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PROFESSIONAL INFORMATION

DEXISUN 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

DEXISUN Concentrated solution for intravenous infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sodium chloride (9,0 mg/ml)

For full list of excipients, see section 6.1

Sugar free.

3 PHARMACEUTICAL FORM

A clear, colourless solution, free from visible extraneous matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DEXISUN is an alpha-2 adrenoreceptor agonist sedative with analgesic properties indicated for:

- ***Intensive Care Unit (ICU) sedation***

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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 has not been studied in children under 18 years of age.

4.2 Posology and method of administration

NOTE: DEXISUN should be administered only by healthcare 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 DEXISUN.

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

DEXISUN should be administered by continuous intravenous infusion not to exceed 24 hours. Fluid supplementation should be administered prior to and during administration of DEXISUN to ensure normovolaemia.

DEXISUN has been administered to patients requiring mechanical ventilation as well as to patients breathing spontaneously after extubation. There is no respiratory depression

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associated with the administration of DEXISUN. Patients receiving DEXISUN 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. DEXISUN has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post extubation. It is not necessary to discontinue DEXISUN prior to extubation.

Posology

Adults:

ICU Sedation:

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

Initiation:

For adult patients, it is recommended to initiate DEXISUN 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).

DEXISUN dosing should be individualised and titrated to the desired clinical effect.

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Initiation:

For adult patients, DEXISUN 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 procedures such as ophthalmic surgery, a loading infusion of 0,5 mcg/kg over 10 minutes may be suitable.

Maintenance of Conscious Sedation:

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

Special populations

Elderly:

Since the elderly are more sensitive to the effects of DEXISUN dosage reductions may need to be considered (see section 5.2).

Impaired Hepatic Function:

Dosage reductions may need to be considered for patients with hepatic impairment, as DEXISUN is metabolised primarily in the liver (see section 4.4 and 5.2).

Impaired Renal Function:

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Since the majority of metabolites are excreted in the urine, dosage reductions may need to be considered for patients with renal impairment (see section 5.2).

Paediatric population

Safety and efficacy of DEXISUN has not been studied in children and adolescents and is therefore not recommended for patients under 18 years of age (see section 5.2).

Dosage Adjustment:

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

Method of administration

For IV infusion only.

A controlled infusion device should be used to administer DEXISUN.

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

Vials are intended for single patient use only.

For information on instructions for preparation or reconstitution see section 6.6.

DEXISUN must not be mixed with other medicinal products or diluents except those mentioned in section 6.6.

4.3 Contraindications

DEXISUN is contraindicated in:

- patients with known hypersensitivity to dexmedetomidine or to any other ingredient of DEXISUN listed in section 6.1.

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- patients with sepsis
- unstable trauma patients
- hypovolaemic patients
- heart block
- uncontrolled cardiac failure
- imminent hepatic failure
- uncontrolled hypotension
- acute cerebrovascular conditions
- pregnancy and lactation (see section 4.6)

4.4 Special warnings and precautions for use

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

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

Safety and efficacy of DEXISUN in non-surgical intensive care patients have not been reported.

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

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 as in DEXISUN 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.

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:

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

DEXISUN 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).

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

Additionally, in situations where the vasodilators or negative chronotropic agents are administered, co-administration of DEXISUN 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 DEXISUN is used concurrently with propofol or midazolam. Therefore, consider a dose reduction of propofol or midazolam (see section 4.5).

Transient Hypertension:

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

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

DEXISUN 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.

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During procedural sedation a small bolus of another sedative may be used if a rapid increase in sedation level is required.

Some patients receiving dexmedetomidine as in DEXISUN have been reported 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 as in DEXISUN normally does not cause deep sedation and patients may be easily roused. DEXISUN is therefore not suitable in patients who will not tolerate this profile of effects, for example those requiring continuous deep sedation.

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

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

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

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

When DEXISUN 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 reported effects of dexmedetomidine, the procedure, concomitant medications, the age and the condition of the patient.

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.

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Patients with neurological disorders

Experience of dexmedetomidine as in DEXISUN 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. DEXISUN 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 DEXISUN.

DEXISUN 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.

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 cardiovascular system (CVS) monitoring is required. Elderly patients (over 65 years) often require lower doses of DEXISUN.

4.5 Interaction with other medicines and other forms of interaction

Cytochrome P-450:

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

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Anaesthetics / Sedatives / Hypnotics / Opioids:

Co-administration of DEXISUN is likely to lead to an enhancement of effects with anaesthetics, sedatives, hypnotics, and opioids. Specific studies have confirmed these enhanced effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam.

No pharmacokinetic interactions between dexmedetomidine and isoflurane, propofol, alfentanil and midazolam have been demonstrated. However, due to pharmacodynamic effects, when co-administered with DEXISUN, a reduction in dosage of these agents may be required.

Neuromuscular Blockers:

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

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

The safety in pregnancy and lactation has not been established.

Pregnancy

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

Labour and delivery

The safety of DEXISUN 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 DEXISUN is excreted in human milk. The use of DEXISUN is not recommended in lactating women.

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Fertility

In the reported 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 DEXISUN was used.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequently reported adverse reactions with DEXISUN are hypotension, hypertension, bradycardia, nausea, dry mouth and hypoxia (see section 4.4).

The following side effects have been reported during clinical trials and post-marketing surveillance and are listed by system organ class and frequencies indicated:

b. Tabulated list of adverse reactions

Table 1: Adverse Events with an Incidence > 2 % - ICU Sedation Population

System Organ class	Frequency	Adverse event
Blood and lymphatic system disorders	Frequent	Anaemia
Metabolism and nutrition disorders	Frequent Less frequent	Hypovolaemia, hyperglycaemia, hypocalcaemia, acidosis Hypoalbuminaemia
Psychiatric disorders	Frequent Less frequent	Agitation Hallucination

Cardiac disorders	Frequent Less frequent	Bradycardia, atrial fibrillation, tachycardia, sinus tachycardia, ventricular tachycardia, myocardial ischaemia or infarction Atrioventricular block, cardiac output decreased, cardiac arrest
Vascular disorders	Frequent	Hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Atelectasis, pleural effusion, hypoxia, pulmonary oedema, wheezing, respiratory depression Dyspnoea, apnoea
Gastrointestinal disorders	Frequent Less frequent	Nausea, dry mouth, vomiting Abdominal distension
Renal and urinary disorders	Less frequent	Polyuria
General disorders and administration site conditions	Frequent Less frequent	Pyrexia, hyperthermia, chills, oedema peripheral, withdrawal syndrome Drug ineffective, thirst
Investigations	Frequent	Urine output decreased
Injury, poisoning and procedural complications	Frequent	Post-procedural haemorrhage

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Table 2 : Adverse Events with an Incidence > 2 % - Conscious Sedation Population

The majority of the adverse events were assessed as mild in severity. The most frequent adverse events were hypotension, bradycardia, and dry mouth. (See section 4.4)

System Organ class	Frequency	Adverse event
Cardiac disorders	Frequent	Bradycardia, tachycardia
Vascular disorders	Frequent	Hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	Frequent	Respiratory depression, hypoxia, bradypnoea
Gastrointestinal disorders	Frequent	Nausea, dry mouth

Post marketing adverse reactions:

System Organ class	Frequency	Adverse event
Infections and infestations	Less frequent	Infection, fungal infection, sepsis
Blood and the lymphatic system disorders	Less frequent	Anaemia, leukocytosis, coagulation disorders, disseminated intravascular coagulation, haematoma, abnormal platelets, decreased prothrombin, thrombocytopenia
Immune system disorders	Less frequent	Allergic reactions

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Metabolism and nutrition disorders	Less frequent	Hyperglycaemia, hypoglycaemia, acidosis, lactic acidosis, respiratory acidosis, diabetes mellitus, hypokalaemia, hyperkalaemia, hypoproteinaemia, increased alkaline phosphate, increased Non-protein nitrogen (NPN), thirst
Psychiatric disorders	Less frequent	Agitation, anxiety, confusion, delirium, depression, hallucination, illusion, nervousness
Nervous system disorders	Less frequent	Convulsion, dizziness, headache, neuralgia, neuritis, neuropathy, paraesthesia, paralysis, paresis, speech disorder, syncope
Eye disorders	Less frequent	Diplopia, photopsia, abnormal vision

Cardiac disorders	Less frequent	Bradycardia, myocardial ischaemia, myocardial infarction, tachycardia Angina pectoris, dysrhythmia, atrial dysrhythmia, atrial fibrillation, AV block, bundle branch block, cardiac arrest, extrasystoles, heart block, hypoxia, supraventricular tachycardia, T-wave inversion, ventricular dysrhythmia, ventricular tachycardia
Vascular disorders	Less frequent	Hypotension, hypertension Haemorrhage, cerebral haemorrhage, peripheral ischaemia, vascular disorder, vasodilation, circulatory failure, cyanosis, abnormal ECG, heart disorder, aggravated hypertension, pulmonary hypertension, postural hypotension, pulmonary hypertension

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Respiratory, thoracic and mediastinal disorders	Less frequent	Adult respiratory distress syndrome, apnoea, bronchial obstruction, bronchospasm, coughing, dyspnoea, emphysema, haemoptysis, hypercapnia, pharyngitis, pleurisy, pneumonia, pneumothorax, pulmonary congestion, pulmonary oedema, respiratory depression, respiratory disorder, respiratory insufficiency, increased sputum, stridor
Gastrointestinal disorders	Less frequent	Abdominal pain, diarrhoea, eructation, mucosal ulceration, nausea, vomiting
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

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Musculoskeletal, connective tissue and 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	Less frequent	Ascites, fever, hyperpyrexia, hypovolaemia, light anaesthesia, oedema, peripheral oedema, pain, withdrawal syndrome, rigors.

c. Description of selected adverse reactions

Withdrawal

ICU Sedation

Although not specifically studied, withdrawal symptoms similar to those reported for another alpha$_2$ adrenergic agent (clonidine) may result when DEXISUN 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 such as DEXISUN (< 6 hours).

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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 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 DEXISUN has the potential to augment bradycardia induced by vagal stimuli, medical practitioners should be prepared to intervene. In clinical trials, atropine and glycopyrrolate were effective in the treatment of DEXISUN-induced bradycardia (see section 4.8).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.9 Other analgesics. Pharmacotherapeutic group: Psycholeptics, other hypnotics and sedatives, ATC code: N05CM18.

Dexmedetomidine is an alpha-2 adrenoreceptor agonist.

The sedative effects are mediated primarily by post-synaptic alpha-2 adrenoreceptors, which in turn act on inhibitory pertusses-toxin-sensitive G protein, thereby increasing conductance through potassium channels. The site of sedative effects of dexmedetomidine has been attributed to the locus ceruleus. The analgesic actions are mediated by a similar mechanism of action at the brain and spinal cord level.

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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

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.

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.

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.

<u>Hepatic Impairment</u>

In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values were reported to be lower than in healthy subjects. The mean clearance values for subjects with mild, moderate, and severe hepatic impairment were reported to be

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74 %, 64 % and 53 % respectively, of those reported in the normal healthy subjects. Mean clearances for free drug were reported to be 59 %, 51 %, and 32 % respectively, of those reported 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).

Renal Impairment

Dexmedetomidine pharmacokinetics (C_{max}, T_{max}, AUC, $t_{½}$, CL and V_{ss}) were not reported to be 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 reported.

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.

5.3 Preclinical safety data

Reported 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 reported reproductive toxicity studies, dexmedetomidine had no effect on male or female fertility in the rat, and no teratogenic effects were reported 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 reported clinically. In the rat, subcutaneous administration

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at the maximum dose, 200 µg/kg/day, caused an increase in embryofetal death and reduced the fetal body weight. These effects were associated with clear maternal toxicity. Reduced fetal 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 reported exposure levels in the rat are below the clinical exposure range.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Sodium chloride
- water for injections.

6.2 Incompatibilities

DEXISUN must not be mixed with other medicinal products or diluents except those mentioned in section 6.6.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at or below 25 ^{o}C in the original container.

Do not refrigerate.

Once diluted, the diluted solution should be used immediately. If not used immediately, the diluted solution may be stored at 2 – 8 ^{o}C during the 24 hour “in use” period. Discard any unused diluted solution after 24 hours.

Keep out of reach of children.

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6.5 Nature and contents of container

DEXISUN is packed in a 2 ml tubular, USP type 1 flint glass vial, with a 13 mm Teflon coated grey rubber stopper and a 13 mm pink aluminium flip-off seal, in a outer carton. Each carton contains 1 or 5 vials.

6.6 Special precautions for disposal and other handling

Preparation of Solution:

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

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

Administration with other fluids:

DEXISUN 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, vercuronium, bromide, succinylcholine, atracurium besylate, mivacurium chloride, glycopyrrolate bromide, phenylephrine HCL, atropine sulphate, midazolam, morphine sulphate, fentanyl citrate and a plasma-substitute (i.e. Haemacel).

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

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill, Ext 1

Roodepoort, 1724

South Africa

8 REGISTRATION NUMBER(S)

54/2.9/0218

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 June 2022

10 DATE OF REVISION OF THE TEXT

Not applicable

Namibia NS3 22/2.9/0009

PROFESSIONELE INLIGTING

DEXISUN moet nie buite die opset van ’n intensiewesorgeenheid of chirurgiese teaters gebruik word nie. Vitale parameters moet deurlopend gemonitor word.

SKEDULERINGSTATUS

S5

1 NAAM VAN DIE MEDISYNE

DEXISUN Gekonsentreerde oplossing vir intraveneuse infusie

2 KWALITATIEWE EN KWANTITATIEWE SAMESTELLING

Elke 1 ml steriele oplossing bevat deksmedetomidienhidrochloried gelykstaande aan 100 mikrogram deksmedetomidien.

Bevat natriumchloried (9,0 mg/ml).

Vir die volledige lys van hulpstowwe, sien afdeling 6.1.

Suiker vry.

3 DOSEERVORM

’n Helder, kleurlose oplossing, sonder enige sigbare vreemde deeltjies.

4 KLINIESE BESONDERHEDE

4.1 Terapeutiese indikasies

DEXISUN is ’n alfa-2-adrenoreseptoragonis-kalmeermiddel met analgetiese eienskappe wat aangedui word vir:

- ***Intensiewesorgeenheid- (ISE-)sedasie***

Sedasie van geïntubeerde en meganies-geventileerde volwasse post-chirurgiese pasiënte tydens behandeling in die opset van ’n intensiewesorgeenheid.

- ***Gemoniteerde narkosesorg (MNS) / Bewuste sedasie in die opset van ’n teater of intensiewesorgeenheid vir:***
    - Mindere chirurgiese prosedures onder plaaslike anestesie
    - Veseloptiese intubasie

Doelmatigheid en veiligheid is nie by kinders jonger as 18 jaar bestudeer nie.

4.2 Posologie en metode van toediening

NOTA: DEXISUN moet slegs toegedien word deur gesondheidsorgdeskundiges wat bekwaam is om pasiënte in die opset van ’n intensiewesorgeenheid te bestuur. Deurlopende monitering van vitale tekens, in die besonder bloeddruk, hartspoed en suurstofversadiging, is verpligtend tydens infusie van DEXISUN.

Ten einde ongewenste farmakologiese newe-effekte te minimaliseer, moet DEXISUN nie as ’n bolus ingespuit word nie.

Klinies beduidende voorvalle van bradikardie en sinusarres het met toediening van deksmedetomidienhidrochlorid by jong, gesonde vrywilligers met hoë vagale tonus gepaardgegaan, of met verskillende toedieningsroetes, insluitende vinnige intraveneuse of bolus toediening van deksmedetomidienhidrochloried.

DEXISUN moet via deurlopende intraveneuse infusie toegedien word, wat nie ’n tydperk van 24 uur oorskry nie.

Vloeistowwe moet aangevul word voor en tydens toediening van DEXISUN ten einde normovolemie te verseker.

DEXISUN is toegedien aan pasiënte wat meganiese ventilasie benodig, asook aan pasiënte wat spontaan asemhaal na ekstubasie. Geen respiratoriese onderdrukking word met toediening van

DEXISUN geassosieer nie. Pasiënte wat DEXISUN ontvang kon wakker gemaak word en was helder toe hulle gestimuleer is. Dit is ’n verwagte komponent van deksmedetomidien-sedasie en in die afwesigheid van ander kliniese tekens en simptome moet dit nie beskou word as ’n bewys van gebrek aan doelmatigheid nie. DEXISUN is aaneenlopend geïnfuseer by meganies-geventileerde pasiënte voor ekstubasie, tydens ekstubasie, en ná ekstubasie. Dit is nie nodig om DEXISUN te staak voor ekstubasie nie.

Posologie

Volwassenes:

ISE-sedasie:

Die dosis van DEXISUN moet tot die verlangde kliniese effek geïndividualiseer en getitreer word.

Inisiasie:

Vir volwasse pasiënte word aanbeveel dat DEXISUN met ’n ladingsdosis van 1,0 mikrogram/kg oor tien minute geïnisieer word.

Instandhouding van ISE-sedasie:

Volwasse pasiënte sal oor die algemeen instandhoudingsinfusie in die reikwydte van 0,2 tot 0,7 mikrogram/kg/h nodig hê. Die tempo van die instandhoudingsinfusie kan aangepas word ten einde die verlangde kliniese effek te verkry. Doserings so laag as 0,05 mikrogram/kg/h is in kliniese studies gebruik.

’n Dosisverlaging van sowel die ladings- as instandhoudingsinfusies behoort oorweeg te word by pasiënte met belemmerde lewer- of nierfunksie en by pasiënte ouer as 65 jaar (sien afdelings 4.3, 4.4 en 5.2).

Bewuste sedasie:

Gemoniteerde narkosesorg (MNS) met ’n genoegsame senuweeblok en wakker veseloptiese intubasie (WVI).

DEXISUN-dosering moet tot die verlangde kliniese effek geïndividualiseer en getitreer word.

Inisiasie:

By volwasse pasiënte word DEXISUN gewoonlik met ’n ladingsinfusie van 1 (een) mikrogram/kg oor 10 minute geïnisieer.

Vir pasiënte ouer as 65 jaar of die wat minder indringende prosedures soos oftalmiese chirurgie ondergaan, mag ’n ladingsinfusie van 0,5 µg/kg oor 10 minute geskik wees.

Instandhouding van bewuste sedasie:

MNS – Ná die ladingsdosis, moet instandhoudingsdosering van DEXISUN oor die algemeen teen 0,6 µg/kg/h begin en getitreer word om die verlangde kliniese effek te verkry met dosisse wat wissel van 0,2 tot 1 µg/kg/h vir alle prosedures. Die tempo van die instandhoudingsinfusie moet aangepas word om die vlak van sedasie te bereik wat verlang word.

WVI – Ná die ladingsdosis by wakker veseloptiese intubasie, moet ’n vaste instandhoudingsdosis van 0,7 µg/kg/h gebruik word.

Spesiale populasies

Bejaarde pasiënte:

Aangesien bejaarde volwassenes meer sensitief vir die effekte van DEXISUN is, mag dit nodig wees om dosisverlaging te oorweeg (sien afdeling 5.2).

Belemmerde lewerfunksie:

Dit mag nodig wees om verlaging van die dosering te oorweeg by pasiënte met hepatiese belemmering, aangesien DEXISUN hoofsaaklik in die lewer gemetaboliseer word (sien afdelings 4.4 en 5.2).

Belemmerde nierfunksie:

Dit mag nodig wees om verlaging van die dosering te oorweeg by pasiënte met hepatiese belemmering, aangesien die meerderheid van die metaboliete in die urine uitgeskei word (sien afdeling 5.2).

Pediatriese populasie

Veiligheid en doelmatigheid van DEXISUN is nie by kinders en adolessente bestudeer nie en word gevolglik nie vir pasiënte jonger as 18 jaar aanbeveel nie (sien afdeling 5.2).

Dosisaanpassing:

Weens moontlike farmakodinamiese interaksies, mag ’n verlaging van die dosis van DEXISUN of ander gepaardgaande anestetika, sedeermiddels, hipnotika of opioïede nodig wees wanneer dit saam toegedien word (sien afdeling 4.5).

Metode van toediening

Slegs vir IV infusie.

’n Gekontroleerde infusie-apparaat behoort gebruik te word om DEXISUN toe te dien.

Parenterale produkte moet voor toediening visueel ondersoek word vir deeltjiemateriaal en verkleuring.

Flessies is bedoel om vir ’n enkele pasiënt gebruik te word.

Vir inligting rakende aanwysings vir voorbereiding of hersamestelling, sien afdeling 6.6.

DEXISUN moenie met ander medisinale produkte of diluente vermeng word nie, buiten die wat genoem word by afdeling 6.6.

4.3 Kontra-indikasies

DEXISUN word teenaangedui by:

- pasiënte met ’n bekende hipersensitiwiteit vir deksmedetomidien of vir enige ander bestanddeel van DEXISUN het, soos gelys by afdeling 6.1
- pasiënte met sepsis
- onstabiele traumapasiënte
- hipovolemiese pasiënte
- hartblok
- ongekontroleerde hartversaking
- dreigende lewerversaking
- ongekontroleerde hipotensie
- akute serebrovaskulêre toestande
- swangerskap en borsvoeding (sien afdeling 4.6).

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik

DEXISUN moet slegs toegedien word deur gesondheidsorgdeskundiges wat bekwaam is om pasiënte in die opset van ’n intensiewesorgeenheid te bestuur en wat volledige opleiding ontvang het in die gebruik van DEXISUN in die opset van ’n ISE.

Aaneenlopende monitering van elektrokardiogram (EKG), bloeddruk en suurstofversadiging is verpligtend tydens infusie van DEXISUN.

Veiligheid en doelmatigheid van DEXISUN by niechirurgiese intensiewesorg pasiënte is nie gerapporteer nie.

Kliniese voorvalle van bradikardie en sinusarres het met DEXISUN-toediening by sommige jong, gesonde vrywilligers met hoë vagale tonus gepaardgegaan, of met verskillende toedieningsroetes, insluitende vinnige intraveneuse of bolus toediening van DEXISUN. Bolus inspuitings van DEXISUN moenie gebruik word nie, ten einde ongewenste farmakologiese newe-effekte te minimaliseer.

Respirasie moet gemonitor word by pasiënte wat nie geïntubeer is nie weens die risiko van respiratoriese onderdrukking en in sommige gevalle apnee (sien afdeling 4.8).

Die tyd tot herstel nadat deksmedetomidien, soos in DEXISUN, gebruik is, is gerapporteer om ongeveer een uur te wees. Wanneer dit in ’n buitepasiënt-opset gebruik word, moet noukeurige waarneming vir ten minste een uur volgehou word (of langer, gegrond op die toestand van die pasiënt), met mediese toesig vir ten minste nog een uur verder om die pasiënt se veiligheid te verseker.

Omsigtigheid is nodig by pasiënte met voorafbestaande bradikardie-versteurings (d.i. gevorderde hartblok), of pasiënte met voorafbestaande erge ventrikulêre disfunksie (bv. uitwerpfraksie < 30 %) insluitende kongestiewe hartversaking en hartversaking waar simpatiese tonus kritiek is om hemodinamiese balans in stand te hou (sien afdeling 4.3).

Hipotensie, bradikardie en sinusarres:

Verlaagde bloeddruk en/of harttempo mag voorkom met die toediening van DEXISUN. Gegrond op kliniese ervaring met DEXISUN, indien mediese ingryping nodig is, mag behandeling insluit verlaging of staking van infusie van DEXISUN, versnelling van die tempo van intraveneuse vloeistoftoediening, oplig van onderste ekstremiteite en die gebruik van pressormedisynes. Omdat DEXISUN die potensiaal het om bradikardie wat geïnduseer word deur vagale stimuli te versterk, moet mediese praktisyns gereed wees om in te gryp. Die intraveneuse toediening van anticholinergiese middels moet oorweeg word om vagale tonus te modifiseer. In kliniese proewe was atropien en glikopirrolaat doeltreffend in die behandeling van die meeste episodes van DEXISUN-geïnduseerde bradikardie. Sommige pasiënte met beduidende kardiovaskulêre disfunksie het egter meer gevorderde resussitasiemaatreëls benodig.

DEXISUN verminder die aktiwiteit van simpatiese senuwees en gevolglik kan verwag word dat hierdie effekte meer uitgesproke sal wees by pasiënte met gedesensitiseerde outonomiese senuweestelselbeheer (d.i. bejaarde pasiënte, diabetes, chroniese hipertensie, erge hartsiekte).

Voorkoming van hipotensie en bradikardie moet die hemodinamiese stabiliteit van die pasiënt in ag neem en normovolemie moet verseker word voor toediening van DEXISUN. Pasiënte wat hipovolemies is, mag tydens DEXISUN-terapie hipotensief raak. Vloeistofaanvulling is dus voor en tydens toediening van DEXISUN nodig.

Bykomend, in situasies waar vasodilators of negatiewe chronotropiese middels toegedien word, kan gesamentlike toediening van DEXISUN ’n additiewe farmakodinamiese effek hê en moet met omsigtigheid en noukeurige titrasie toegedien word (sien afdeling 4.5).

Kliniese gevalle van bradikardie of hipotensie mag gepotensieer word wanneer DEXISUN gepaardgaande met propofol of midasolaam gebruik word. Verlaging van die dosis van propofol of midasolaam moet dus oorweeg word (sien afdeling 4.5).

Kortstondige hipertensie:

Kortstondige hipertensie is waargeneem, hoofsaaklik tydens die ladingsinfusie, geassosieer met die aanvanklike perifere vasokonstriktiewe effekte van DEXISUN en relatief hoër plasmakonsentrasies wat bereik word tydens die ladingsinfusie. Indien ingryping nodig is, kan oorweeg word om die tempo van die ladingsinfusie te verlaag. Ná die ladingsinfusie domineer die sentrale effekte van DEXISUN en die bloeddruk verlaag gewoonlik.

DEXISUN mag verminderde traansekresie veroorsaak. Smering van die pasiënt se oë kan oorweeg word om droogheid van die kornea te voorkom wanneer DEXISUN toegedien word.
DEXISUN moet nie as ’n bolus dosis gegee word nie en in die ISE word ’n ladingsdosis nie aanbeveel nie. Gebruikers moet dus gereed wees om ’n alternatiewe sedeermiddel te gebruik vir

akute beheer van agitasie of tydens prosedures, veral gedurende die eerste paar uur van behandeling. Tydens prosedurele sedasie mag ’n klein bolus van ’n ander sedeermiddel gebruik word indien ’n vinnige toename in sedasie vereis word.

Sommige pasiënte wat deksmedetomidien, soos in DEXISUN, ontvang kon wakker gemaak word en was helder toe hulle gestimuleer is. In die afwesigheid van ander kliniese tekens en simptome moet dit nie beskou word as ’n bewys van gebrek aan doelmatigheid nie.

Deksmedetomidien, soos in DEXISUN, veroorsaak gewoonlik nie diep sedasie nie en pasiënte kan maklik wakker gemaak word. DEXISUN is gevolglik nie geskik by pasiënte wat nie hierdie effekprofiel sal verduur nie, byvoorbeeld dié wat aaneenlopende diep sedasie vereis.

DEXISUN moenie as ’n middel vir induksie van algemene narkose vir intubasie gebruik word nie of om sedasie teweeg te bring tydens gebruik van spierverslappers nie.

DEXISUN het nie die antikonvulsantwerking wat party ander sedeermiddels het nie en sal dus nie onderliggende toeval-aktiwiteit onderdruk nie.

Sorg moet geneem word wanneer DEXISUN gekombineer word met ander verbindings met sedatiewe of kardiovaskulêre werking, aangesien additiewe effekte mag voorkom.

DEXISUN word nie aanbeveel vir pasiënt gekontroleerde sedasie nie. Daar is nie voldoende data beskikbaar nie.

Wanneer DEXISUN in ’n buitepasiënt-opset gebruik word, moet pasiënte normaalweg in die sorg van ’n geskikte ander persoon ontslaan word. Pasiënte moet geadviseer word om nie te bestuur of ander gevaarlike take uit te voer nie en om waar moontlik die gebruik van ander middels wat sedasie kan veroorsaak (bv. bensodiasepiene, opioïede, alkohol) vir ’n toepaslike tydperk te vermy op grond van effekte gerapporteer vir deksmedetomidien, die prosedure, gepaardgaande medikasies, die ouderdom en toestand van die pasiënt.

Pasiënte met belemmerde lewerfunksie

Sorg moet geneem word by erg belemmerde lewerfunksie aangesien oormatige dosering die risiko kan vergroot van ongunstige reaksies, oor-sedasie of verlengde effek weens verminderde opruiming van deksmedetomidien.

Pasiënte met neurologiese versteurings

Ondervinding met deksmedetomidien, soos in DEXISUN, by erge neurologiese versteurings soos hoofbesering en na neurochirurgie is beperk en dit moet in sulke gevalle met sorg gebruik word, veral indien diep sedasie nodig is. DEXISUN mag serebrale bloedvloei en intrakraniale druk verminder en dit moet in ag geneem word wanneer die keuse van terapie gemaak word.

Ander

Alfa-2-agoniste het minder dikwels gepaardgegaan met onttrekkingsreaksies toe dit meteens gestaak is nadat dit vir ’n lang tyd gebruik is. Hierdie moontlikheid moet in ag geneem word indien die pasiënt agitasie en hipertensie ontwikkel kort nadat DEXISUN gestaak is.

DEXISUN kan hipertermie induseer, wat weerstandig teen tradisionele metodes van afkoeling mag wees. Deksmedetomidien-behandeling moet gestaak word in die geval van volgehoue, onverklaarde koors en word nie aanbeveel vir gebruik by maligne hipertermie-sensitiewe pasiënte nie.

Bejaarde pasiënte:

Bejaarde volwassenes is meer geneig tot kardiovaskulêre ongunstige effekte, bv. hipotensie en bradikardie, en die dosis moet met sorg getitreer word om die verlangde effek te verkry. Noulettende monitering van die kardiovaskulêre stelsel (KVS) is nodig. Bejaarde pasiënte (ouer as 65 jaar) het dikwels laer dosisse DEXISUN nodig.

4.5 Interaksie met ander medisynes en ander vorms van interaksie

Sitochroom P450:

In vitro-studies het aangedui dat klinies relevante sitochroom P450-bemiddelde interaksies onwaarskynlik is.

Anestetika / Sedeermiddels / Hipnotika / Opioïede:

Gepaardgaande toediening met DEXISUN sal waarskynlik lei tot versterking van effekte van anestetika, sedeermiddels, hipnotika en opioïede. Spesifieke studies het hierdie versterking van effekte van sevofluraan, isofluraan, propofol, alfentaniel en midasolaam bevestig.

Geen farmakokinetiese interaksies tussen deksmedetomidien en isofluraan, propofol, alfentaniel en midasolaam is gedemonstreer nie. Wanneer dit gepaardgaande met DEXISUN toegedien word, mag dit egter nodig wees om die dosis van hierdie middels te verlaag weens die farmakodinamiese effekte.

Neuromuskulêre blokkers:

Geen klinies betekenisvolle toename in die grootte van neuromuskulêre blokkade en geen farmakokinetiese interaksies is waargeneem met toediening van DEXISUN en rokuronium nie.

Die moontlikheid van versterkte hipotensiewe en bradikardiale effekte moet in ag geneem word by pasiënte wat ander medisynes ontvang wat hierdie effekte veroorsaak, byvoorbeeld betablokkers, alhoewel addisionele effekte in ’n interaksiestudie met esmolol klein was.

4.6 Vrugbaarheid, swangerskap en borsvoeding

Dit is nie vasgestel of dit veilig is om tydens swangerskap en borsvoeding te gebruik nie.

Swangerskap

Daar is nie voldoende en goedgekontroleerde studies by swanger vrouens uitgevoer nie. Gebruik van DEXISUN word nie tydens swangerskap aanbeveel nie.

Kraam en verlossing

Die veiligheid van DEXISUN tydens kraam en verlossing is nie bestudeer nie en word gevolglik nie aanbeveel vir obstetrie nie, insluitende keisersneë.

Borsvoeding

Dit is nie bekend of DEXISUN in menslike melk uitgeskei word nie. Gebruik van DEXISUN word nie aanbeveel by vrouens wat borsvoed nie.

Vrugbaarheid

In die gerapporteerde rot-vrugbaarheidstudie, het deksmedetomidien geen effek op manlike of vroulike vrugbaarheid gehad nie. Geen data rakende vrugbaarheid by mense is beskikbaar nie.

4.7 Uitwerking op die vermoë om te bestuur en masjiene te gebruik:

Die pasiënt moenie bestuur, masjinerie hanteer of besluite neem wat wetlike implikasies het nie tot 24 uur nadat hul herstel het van ’n chirurgiese prosedure waar DEXISUN gebruik is.

4.8 Ongewenste effekte

a. Opsomming van die veiligheidsprofiel

Ongunstige reaksies wat die gereeldste met DEXISUN gerapporteer is, is hipotensie, hipertensie, bradikardie, naarheid, droë mond en hipoksie (sien afdeling 4.4).

Die volgende newe-effekte is tydens kliniese proewe en met waarneming na bemarking gerapporteer en word volgens stelsel-orgaan-klas met aangeduide frekwensies gelys:

b. Getabuleerde lys van ongunstige reaksies

Tabel 1: Ongunstige reaksies met ’n insidensie > 2 % – ISE-sedasie populasie

Stelsel-orgaan-klas	**Frekwensie**	**Newe-effek**
Bloed- en limfstelselversteurings	Dikwels	Anemie
Metabolisme- en voedingsversteurings	Dikwels Minder dikwels	Hipovolemie, hiperglukemie, hipokalsemie, asidose Hipoalbuminemie
Psigiatriese versteurings	Dikwels Minder dikwels	Agitasie Hallusinasies

Stelsel-orgaan-klas	**Frekwensie**	**Newe-effek**
Kardiale versteurings	Dikwels	Bradikardie, atriale fibrillasie, tagikardie, sinus tagikardie, ventrikulêre tagikardie, miokardiale iskemie of infarksie
	Minder dikwels	Atrioventrikulêre blok, verminderde kardiale uitset, hartstilstand
Vaskulêre versteurings	Dikwels	Hipotensie, hipertensie
Respiratoriese, torakale en mediastinale versteurings	Dikwels	Atelektase, pleurale effusie, hipoksie, pulmonêre edeem, gehyg, respiratoriese onderdrukking
	Minder dikwels	Dispnee, apnee
Gastroïntestinale versteurings	Dikwels	Naarheid, droë mond, braking
	Minder dikwels	Buikuitsetting
Nier- en urienwegversteurings	Minder dikwels	Poliurie
Algemene versteurings en toestande by die plek van toediening	Dikwels	Pireksie, hipertermie, kouekoors, perifere edeem, onttrekkingsindroom
	Minder dikwels	Geneesmiddel oneffektief, dors
Ondersoeke	Dikwels	Verminderde urienuitset
Besering, vergiftiging en komplikasies met prosedures	Dikwels	Bloeding na die prosedure

Tabel 2: Ongunstige reaksies met ’n insidensie > 2 % – Bewuste sedasie populasie

Die meerderheid van die ongunstige reaksies is geassesseer met geringe ernstigheidsgraad. Ongunstige effekte wat die gereeldste voorgekom het, was hipotensie, bradikardie en droë mond (sien afdeling 4.4).

Stelsel-orgaan-klas	**Frekwensie**	**Newe-effek**
Kardiale versteurings	Dikwels	Bradikardie, tagikardie
Vaskulêre versteurings	Dikwels	Hipotensie, hipertensie
Respiratoriese, torakale en mediastinale versteurings	Dikwels	Respiratoriese onderdrukking, hipoksie, bradipnee
Gastroïntestinale versteurings	Dikwels	Naarheid, droë mond

Ongunstige reaksies na-bemarking:

Stelsel-orgaan-klas	**Frekwensie**	**Newe-effek**
Infeksies en infestasies	Minder dikwels	Infeksie, swaminfeksie, sepsis
Bloed- en limfstelselversteurings	Minder dikwels	Anemie, leukositose, koagulasieversteurings, dissemineerde intravaskulêre stolling, hematoom, abnormale plaatjies, verlaagde protrombien, trombositopenie
Immuunstelselversteurings	Minder dikwels	Allergiese reaksies
Metabolisme- en voedingsversteurings	Minder dikwels	Hiperglukemie, hipoglukemie, asidose, melksuurasidose, respiratoriese asidose, diabetes mellitus, hipokalemie, hiperkalemie, hipoproteïnemie, verhoogde alkaliese fosfatase, verhoogde nieproteïenstikstof (NPN), dors

Psigiatriese versteurings	Minder dikwels	Agitasie, angstigheid, verwardheid, delirium, depressie, hallusinasies, illusies, senuweeagtigheid
Senuweestelselversteurings	Minder dikwels	Konvulsies, duiseligheid, hoofpyn, neuralgie, neuritis, neuropatie, parestesie, paralise, parese, spraaksteuring, sinkopee
Oogversteurings	Minder dikwels	Diplopie, fotopsie, abnormale visie
Kardiale versteurings	Minder dikwels	Bradikardie, miokardiale iskemie, miokardiale infarksie, tagikardie, angina pectoris, disritmie, atriale disritmie, atriale fibrillasie, AV-blok, bondeltakblok, kardiale arres, ekstrasistole, hartblok, hipoksie, supraventrikulêre tagikardie, T-golf-inversie, ventrikulêre disritmie, ventrikulêre tagikardie
Vaskulêre versteurings	Minder dikwels	Hipotensie, hipertensie, bloeding, serebrale bloeding, perifere iskemie, vaskulêre versteuring, vasodilatasie, sirkulatoriese versaking, sianose, abnormale EKG, hartsteuring, verergerde hipertensie, pulmonêre hipertensie, posturale hipotensie
Respiratoriese, torakale en mediastinale versteurings	Minder dikwels	Volwasse respiratoriesenoodsindroom, apnee, brongiale obstruksie, brongospasma, hoes, dispnee, emfiseem, hemoptise, hiperkapnie, faringitis, pleuritis, pneumonie, pneumotoraks, pulmonêre kongestie, pulmonêre edeem, respiratoriese onderdrukking, respiratoriese

		versteuring, respiratoriese ontoereikendheid, verhoogde speekselafskeiding, stridor
Gastroïntestinale versteurings	Minder dikwels	Buikpyn, diarree, eruktasie, mukosale ulserasie, naarheid, braking
Hepatobiliêre versteurings	Minder dikwels	Verhoogde albumien tot globulien (AG) verhouding, verhoogde gamma-glutamieltranspepsidase (GGT), abnormale lewerfunksie, hiperbilirubinemie, verhoogde aspartaattransaminase (AST), verhoogde alanientransaminase (ALT), geelsug
Vel- en subkutaneweefselversteurings	Minder dikwels	Eritemateuse uitslag, verhoogde sweetafskeiding
Muskuloskeletale en bindweefselversteurings	Minder dikwels	Spierswakheid
Nier- en urienwegversteurings	Minder dikwels	Verhoogde bloedureum, oligurie, hematurie, akute nierversaking, abnormale nierfunksie, urienterughouding
Algemene versteurings en toestande by die plek van toediening	Minder dikwels	Askites, koors, hiperpireksie, hipovolemie, ligte anestesie, edeem, perifere edeem, pyn, onttrekkingsindroom, rigors.

c. Beskrywing van uitgesoekte ongunstige reaksies

Onttrekking

ISE-sedasie

Alhoewel dit nie spesifiek bestudeer is nie, mag onttrekkingsimptome soortgelyk aan die

gerapporteer vir ’n ander alfa-2-adrenergiese middel (klonidien) voorkom wanneer DEXISUN vir meer as 24 uur toegedien en skielik gestop word.

Hierdie simptome sluit in senuweeagtigheid, agitasie en hoofpyn gepaardgaande met of gevolg deur ’n vinnige styging in bloeddruk en verhoogde plasmakonsentrasie van katesjolamiene.

Bewustelike sedasie

Onttrekkingsimptome is nie gesien na staking van korttermyn-infusies van deksmedetomidien, soos in DEXISUN, nie (< 6 uur).

Rapportering van vermoedelike newe-effekte:

Dit is belangrik om vermoedelike newe-effekte wat gesien word nadat die medisyne geregistreer is, te rapporteer. Dit help met volgehoue monitering van die voordeel/risiko-balans van die medisyne. Gesondheidsorgverskaffers moet asseblief enige vermoedelike newe-effekte aan SAHPRA rapporteer via die vorm om ongunstige geneesmiddelreaksies te rapporteer, wat aanlyn by SAHPRA se publikasies beskikbaar is:

https://www.sahpra.org.za/Publications/index/8.

4.9 Oordosering

Eerstegraadse AV-blok en tweedegraadse hartblok mag voorkom.

Bradikardie, met of sonder hipotensie, en kardiale arres mag voorkom.

Omdat DEXISUN die potensiaal het om bradikardie wat deur vagale stimuli geïnduseer word te vererger, moet mediese praktisyns gereed wees om in te tree. In kliniese proewe was atropien en glikopirrolaat doeltreffend in die behandeling van DEXISUN-geïnduseerde bradikardie (sien afdeling 4.8).

5 FARMAKOLOGIESE EIENSKAPPE

5.1 Farmakodinamiese eienskappe

A 2.9 Ander analgetika. Farmakoterapeutiese groep: Psigoleptiese middels, ander hipnotika en sedeermiddels, ATC-kode: N05CM18.

Deksmedetomidien is ’n alfa-2-adrenoreseptoragonis.

Die sedatiewe effekte word hoofsaaklik bemiddel deur post-sinaptiese alfa-2-adrenoreseptors, wat op hul beurt inwerk op inhibitoriese pertussistoksien-sensitiewe G proteïen, om sodoende geleidingsvermoë deur die kaliumkanale te verhoog. Die setel van die sedatiewe effekte van deksmedetomidien word aan die locus coeruleus toegeskryf. Die analgetiese werking word bemiddel deur ’n soortgelyke werkingsmeganisme op die vlak van die brein en ruggraat.

Alfa-2-selektiwiteit word gesien na lae en medium dosisse wat stadig gegee word. Alfa-2- en alfa-1-aktiwiteit word na vinnige toediening gesien. Deksmedetomidien het geen affiniteit vir beta-adrenergiese, muskariniese, dopaminergiese of serotonienreseptors nie.

5.2 Farmakokinetiese eienskappe

Deksmedetomidien vertoon die volgende farmakokinetiese kenmerke na toediening: vinnige verspreidingsfase met ’n verspreidingshalfleeftyd ($t_{1/2\alpha}$) van ongeveer 6 minute; terminale eliminasiehalfleeftyd ($t_{1/2}$) van ongeveer twee uur; gelykvlak volume van verspreiding (V_{ss}) van ongeveer 118 liter. Die geraamde waarde van opruiming is ongeveer 39 L/h. Die gemiddelde liggaamsgewig geassosieer met hierdie geraamde opruiming was 72 kg.

Deksmedetomidien-proteïenbinding is geassesseer in die plasma van normale gesonde manlike en vroulike menslike studiedeelnemers: die gemiddelde binding was 94 % en was konstant oor die verskillende konsentrasies wat getoets is. Proteïenbinding was soortgelyk by mans en vrouens. Die fraksie van deksmedetomidien wat aan plasmaproteïene gebind is, was statisties betekenisvol minder by studiedeelnemers met hepatiese belemmering in vergelyking met gesonde studiedeelnemers.

Dit is onwaarskynlik dat deksmedetomidien klinies beduidende veranderings in die plasmaproteïenbinding van fentaniel, ketorolak, teofillien, digoksien, lidokaïen, fenitoïen, warfarien, ibuprofeen en propranolol sal veroorsaak.

Deksmedetomidien word feitlik uitsluitlik deur metabolisme geëlimineer, met 95 % van 'n radio-gemerkte dosis wat in die urine en 4 % in die feses uitgeskei word. Ongeveer 34 % van die uitgeskeide metaboliete is produkte van *N*-glukuronidasie.

Hepatiese belemmering

By studiedeelnemers met wisselende grade van hepatiese belemmering (Child-Pugh Klas A, B of C), was die opruimingswaardes laer as by gesonde studiedeelnemers. Die gemiddelde opruimingswaardes vir studiedeelnemers met geringe, matige, en hewige hepatiese belemmering was 74 %, 64 % en 53 %, onderskeidelik, van dit wat by normale gesonde studiedeelnemers gerapporteer is. Gemiddelde opruiming vir die vry medisyne was 59 %, 51 %, en 32 %, onderskeidelik, van dit wat by normale gesonde studiedeelnemers gerapporteer is.

Alhoewel deksmedetomidien tot effek gedoseer word, mag dit nodig wees om verlaging van die dosis te oorweeg afhangende van die graad van hepatiese belemmering (sien afdeling 4.2).

Renale belemmering

Dit is nie gerapporteer dat die farmakokinetika van deksmedetomidien (C_{maks}, T_{maks}, AOK, $t_{½}$, CL en V_{ss}) verskillend was by studiedeelnemers met hewige renale belemmering (Cr Cl: < 30 ml/min) in vergelyking met gesonde studiedeelnemers nie.

Geslag

Geen verskil in die farmakokinetika van deksmedetomidien weens geslag is gerapporteer nie.

Bejaarde pasiënte

Die farmakokinetiese profiel van deksmedetomidien is nie deur ouderdom gewysig nie. Bejaarde volwassenes is meer sensitief vir die effekte van deksmedetomidien. In kliniese proewe was daar ’n hoë voorkoms van bradikardie en hipotensie by bejaarde pasiënte (> 65 jaar oud).

Pediatriese populasie

Die farmakokinetiese profiel van deksmedetomidien is nie bestudeer by studiedeelnemers jonger as 18 jaar nie.

5.3 Prekliniese veiligheidsdata

Gerapporteerde niekliniese data toon geen spesifieke gevaar vir mense gegrond op konvensionele studies van veiligheidsfarmakologie, toksisiteit met enkele en herhaalde dosisse, en genotoksisiteit nie.

In die gerapporteerde studies van reproduktiewe toksisiteit, het deksmedetomidien geen uitwerking op manlike of vroulike vrugbaarheid by die rot gehad nie, en geen teratogeniese effekte is by die rot of konyn gerapporteer nie. In die konynstudie het intraveneuse toediening van die maksimum dosis, 96 µg/kg/dag, blootstellings geproduseer wat soortgelyk is aan die wat klinies gerapporteer is. By die rot het subkutane toediening teen die maksimum dosis, 200 µg/kg/dag, ’n toename in embriofetale sterfte veroorsaak en die fetale liggaamsgewig was verlaag. Hierdie effekte het met duidelike maternale toksisiteit gepaardgegaan. Verlaagde fetale liggaamsgewig is ook by die rotvrugbaarheidstudie teen ’n dosis van 18 µg/kg/dag waargeneem en het gepaardgegaan met vertraagde ossifikasie teen ’n dosis van 54 µg/kg/dag. Die gerapporteerde blootstellingsvlakke by die rot is onder die kliniese blootstellingsreikwydte.

6 FARMASEUTIESE BESONDERHEDE

6.1 Lys van hulpstowwe

- Natriumchloried
- Water vir inspuitings.

6.2 Onverenigbaarhede

DEXISUN moet nie met ander medisinale produkte of diluente gemeng word nie, buiten die wat genoem word by afdeling 6.6.

6.3 Rakleeftyd

24 maande.

6.4 Spesiale voorsorgmaatreëls vir bewaring

Bewaar by of onder 25 °C in die oorspronklike houer.

Moenie in die yskas bewaar nie.

Sodra dit verdun is, moet die verdunde oplossing onmiddellik gebruik word. Indien dit nie onmiddellik gebruik word nie, mag die verdunde oplossing tydens die 24 uur “in-gebruik” tydperk teen 2 – 8 °C bewaar word. Enige ongebruikte verdunde oplossing moet na 24 uur weggedoen word.

Hou buite bereik van kinders.

6.5 Aard en inhoud van die houer

DEXISUN is verpak in 'n 2 ml buisvormige, USP tipe 1 flintglasflessie, met 'n 13 mm Teflon-bedekte grys rubberprop en 'n 13 mm pienk aluminium afdraaiseël, in 'n buitekarton. Elke karton bevat 1 of 5 flessies.

6.6 Spesiale voorsorgmaatreëls vir wegdoening en ander hantering

Voorbereiding van die oplossing:

Streng aseptiese tegniek moet altyd toegepas word wanneer DEXISUN-infusie hanteer word.

Voorbereiding van die infusie-oplossings is dieselfde vir die ladingsdosis en vir die instandhoudingsdosis.

Om die infusie voor te berei, onttrek 2 ml DEXISUN-konsentraat en voeg by 48 ml 0,9 % natriumchloriedoplossing vir ’n totaal van 50 ml. Skud liggies om goed te meng.

Na verdunning moet DEXISUN onmiddellik gebruik word en moet na 24 uur weggedoen word.

Toediening saam met ander vloeistowwe:

DEXISUN is verenigbaar met die volgende intraveneuse vloeistowwe en medisynes:

Gelakteerde Ringer se oplossing, 5 % Dekstrose in Water, 0,9 % Natriumchloried in Water, 20 % Mannitol, natriumtiopentaal, etomidaat, verkuroniumbromied, suksinielcholien, atrakuriumbesilaat, mivakuriumchloried, glikopirrolaatbromied, fenielefrien HCL, atropiensulfaat, midasolaam, morfiensulfaat, fentanielsitraat en ’n plasma-vervanger (d.i. Haemacel).

Verenigbaarheidstudies het getoon dat daar ’n potensiaal is vir adsorpsie van DEXISUN aan party soorte natuurlike rubber. Alhoewel DEXISUN tot effek gedoseer word, is dit raadsaam om komponente met pakstukke van sintetiese of bedekte natuurlike rubber te gebruik.

DEXISUN moenie met ander medisinale produkte of diluente vermeng word nie, buiten die wat hier bo genoem word.

7 HOUER VAN DIE REGISTRASIESERTIFIKAAT

Ranbaxy Pharmaceuticals (Edms.) Bpk.

Lautreweg 14

Stormill, Uitbr.1

Roodepoort 1724

Suid-Afrika

8 REGISTRASIENOMMER

54/2.9/0218

9 DATUM VAN EERSTE MAGTIGING

21 June 2022

10 DATUM VAN HERSIENING VAN DIE TEKS