, hyperpyrexia, hypovolaemia, light anaesthesia, oedema, peripheral oedema, pain, syncope, rigors

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.

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.

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 asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions & Quality Problem Reporting Form**", found online under SAHPRA's publications:

https://sahpra.org.za/wp-content/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

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 SEDMEDEX 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 SEDMEDEX-induced bradycardia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, other hypnotics and sedatives, ATC code: N05CM18

Pharmacological classification: A2.9 Other Analgesics

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 ($t_{1/2\alpha}$) of about 6 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 about 39 L/h. The mean body weight associated with this clearance estimate was 72 kg.

Elimination

Dexmedetomidine is on average 94 % bound to plasma protein. 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

Gender and age

No major pharmacokinetic differences have been observed based on gender or age.

Hepatic impairment

Dexmedetomidine plasma protein binding is decreased in subjects with hepatic impairment compared with healthy subjects. It may be necessary to consider initial/maintenance dose reduction in patients with hepatic impairment depending on the degree of impairment and the response.

Renal impairment

The pharmacokinetics of dexmedetomidine in subjects with severe renal impairment (creatinine clearance <30 ml/min) is not altered relative to healthy subjects.

Paediatric population

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxicity.

In the reproductive toxicity studies, dexmedetomidine had no effect on male or female fertility in the rat, and no teratogenic effects were observed in the rat or rabbit. In the rabbit study intravenous administration of the maximum dose, 96 µg/kg/day, produced exposures that are similar to those observed clinically. In the rat, subcutaneous administration at the maximum dose, 200 µg/kg/day, caused an increase in embryofoetal death and reduced the foetal body weight. These effects were associated with clear maternal toxicity. Reduced foetal body weight was noted also in the rat fertility study at dose 18 µg/kg/day and was accompanied with delayed ossification at dose 54 µg/kg/day. The observed exposure levels in the rat are below the clinical exposure range.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

24 months

After dilution

Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to the use are the responsibility of the user and would not normally be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the vials in the outer carton in order to protect from light.

For storage conditions after dilution of the medicine, see section 6.3.

6.5 Nature and contents of container

SEDMEDEX is packed as 200 µg in 2 ml USP Type I clear glass vial, stoppered with 13 mm ready to sterilize grey colour rubber stopper sealed with 13 mm aluminium flip-off seal.

Pack size: 5 x 2 ml vials.

6.6 Special precautions for disposal and other handling

The vials are intended for single patient use only.

Preparation of solution

Strict aseptic technique must always be maintained during handling of SEDMEDEX 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 SEDMEDEX concentrate and add to 48 ml of 0,9 % sodium chloride solution to total 50 ml. Shake gently to mix well.

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

Administration with other fluids

SEDMEDEX has been shown to be compatible when administered with the following intravenous fluids and medicines:

0,9 % Sodium chloride injection, Lactated Ringers, 5 % Dextrose in water, 20 % mannitol, thiopental sodium, etomidate, vecuronium bromide, succinylcholine, atracurium besylate, mivacurium chloride, glycopyrrolate bromide, phenylephrine HCl, atropine sulphate, midazolam, morphine sulphate, fentanyl citrate and a plasma-substitute (i.e. Haemacel).

Compatibility studies have shown potential for adsorption of dexmedetomidine to some types of natural rubber. Although dexmedetomidine is dosed to effect, it is advisable to use components with synthetic or coated natural rubber gaskets.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Kahma Biotech (Pty) Ltd

106,16th Road

Midrand

8 REGISTRATION NUMBER

540696

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 February 2023

10 DATE OF REVISION OF THE TEXT