PROFESSIONAL INFORMATION FOR PRECIA

PRECIA should not be used outside an intensive care unit (ICU) setting or surgical operating theatres. There should be continuous monitoring of vital parameters.

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

PRECIA solution for intravenous infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 mL vial contains dexmedetomidine hydrochloride equivalent to 200 µg dexmedetomidine.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

A clear, colourless, solution, pH 4.5 – 7.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PRECIA is an alpha$_2$ adrenoreceptor agonist sedative with analgesic properties

indicated for:

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

- Monitored Anaesthesia Care (MAC)/Conscious sedation in a theatre or intensive

care setting for:

- Minor surgical procedures under local anaesthesia.
- Fibreoptic intubation.

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

4.2 Posology and method of administration

PRECIA should be administered only by health professionals skilled in the management of patients in the intensive care setting. Continuous monitoring of vital signs, in particular blood pressure, heart rate and oxygen saturation is mandatory during infusion of **PRECIA**.

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

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

PRECIA had 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 **PRECIA**. Patients receiving **PRECIA** 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. **PRECIA** 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:

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

Initiation:

For adult patients, it is recommended to initiate **PRECIA** with a loading dose of 1,0 µg/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 µg/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 µg/kg/hr have been used in clinical studies.

A dose reduction for both the loading and maintenance infusions should be considered in patients with impaired hepatic or renal function and in patients over 65 years of age (see section 4.3 and 4.4).

Conscious Sedation:

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

Initiation:

For adult patients, **PRECIA** is generally initiated with a loading infusion of 1 (one) µg/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 µg/kg over 10 minutes may be suitable.

Maintenance of conscious sedation:

MAC – Following the load, maintenance dosing of **PRECIA** should generally be initiated at 0,6 µg/kg/h and titrated to achieve desired clinical effect with doses ranging from 0,2 to1 µg/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 µg/kg/hr should be used.

Dosage adjustments:

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

Impaired hepatic function:

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

Impaired renal function:

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

Elderly:

Since the elderly are more sensitive to the effects of **PRECIA** dosage reductions may need to be considered (see section 4.4).

Paediatric population:

Safety and efficacy of **PRECIA** has not been studied in children and adolescents and is

therefore not recommended for patients under 18 years of age.

Method of administration:

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

A controlled infusion device should be used to administer **PRECIA**.

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

Vials are intended for single patient use only.

For instructions on dilution of **PRECIA** before administration, see section 6.6.

4.3 Contraindications

PRECIA is contraindicated in:

- Patients with a known hypersensitivity to dexmedetomidine,
- Patients with sepsis,
- Unstable trauma patients,
- Hypovolaemic patients,
- Heart block,
- Uncontrolled cardiac failure,
- Imminent hepatic failure,
- Acute cerebrovascular conditions.

4.4 Special warnings and precautions for use

Monitoring:

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

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

established.

The use in other environments is not recommended. All patients should have continuous cardiac monitoring during **PRECIA** infusion. Respiration should be monitored in non-intubated patients due to the risk of respiratory depression and in some case apnoea (see section 4.8).

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

The time to recovery after the use of **PRECIA** was reported to be approximately one hour. When used in an outpatient setting, close monitoring should continue for at least one hour (or longer based on the patient condition), with medical supervision continued for at least one further hour to ensure the safety of the patient.

General precautions:

Some patients receiving **PRECIA** 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.

PRECIA normally does not cause deep sedation and patients may be easily roused. **PRECIA** is therefore not suitable in patients who will not tolerate this profile of effects, for example those requiring continuous deep sedation.

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

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

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

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

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 dexmedetomidine, the procedure, concomitant medications, the age and the condition of the patient.

Cardiovascular effects, hypotension, bradycardia and sinus arrest, transient hypertension:

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

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 **PRECIA** 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).

Decreased blood pressure and/or heart rate may occur with the administration of **PRECIA** through central sympatholysis but at higher concentrations causes peripheral vasoconstriction leading to hypertension. If medical intervention is required, treatment may include decreasing or stopping the infusion of **PRECIA**, increasing the rate of intravenous fluid administration, elevation of the lower extremities and use of pressor medicines. Because **PRECIA** has the potential to augment bradycardia induced by vagal stimuli, clinicians should be prepared to intervene. The intravenous administration of anti-cholinergic medicines should be considered to modify vagal tone. Atropine and glycopyrrolate were effective in the treatment of most episodes of **PRECIA**-induced bradycardia. However, in some patients with significant cardiovascular dysfunction, more advanced resuscitative measures were required. **PRECIA** is therefore not suitable in patients with severe cardiovascular instability.

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

The hypotensive effects of dexmedetomidine may be of greater significance in those patients with pre-existing hypotension (especially if not responsive to vasopressors), hypovolaemia, chronic hypotension or reduced functional reserve such as patients with severe ventricular dysfunction and the elderly and special care is warranted in these cases. Hypotension does not normally require specific treatment but, where needed, users should be ready to intervene with dose reduction, fluids and/or vasoconstrictors. 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 **PRECIA**. Patients who are hypovolaemic may become hypotensive under **PRECIA** therapy. Therefore, fluid supplementation should be administered

prior to and during the administration of **PRECIA**.

Additionally, in situations where other vasodilators or negative chronotropic medicines are administered, co-administration of **PRECIA** 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 **PRECIA** 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 **PRECIA** together with spinal or epidural anaesthesia due to possible increased risk of hypotension or bradycardia.

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

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. **PRECIA** is contraindicated in patients with acute cerebrovascular conditions (see section 4.3).

Elderly:

The elderly are more prone to cardiovascular adverse events e.g. hypotension and bradycardia and the dose must be carefully titrated to obtain the desired effect. Close

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

Patients with hepatic impairment:

Care should be taken in severe hepatic impairment as excessive dosing may increase the risk of adverse reactions, over-sedation or prolonged effect as a result of reduced dexmedetomidine clearance.

Patients with neurological disorders:

Experience of dexmedetomidine in severe neurological disorders such as head injury and after neurosurgery is limited and it should be used with caution here, especially if deep sedation is required. Dexmedetomidine may reduce cerebral blood flow and intracranial pressure and this should be considered when selecting therapy.

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

Other:

Withdrawal symptoms:

ICU sedation:

Withdrawal symptoms similar to those reported for another alpha$_2$ adrenergic medicine (clonidine) may result when **PRECIA** 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 **PRECIA** (< 6 hours).

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

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

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

4.5 Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

Cytochrome P450:

Inhibition of CYP enzymes including CYP2B6 by dexmedetomidine has been studied in human liver microsome incubations. *In vivo* 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.

Anaesthetics/sedatives/hypnotics/opioids:

Co-administration of **PRECIA** is likely to lead to an enhancement of effects with anaesthetics, sedatives, hypnotics and opioids including sedative, anaesthetic and cardiorespiratory effects. 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 **PRECIA**, 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 **PRECIA** and rocuronium administration.

Other:

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 **PRECIA** is not recommended in pregnancy.

Studies in animals have shown reproductive toxicity. **PRECIA** should not be used during pregnancy unless the clinical condition of the woman requires treatment with dexmedetomidine.

Labour and delivery:

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

Breastfeeding:

Dexmedetomidine is excreted in human milk, however levels will be below the limit of detection by 24 hours following treatment discontinuation. A risk to infants cannot be excluded.

The use of **PRECIA** 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 surgical procedure in which **PRECIA** was used.

4.8 Undesirable effects

Summary of the safety profile:

ICU (Intensive Care Unit) sedation:

The most frequently observed treatment-emergent adverse events include hypotension, hypertension, bradycardia, nausea, dry mouth and hypoxia (see section 4.8).

Conscious Sedation:

The majority of the adverse events were assessed as mild in severity. The most frequent adverse events were hypotension, bradycardia, dry mouth and respiratory depression.

Tabulated summary of adverse reactions:

System Organ Class	Frequency	Side effects

Infections and infestations	Frequency unknown	Infection, fungal infection, sepsis
Blood and the lymphatic system disorders	Frequent Frequency unknown	Anaemia Coagulation disorders, disseminated intravascular coagulation, haematoma, abnormal platelets, decreased prothrombin, thrombocytopenia, leucocytosis
Immune system disorders	Frequency unknown	Allergic reaction
Metabolism and nutrition disorders	Frequent Less frequent Frequency unknown	Hypovolaemia, hyperglycaemia Hypocalcaemia, metabolic acidosis, hypoalbuminaemia Lactic acidosis, respiratory acidosis, diabetes mellitus, hypokalaemia, hyperkalaemia, hypoproteinaemia, increased alkaline phosphatase, increased non-protein nitrogen (NPN), hypovolaemia
Psychiatric disorders	Frequent Frequency unknown	Agitation Anxiety, confusion, delirium, depression, hallucination, illusion, nervousness

Nervous system disorders	Frequency unknown	Convulsions, dizziness, headache, neuralgia, neuritis, neuropathy, paraesthesia, paralysis, paresis, speech disorder
Eye disorders	Frequency unknown	Diplopia, photopsia, abnormal vision
Cardiac disorders	Frequent Less frequent Frequency unknown	Bradycardia, atrial fibrillation, tachycardia Sinus tachycardia, ventricular tachycardia Abnormal electrocardiogram (ECG), heart disorder, myocardial infarction, dysrhythmia, atrial dysrhythmia, atrioventricular (AV) block, bundle branch block, cardiac arrest, extrasystoles, heart block, supraventricular tachycardia, T wave inversion, ventricular dysrhythmia, angina pectoris, myocardial ischaemia
Vascular disorders	Frequent Frequency unknown	Hypotension, hypertension Blood pressure fluctuation, circulatory failure, cyanosis, aggravated hypertension,

		pulmonary hypertension, postural hypotension, haemorrhage, cerebral haemorrhage, peripheral ischaemia, vascular disorder, vasodilatation
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent Frequency unknown	Atelectasis, pleural effusion, hypoxia, respiratory depression Pulmonary oedema, wheezing Apnoea, bronchial obstruction, bronchospasm, coughing, dyspnoea, emphysema, haemoptysis, hypercapnia, hypoventilation, pharyngitis, pleurisy, pneumonia, pneumothorax, pulmonary congestion, respiratory disorder, respiratory insufficiency, increased sputum, stridor
Gastrointestinal disorders	Frequent Frequency unknown	Nausea, dry mouth, vomiting Abdominal pain, diarrhoea, eructation, mucosal ulceration
Hepato-biliary disorders	Frequency unknown	Increased albumin/globulin (AG) ratio, increased: gamma glutamyl transferase (GGT), alanine transaminase, aspartate

		aminotransferase, aspartate transaminase (AST), alanine transaminase (ALT), abnormal hepatic function, hyperbilirubinaemia, jaundice
Skin and subcutaneous tissue disorders	Frequency unknown	Oedema, erythematous rash, increased sweating
Musculoskeletal, and connective tissue disorders	Frequency unknown	Muscle weakness
Renal and urinary disorders	Less frequent Frequency unknown	Decreased urine output Increased blood urea, oliguria, haematuria, acute renal failure, abnormal renal function, urinary retention, polyuria
General disorders and administration site conditions	Frequent Less frequent Frequency unknown	Pyrexia, hyperthermia, chills Peripheral oedema, drug ineffective, thirst Rigors, light anaesthesia, withdrawal syndrome, hyperpyrexia, pain, syncope, ascites
Injury, poisoning and procedural complications	Frequent	Post-procedural haemorrhage

Description of selected adverse reactions

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.

Reporting of suspected adverse reactions:

Reporting of 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 asked to report any suspected adverse reactions to SAHPRA via the "**.6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms:

First-degree AV block and second-degree heart block may occur. Bradycardia, with or without hypotension, and cardiac arrest may occur. Because **PRECIA** has the potential to augment bradycardia induced by vagal stimuli, health care professionals should be prepared to intervene.

Several cases of dexmedetomidine overdose have been reported both in the clinical trial and the post-marketing data. The reported highest infusion rates of dexmedetomidine in these cases have reached up to 60 µg/kg/h for 36 minutes and 30 µg/kg/h for 15 minutes

in a 20-month-old child and in an adult, respectively. The most common adverse reactions reported in conjunction with overdose include bradycardia, hypotension, hypertension, over sedation, respiratory depression and cardiac arrest.

Management:

In cases of overdose with clinical symptoms, dexmedetomidine infusion should be reduced or stopped. Expected effects are primarily cardiovascular and should be treated as clinically indicated. At high concentration hypertension may be more prominent than hypotension. Atropine and glycopyrrolate are effective in the treatment of **PRECIA**-induced bradycardia. Resuscitation was required in isolated cases of severe overdose resulting in cardiac arrest.

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 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:

Dexmedetomidine is rapidly distributed following administration, with a distribution half-life ($t_{½\alpha}$) of approximately 6 minutes; a terminal elimination half-life ($t_{½}$) of approximately 2 hours and a steady state volume of distribution (V_{ss}) of approximately 118 litres. It has a clearance of about 39 L/h. The mean body weight associated with this clearance estimate was 72 kg.

Protein binding:

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.

Biotransformation and elimination:

Dexmedetomidine is eliminated almost exclusively by metabolism with 95 % 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:

Clearance values are lower in subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B or C), compared to healthy subjects. The mean clearance values

for subjects with mild, moderate and severe hepatic impairment are 74 %, 64 % and 53 % respectively, of those observed in the normal healthy subjects. The mean clearances for free dexmedetomidine are 59 %, 51 % and 32 % respectively, of those observed in the normal healthy subjects.

Although the dose of dexmedetomidine is administered according to the desired effect, it may be necessary to consider a dose reduction depending on the degree of hepatic impairment (see section 4.2 and 4.4).

Renal impairment:

Dexmedetomidine pharmacokinetics (C_{max}, T_{max}, AUC, $t_{½}$, CL and V_{ss}) were not different in subjects with severe renal impairment (Cr CI: < 30 mL/min) compared with healthy subjects.

Gender:

No difference in dexmedetomidine pharmacokinetics due to gender was observed.

Elderly:

The elderly are more sensitive to the effects of dexmedetomidine. A higher incidence of bradycardia and hypotension in elderly patients (> 65 years of age) has been reported (see section 4.4). The pharmacokinetic profile of dexmedetomidine is not altered by age.

Paediatrics and adolescents:

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Water for injection

6.2 Incompatibilities

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

PRECIA should not be co-administered through the same intravenous catheter with blood or plasma because physical compatibility has not been established.

PRECIA has been shown to be incompatible when administered with the following medicines: amphotericin B or diazepam.

6.3 Shelf life

24 months.

After dilution:

Chemical and physical in-use stability has been demonstrated for 48 hours at room temperature (at 25 °C).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store at or below 30 °C.

For storage conditions of **PRECIA** after dilution, see section 6.3

6.5 Nature and contents of container

2 mL Type I, clear glass vial, sealed with a dark grey bromobutyl type I rubber stopper and an orange aluminium flip-off seal.

Pack sizes: 1 x 2 mL or 5 x 2 mL packed in an outer carton.

6.6 Special precautions for disposal and other handling

Ampoules/vials are intended for single patient use only.

Preparation of solution:

- Strict aseptic technique must always be maintained during the handling of **PRECIA** 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 **PRECIA** concentrate and add to 48 mL 0,9 % sodium chloride solution to make a total volume of 50 mL.
- Shake gently to mix well.
- Parenteral products should be inspected visually for particulate matter and discolouration prior to administration.
- After dilution, **PRECIA** is intended for immediate use and should be discarded after 48 hours (see section 6.3).

Administration with other fluids:

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

Lactated Ringer's solution, 5 % dextrose in water, 0,9 % sodium chloride in water, and 20 % Mannitol.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Lamar International (Pty) Ltd

2 Waterford Mews

Waterford Place

Century City

7441

Cape Town

South Africa

8. REGISTRATION NUMBER

52/2.9/0345

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: April 2022

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