PROFESSIONAL INFORMATION

SEDMEDEX RTU 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 RTU 50 mL and **SEDMEDEX RTU 100 mL** solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of Dexmedetomidine hydrochloride in 0,9 % sodium chloride contains 4,72 µg/mL equivalent to 4 µg/mL of dexmedetomidine.

Sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

A clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

SEDMEDEX RTU 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

- 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: SEDMEDEX RTU should be administered only by health care providers 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 RTU.

In order to minimise undesirable pharmacologic side effects, bolus injections of SEDMEDEX RTU should not be used. Clinically significant events of bradycardia and sinus arrest have been associated with dexmedetomidine administration in young healthy volunteers with high vagal tone, or with different routes of administration including rapid intravenous or bolus administration of dexmedetomidine.

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

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

Dexmedetomidine as in SEDMEDEX RTU 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 dexmedetomidine. Patients receiving dexmedetomidine 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. Dexmedetomidine 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

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

Initiation

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

Initiation

For adult patients, SEDMEDEX RTU 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 microgram/kg over 10 minutes may be suitable.

Maintenance of conscious sedation

MAC

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

Dosage adjustment

Due to possible pharmacodynamic interactions a reduction in dosage of SEDMEDEX RTU 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 RTU 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 population

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

Paediatric population

Safety and efficacy of dexmedetomidine as in SEDMEDEX RTU have not been studied in children and adolescents and it is therefore not recommended for patients under 18 years of age.

Method of administration

For intravenous infusion.

For instructions on the use of SEDMEDEX RTU, see section 6.6.

4.3 Contraindications

SEDMEDEX RTU is contraindicated in:

- patients with a known hypersensitivity to dexmedetomidine or to any of the excipients of SEDMEDEX RTU (see 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

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

Safety and efficacy of dexmedetomidine as in SEDMEDEX RTU in non-surgical intensive care patients have not been established.

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.

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

General precautions

Some patients receiving dexmedetomidine 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.

SEDMEDEX RTU normally does not cause deep sedation and patients may be easily roused.

SEDMEDEX RTU is therefore not suitable in patients who will not tolerate this profile of effects, for example those requiring continuous deep sedation.

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

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

Care should be taken if combining SEDMEDEX RTU with other medicines with sedative or cardiovascular actions as additive effects may occur.

SEDMEDEX RTU is not recommended for patient-controlled sedation. Adequate data is not available.

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

Elderly population

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 SEDMEDEX RTU.

Special precautions

NOTE: SEDMEDEX RTU should be administered only by health care providers skilled in the management of patients in the intensive care setting. Continuous electrocardiogram (ECG), blood pressure and oxygen saturation monitoring are mandatory during infusion of SEDMEDEX RTU.

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).
Data on the effects of SEDMEDEX RTU 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).

Hypotension, bradycardia and sinus arrest

Clinical events of bradycardia and sinus arrest have been associated with dexmedetomidine administration in young, healthy volunteers with high vagal tone, or with different routes of administration including rapid intravenous or bolus administration of SEDMEDEX RTU (see boxed warning above).

Decreased blood pressure and/or heart rate may occur with the administration of SEDMEDEX RTU. Based on clinical experience with SEDMEDEX RTU, if medical intervention is required, treatment may include decreasing or stopping the infusion of SEDMEDEX RTU, increasing the rate of intravenous fluid administration, elevation of the

lower extremities and use of pressor medicines. The intravenous administration of anticholinergic medicines should be considered to modify vagal tone. Atropine and glycopyrrolate were effective in the treatment of most episodes of SEDMEDEX RTU-induced bradycardia. However, in some patients with significant cardiovascular dysfunction, more advanced resuscitative measures were required. SEDMEDEX RTU is therefore not suitable in patients with severe cardiovascular instability.

SEDMEDEX RTU 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 RTU. Patients who are hypovolaemic may become hypotensive under SEDMEDEX RTU therapy. Therefore, fluid supplementation should be administered prior to and during the administration of
SEDMEDEX RTU.

Additionally, in situations where other vasodilators or negative chronotropic medicines are administered, co-administration of SEDMEDEX RTU could have an additive pharmacodynamic 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 RTU is used concurrently with propofol or midazolam. Therefore, consider a dose reduction of propofol or midazolam (see section 4.5).

Caution is advised when administering SEDMEDEX RTU together with spinal or epidural

anaesthesia due to possible increased risk of hypotension or bradycardia.

Cardiovascular effects and precautions

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

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.

Transient hypertension

Transient hypertension has been observed primarily during the loading infusion, associated with initial peripheral vasoconstrictive effects of SEDMEDEX RTU 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 RTU dominate and the blood pressure usually decreases.

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

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 SEDMEDEX RTU clearance.

Neurological disorders

Experience of SEDMEDEX RTU 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.

SEDMEDEX RTU 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 SEDMEDEX RTU.

SEDMEDEX RTU 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.

Diabetes insipidus has been reported in association with dexmedetomidine treatment. If polyuria occurs, it is recommended to stop SEDMEDEX RTU and check serum sodium level and urine osmolality.

4.5 Interaction with other medicines and other forms of interaction

Cytochrome P-450

In vitro studies indicate that clinically relevant cytochrome P450 mediated medicine interactions are unlikely.

Anaesthetics/sedatives/hypnotics/opioids

Co-administration of SEDMEDEX RTU is likely to lead to an enhancement of effects with anaesthetics, sedatives, hypnotics and opioids. Specific studies have confirmed these effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam. No

pharmacokinetic interactions between dexmedetomidine and isoflurane, propofol, alfentanil, and midazolam were demonstrated. However, due to pharmacodynamic effects, when co-administered with SEDMEDEX RTU a reduction in dosage of these medicines may be required.

Neuromuscular blockers

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

Other

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.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Pregnancy

There are no adequate and well-controlled studies in pregnant women. The use of SEDMEDEX RTU is not recommended in pregnancy.

Labour and delivery

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

Breastfeeding

It is not known whether dexmedetomidine as in SEDMEDEX RTU is excreted in human milk. The use of SEDMEDEX RTU is not recommended in lactating women.

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 a surgical procedure in which SEDMEDEX RTU was used.

4.8 Undesirable effects

a. Summary of the safety profile

ICU sedation

The most frequently observed treatment-emergent adverse events include hypotension, hypertension, bradycardia, nausea, dry mouth and hypoxia (see section 4.4).

Conscious sedation

The most frequent adverse events were hypotension, bradycardia, and dry mouth (see section 4.4)

b. Tabulated summary of adverse reactions

The frequency of adverse reactions listed below is defined using the following convention: frequent; less frequent or frequency unknown (cannot be estimated from the available data).

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequency unknown	Infection, fungal infection, sepsis
Blood and lymphatic system disorders	Frequent	Anaemia
	Frequency unknown	Coagulation disorders, disseminated intravascular coagulation, haematoma, abnormal platelets, decreased prothrombin, thrombocytopenia, leukocytosis
Endocrine disorders	Frequency unknown	Diabetes mellitus, diabetes insipidus
Metabolism and nutrition disorders	Frequent	Hypoglycaemia, hyperglycaemia
	Less frequent	Hypocalcaemia, hypoalbuminaemia, metabolic acidosis
	Frequency unknown	Lactic acidosis, respiratory acidosis, hypokalaemia, hyperkalaemia, hypoproteinaemia, increased alkaline phosphatase, increased nonprotein

MedDRA system organ class	**Frequency**	**Adverse reactions**
		nitrogen (NPN)
Psychiatric disorders	Frequent	Agitation
	Less frequent	Hallucination
	Frequency unknown	Anxiety, confusion, delirium, depression, illusion, nervousness
Nervous system disorders	Frequency unknown	Convulsion, dizziness, headache, neuralgia, neuritis, neuropathy, paraesthesia, paralysis, paresis, speech disorder
Eye disorders	Frequency unknown	Diplopia, photopsia, abnormal vision
Cardiac disorders	Frequent	Atrial fibrillation, myocardial ischaemia or infarction, bradycardia, tachycardia
	Less frequent	Sinus tachycardia, ventricular tachycardia, atrioventricular block, decreased cardiac output, cardiac arrest
	Frequency unknown	Dysrhythmia, atrial dysrhythmia, AV block, bundle branch block, extrasystoles, heart block, hypoxia, supraventricular tachycardia, T-wave inversion, ventricular dysrhythmia, angina pectoris, abnormal ECG, heart disorder
Vascular disorders	Frequent	Hypovolaemia, hypotension, hypertension
	Frequency	Blood pressure fluctuation, circulatory

MedDRA system organ class	**Frequency**	**Adverse reactions**
	unknown	failure, cyanosis, aggravated hypertension, pulmonary hypertension, postural hypotension, pulmonary hypertension, haemorrhage, cerebral haemorrhage, peripheral ischaemia, vascular disorder, vasodilation
Respiratory, thoracic and mediastinal disorders	Frequent	Atelectasis, pleural effusion, hypoxia, bradypnoea, respiratory depression
	Less frequent	Pulmonary oedema, wheezing, dyspnoea, apnoea
	Frequency unknown	Syncope, adult respiratory distress syndrome, bronchial obstruction, bronchospasm, coughing, emphysema, haemoptysis, hypercapnia, hypoventilation, pharyngitis, pleurisy, pneumonia, pneumothorax, pulmonary congestion, respiratory disorder, respiratory insufficiency, increased sputum, stridor
Gastrointestinal disorders	Frequent	Nausea, vomiting, dry mouth
	Less frequent	Abdominal distension
	Frequency unknown	Abdominal pain, diarrhoea, eructation, mucosal ulceration

MedDRA system organ class	**Frequency**	**Adverse reactions**
Hepato-biliary disorders	Frequency unknown	Increased AG ratio, increased GGT, abnormal hepatic function, hyperbilirubinaemia, increased aspartate transaminase (AST), increased alanine transaminase (ALT), jaundice
Skin and subcutaneous tissue disorders	Frequency unknown	Rash erythematous, increased sweating
Musculoskeletal and connective tissue disorders	Frequency unknown	Muscle weakness
Renal and urinary disorders	Frequency unknown	Increased blood urea, oliguria, haematuria, acute renal failure, abnormal renal function, urinary retention
General disorders and administration site conditions	Frequent	Pyrexia, chills, withdrawal syndrome, hyperthermia
	Less frequent	Peripheral oedema, medicine ineffective, thirst
	Frequency unknown	Allergic reaction, ascites, fever, hyperpyrexia, light anaesthesia, oedema, pain, rigors
Investigations	Less frequent	Decreased urine output
Injury, poisoning and procedural complications	Frequent	Post-procedural haemorrhage

Withdrawal

ICU sedation

Although not specifically studied, withdrawal symptoms similar to those reported for another alpha$_2$ adrenergic medicine (clonidine) may result when SEDMEDEX RTU is administered in excess of 24 hours and stopped abruptly. These symptoms include nervousness, agitation and headache accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma.

Conscious sedation

Withdrawal symptoms were not seen after discontinuation of short term infusions of dexmedetomidine as in SEDMEDEX RTU (< 6 hours).

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, who received 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

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

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 RTU has the potential to augment bradycardia induced by vagal stimuli, medical practitioners should be prepared to intervene. Atropine and glycopyrrolate were effective in the treatment of SEDMEDEX RTU-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 ($t_{½\ \alpha}$) of about six minutes; terminal elimination half-life ($t_{½}$) of approximately two hours; steady-state volume of distribution (V_{ss}) 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 (C_{max}, T_{max}, AUC, $t_{½}$, 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 population

The pharmacokinetic profile of dexmedetomidine was not altered by age. The elderly are more sensitive to the effects of dexmedetomidine. 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.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Water for injection

6.2 Incompatibilities

This medicine must not be mixed with other medicines.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

SEDMEDEX RTU 50 mL: 50 mL clear glass moulded vial with a grey bromobutyl rubber stopper and a yellow or dark blue aluminium flip-off seal.

SEDMEDEX RTU 100 mL: 100 mL clear glass moulded vial with a grey bromobutyl rubber stopper and a yellow or dark blue aluminium flip-off seal.

Pack size: 1, 5 or 10 vials packed in an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Directions for use

SEDMEDEX RTU solution for infusion should not be diluted before use: it is supplied ready to use. It should not be mixed with other medicines.

A controlled infusion device should be used to administer SEDMEDEX RTU.

SEDMEDEX RTU should not be given as a bolus dose (see section 4.4).

Parenteral medicines should be inspected visually for particulate matter and discolouration prior to administration.

Vials are intended for single patient use only.

The solution should be used immediately after opening.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Juno Pharma SA (Pty) Ltd

Address: 3 Gwen Lane, 4th Floor, Sandton, 2031.

Contact No.: +27 (0)10 594 5610

PV Email Address: pv@trinitypharma.co.za

8 REGISTRATION NUMBERS

SEDMEDEX RTU 50 mL: 59/2.9/0983

SEDMEDEX RTU 100 mL: 59/2.9/0984

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09 June 2026

10 DATE OF REVISION OF THE TEXT

To follow