1.3.1.1.1 APPROVED PROFESSIONAL INFORMATION

PREXUJECT 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

PREXUJECT™ 200 µg/50 ml RTU, solution for infusion

PREXUJECT™ 400 µg/100 ml RTU, solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of ready-to-use solution contains dexmedetomidine hydrochloride equivalent to 4 micrograms dexmedetomidine.

Each 50 ml vial contains 200 micrograms of dexmedetomidine.

Each 100 ml vial contains 400 micrograms of dexmedetomidine.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ready-to-use solution for intravenous infusion.

The solution is clear and colourless, with pH 4,5 – 7,0.

Osmolality: 260 - 320 mOsmol/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PREXUJECT is an alpha$_2$ adrenoreceptor agonist sedative with analgesic properties indicated for:

Intensive care unit sedation

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

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

- Minor surgical procedures under local anaesthesia
- Fibreoptic intubation.

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

4.2 Posology and method of administration

NOTE: PREXUJECT 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 PREXUJECT.

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

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

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

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

Posology

Adults

Intensive Care Unit (ICU) sedation

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

Initiation

For adult patients, it is recommended to initiate PREXUJECT 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)

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

Initiation:

For adult patients, PREXUJECT 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 PREXUJECT 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 PREXUJECT 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 PREXUJECT 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 [PRODUCT NAME], dosage reductions may need to be considered.

Paediatric population

Safety and efficacy of [PRODUCT NAME] 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.

[PRODUCT NAME] must be administered only as an intravenous infusion using a controlled infusion device.

[PRODUCT NAME] should not be diluted before use: it is supplied ready-to-use. [PRODUCT NAME] should not be mixed with other medicines.

4.3 Contraindications

- Hypersensitivity to dexmedetomidine or to any of the excipients of [PRODUCT NAME] listed in section 6.1
- Patients with sepsis
- Unstable trauma patients
- Hypovolaemic patients
- Heart block
- Uncontrolled cardiac failure
- Imminent hepatic failure

4.4 Special warnings and precautions for use

[PRODUCT NAME] 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 [PRODUCT NAME] in the ICU setting.

Safety and efficacy of PREXUJECT in non-surgical intensive care patients have not been established.

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

Potential risk of mortality in ICU patients ≤ 65 years of age

There is an increased risk of mortality in intensive care unit (ICU) patients 65 years of age and under that is associated with the use of dexmedetomidine. Continuous monitoring is essential.

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 PREXUJECT.

Special precautions

NOTE: PREXUJECT 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 PREXUJECT.

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).

Risk of diabetes insipidus and polyuria

There is a possible causal relationship between diabetes insipidus, polyuria and the use of dexmedetomidine.

Hypotension, bradycardia and sinus arrest

Clinical events of bradycardia and sinus arrest have been associated with PREXUJECT administration in young, healthy volunteers with high vagal tone, or with different routes of

administration including rapid intravenous or bolus administration of PREXUJECT (see boxed warning above).

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

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

Additionally, in situations where other vasodilators or negative chronotropic medicines are administered, co-administration of PREXUJECT 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 PREXUJECT 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 PREXUJECT 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 PREXUJECT dominate and the blood pressure usually decreases.

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

PREXUJECT contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

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 PREXUJECT 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 PREXUJECT and isoflurane, propofol, alfentanil, and midazolam were demonstrated. However, due to pharmacodynamic effects, when co-administered with PREXUJECT 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 PREXUJECT 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

Women of childbearing age

Safety in pregnancy and lactation has not been established.

Pregnancy

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

Labour and delivery:

The safety of dexmedetomidine as in PREXUJECT 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 PREXUJECT is excreted in human milk. The use of PREXUJECT is not recommended in lactating women.

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 PREXUJECT was used.

4.8 Undesirable effects

Summary of the safety profile

Sedation of adult ICU (Intensive Care Unit) patients

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

Procedural/awake sedation

The most frequently reported adverse reactions with dexmedetomidine in procedural sedation are:

- Hypotension
- Respiratory depression
- Bradycardia
- Dry mouth (see section 4.4)

Tabulated list of adverse reactions

The adverse reactions listed in Table 1 have been obtained from pooled data of patients in intensive care.

Table 1. Adverse reactions

System organ class/ Frequency	**Adverse event**
Infections and infestations	
Frequency unknown:	Infection, fungal infection, sepsis
Blood and lymphatic system disorders	
Frequency unknown:	Coagulation disorders, disseminated intravascular coagulation, haematoma, abnormal platelets, decreased prothrombin, thrombocytopenia, anaemia, leukocytosis
Immune system disorders	
Frequency unknown:	Allergic reaction
Endocrine disorders	
Frequency unknown:	Diabetes insipidus
Metabolism and nutrition disorders	
Frequent:	Hyperglycaemia, hypoglycaemia
Less frequent:	Metabolic acidosis, hypoalbuminaemia
Frequency unknown:	Acidosis, lactic acidosis, respiratory acidosis, diabetes mellitus, hyperglycaemia, hypoglycaemia, hypokalaemia, hyperkalaemia, hypoproteinaemia, increased alkaline phosphatase, increased non-protein nitrogen (NPN)
Psychiatric disorders	
Frequent:	Agitation
Less frequent:	Hallucination
Frequency unknown:	Anxiety, confusion, delirium, depression, nervousness

Nervous system disorders

Frequency unknown:	Convulsion, dizziness, headache, neuralgia, neuritis, neuropathy, paraesthesia, paralysis, paresis, speech disorder

Cardiac disorders

Frequent:	Bradycardia[1, 2], myocardial ischaemia or infarction, tachycardia
Less frequent:	Atrioventricular block[1], cardiac output decreased, cardiac arrest[1]
Frequency unknown:	Abnormal ECG, heart disorder, myocardial infarction, dysrhythmia, atrial dysrhythmia, atrial fibrillation, bundle branch block, extrasystoles, heart block, hypoxia, supraventricular tachycardia, T wave inversion, ventricular dysrhythmia, ventricular tachycardia, angina pectoris, myocardial infarction, myocardial ischaemia

Vascular disorders

Frequent:	Hypotension[1, 2], hypertension[1, 2]
Frequency unknown:	Blood pressure fluctuation, circulatory failure, cyanosis, aggravated hypertension, pulmonary hypertension, postural hypotension, haemorrhage, cerebral haemorrhage, peripheral ischaemia, vascular disorder, vasodilation

Respiratory, thoracic and mediastinal disorders

Frequent:	Respiratory depression[2, 3]
Less frequent:	Dyspnoea, apnoea
Frequency unknown	Adult respiratory distress syndrome, bronchial obstruction, bronchospasm, coughing, emphysema, haemoptysis, hypercapnia, hypoventilation, hypoxia, pharyngitis, pleurisy, pneumonia, pneumothorax, pulmonary congestion, pulmonary

	oedema, respiratory disorder, respiratory insufficiency, increased sputum, stridor
Gastrointestinal disorders	
Frequent:	Nausea[2], vomiting, dry mouth[2]
Less frequent:	Abdominal distension
Frequency unknown:	Abdominal pain, diarrhoea, eructation, mucosal ulceration
Hepatobiliary 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:	Erythematous rash, increased sweating
Musculoskeletal and connective tissue disorders	
Frequency unknown:	Muscle weakness
Renal disorders	
Frequency unknown	Increased blood urea, oliguria, haematuria, acute renal failure, abnormal renal function, urinary retention
General disorders and administration site conditions	
Frequent:	Withdrawal syndrome, hyperthermia
Less frequent:	Medicine ineffective, thirst
Frequency unknown:	Allergic reaction, ascites, fever, hyperpyrexia, hypovolaemia, light anaesthesia, oedema, peripheral oedema, pain, syncope, rigors

1 See section on Description of selected adverse reactions

2 Adverse reaction observed also in procedural sedation studies

3 Incidence ‘Frequent’ in ICU sedation studies

Description of selected adverse reactions

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

Bradycardia

In patients treated with dexmedetomidine, bradycardia has led to sinus arrest or pause (see section 4.4). The symptoms responded to leg raising and anticholinergics such as atropine or glycopyrrolate. In some 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

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.

Withdrawal

ICU sedation

Withdrawal symptoms similar to those reported for another alpha2 adrenergic medicine (clonidine) may result when PREXUJECT 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 (< 6 hours).

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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 PREXUJECT has the potential to augment bradycardia induced by vagal stimuli, clinicians should be prepared to intervene. Atropine and glycopyrrolate proved to be effective in the treatment of dexmedetomidine-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 a selective alpha$_{2-}$ adrenoreceptor agonist.

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

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

5.2 Pharmacokinetic properties

Distribution

Following administration, dexmedetomidine exhibits the following pharmacokinetic characteristics: rapid distribution phase with a distribution half-life ($t_{½\,\alpha}$) 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. Mean clearances for free medicine were less than 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, t½, 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. In clinical trials, there was a higher incidence of bradycardia and hypotension in elderly patients (> 65 years of age).

Paediatric population

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

48 months

6.4 Special precautions for storage

PREXUJECT should be stored in the original container at room temperature (at or below 30 °C

6.5 Nature and contents of container

PREXUJECT is packed in Type I transparent glass vials with 50 ml and 100 ml capacity, closed by coated chlorobutyl rubber stoppers and sealed by aluminium caps.

Each 50 ml vial contains 200 micrograms of dexmedetomidine in 50 ml solution.

Each 100 ml vial contains 400 micrograms of dexmedetomidine in 100 ml solution.

Pack sizes:

1, 5, 10 or 25 vials of 50 ml packed in carton boxes.

1, 5, 10 or 25 vials of 100 ml packed in carton boxes

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Vials are intended for single patient use only.

A controlled infusion device should be used to administer PREXUJECT ready-for-use solution for infusion.

Only a clear, free of particulate matter and colourless solution should be used. Parenteral products should be inspected visually for particulate matter and discolouration prior to administration.

The solution should be used immediately after opening.

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

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Abex Pharmaceutica (Pty) Ltd

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8. REGISTRATION NUMBER(S)

PREXUJECT™ 200 µg/50 ml RTU: 59/2.9/0098.096

PREXUJECT™ 400 µg/100 ml RTU: 59/2.9/0099.097

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 June 2026

10 DATE OF REVISION OF THE TEXT

Not applicable