AUSTRALIAN PRODUCT INFORMATION – PRECEDEX® READY TO USE (DEXMEDETOMIDINE HYDROCHLORIDE)

1. NAME OF THE MEDICINE

Dexmedetomidine hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PRECEDEX READY TO USE is a sterile, non-pyrogenic solution suitable for intravenous (IV) infusion.

Each 1 mL of PRECEDEX READY TO USE contains 4.72 micrograms of dexmedetomidine HCl (equivalent to 4 micrograms dexmedetomidine base) and 9 mg of sodium chloride in water for injections. The solution is preservative-free and contains no additives or chemical stabilisers.

3. PHARMACEUTICAL FORM

PRECEDEX READY TO USE dexmedetomidine hydrochloride 4 micrograms/mL is supplied as a clear, colourless, isotonic solution with a pH of 4.5 to 8.0. PRECEDEX READY TO USE is presented in 20 mL vials, and 50 mL or 100 mL glass bottles, and **DOES NOT REQUIRE DILUTION PRIOR TO USE.**

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Intensive Care Unit (ICU) Sedation

For sedation of initially intubated adult patients during treatment in an intensive care setting. The use of PRECEDEX READY TO USE by continuous infusion in these patients should not exceed 24 hours.

Procedural Sedation

For sedation of non-intubated adult patients prior to and/or during surgical and other procedures.

4.2 Dose and method of administration

NOTE: Dexmedetomidine should be administered only by persons skilled in anaesthetics or in the management of patients in the intensive care setting. Due to the known pharmacological effects, patients should be continuously monitored.

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.

Adults: Dexmedetomidine should be individualised and titrated to the desired clinical effect.

ICU Sedation

Initiation

For adult patients, PRECEDEX READY TO USE may be initiated with a loading infusion of 1 (one) microgram/kg over 10 to 20 minutes, if needed. The use of PRECEDEX READY TO USE by continuous infusion in these patients should not exceed 24 hours.

The use of loading dose of dexmedetomidine was associated with an increased rate of adverse event, including hypotension, hypertension and bradycardia, in clinical trials involving adult ICU patients.

For patients being converted from alternate sedative therapy a loading dose may not be required.

Maintenance of ICU Sedation

Adult patients will generally require a maintenance infusion of 0.2 to 1 microgram/kg/h. The rate of the maintenance infusion should be adjusted to achieve the desired level of sedation. As a guide, it is recommended that 0.4 microgram/kg/h should be the initial maintenance infusion. If after approximately 5 minutes sedation is not adequate, the rate of infusion can be increased in increments of 0.1 microgram/kg/h or higher. Dosages as low as 0.05 microgram/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 function and in patients over 65 years of age (see **4.4 Special warnings and precautions for use** and **5.2 Pharmacokinetic properties**).

PRECEDEX READY TO USE has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post-extubation. It is not necessary to discontinue PRECEDEX READY TO USE prior to extubation.

Procedural Sedation

Based on sedation scores, the loading infusion provides clinically effective onset of sedation 10 to 15 minutes after start of infusion.

Initiation

For adult patients, PRECEDEX READY TO USE is generally initiated with a loading infusion of 1 (one) microgram/kg over 10 to 20 minutes for sedation of non-intubated patients undergoing surgical and other procedures, as well as, for initiation of awake fibreoptic intubation.

For patients with impaired hepatic function and in patients over 65 years of age, the loading dose may be omitted or reduced, e.g. 0.5 microgram/kg over 10 minutes may be suitable.

For patients undergoing less invasive procedures, such as ophthalmic surgery, the loading dose may be reduced, e.g. 0.5 micrograms/kg over 10 minutes may be suitable.

Maintenance of Procedural Sedation

Following the loading dose, maintenance dosing of PRECEDEX READY TO USE should generally be initiated at 0.6 microgram/kg/h and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 microgram/kg/h for all procedures. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation.

Following the loading dose in awake fibreoptic intubation, a fixed maintenance dose of 0.7 microgram/kg/h should be used until the endotracheal tube is secured.

A dose reduction should be considered in patients with impaired hepatic function and in patients over 65 years of age (see **4.4 Special warnings and precautions for use** and **5.2 Pharmacokinetic properties**).

Paediatric Use

Safety of dexmedetomidine has not been sufficiently established in paediatric patients (see **4.4 Special warnings and precautions for use**).

Administration

A controlled infusion device should be used to administer dexmedetomidine.

Strict aseptic technique must always be maintained during handling of dexmedetomidine infusion.

Preparation

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

PRECEDEX READY TO USE, 4 micrograms/mL, is supplied in 20 mL vials, and 50 mL or 100 mL bottles containing a ready to use dexmedetomidine hydrochloride solution in 0.9% sodium chloride in water for injections.

NO FURTHER DILUTION IS NECESSARY PRIOR TO ADMINISTRATION.

Vials and bottles are intended for single patient use only.

Dexmedetomidine has been found to be compatible with water solutions of the following drugs when administered via Y-site injection: thiopental sodium, vecuronium bromide, pancuronium bromide, glycopyrrolate, phenylephrine hydrochloride.

4.3 Contraindications

Dexmedetomidine hydrochloride is contraindicated in patients with a known hypersensitivity to dexmedetomidine, or any of the excipients contained in PRECEDEX READY TO USE (see **6.1 List of excipients).**

4.4 Special warnings and precautions for use

Drug Administration

Dexmedetomidine hydrochloride is for hospital use only. PRECEDEX READY TO USE should be administered only by persons skilled in the management of patients in the intensive care or

operating room setting. Due to the known pharmacological effects of dexmedetomidine hydrochloride, patients should be continuously monitored (MAC: Monitored Anaesthesia Care) for early signs of hypotension, hypertension, bradycardia, respiratory depression, airway obstruction, apnoea, dyspnoea and/or oxygen desaturation while receiving dexmedetomidine hydrochloride. Supplemental oxygen should be immediately available and provided when indicated.

Continuous electrocardiogram (ECG), blood pressure, and oxygen saturation monitoring are recommended during infusion of PRECEDEX READY TO USE. Dexmedetomidine may cause reduced lacrimation. Lubrication of the patient's eyes should be considered when administering dexmedetomidine to avoid corneal dryness.

PRECEDEX READY TO USE is only to be used for procedural sedation with the provision of appropriate monitoring and under the constant supervision of an appropriately trained medical practitioner. Although PRECEDEX READY TO USE has sedative effects, it has not been shown to be amnestic. Should amnesia be desired during procedural sedation then a drug with amnestic properties (such as a benzodiazepine) should be co-administered.

Hypotension, Bradycardia and Sinus Arrest

Clinical events of bradycardia and sinus arrest have been associated with dexmedetomidine administration in young, healthy adult volunteers with high vagal tone or with different routes of administration including rapid intravenous or bolus administration of dexmedetomidine.

Decreased blood pressure and/or heart rate may occur with the administration of dexmedetomidine. Dexmedetomidine decreases sympathetic nervous activity and therefore, these effects may be expected to be most pronounced in patients with desensitised autonomic nervous system control (i.e. ageing, diabetes, chronic hypertension, severe cardiac disease).

Reports of hypotension and bradycardia have been associated with dexmedetomidine infusion. Some of these cases have resulted in fatalities. If medical intervention is required, treatment may include decreasing or stopping the infusion of PRECEDEX READY TO USE, increasing the rate of IV fluid administration, elevation of the lower extremities, and use of pressor agents. Because dexmedetomidine has the potential to augment bradycardia induced by vagal stimuli, clinicians should be prepared to intervene. The intravenous administration of anticholinergic agents (e.g., glycopyrrolate, atropine) should be considered to modify vagal tone. In clinical trials, glycopyrrolate or atropine were effective in the treatment of most episodes of dexmedetomidine induced bradycardia. However, in some patients with significant cardiovascular dysfunction, more advanced resuscitative measures were required.

Caution should be exercised when administering PRECEDEX READY TO USE to patients with advanced heart block and/or severe ventricular dysfunction. Because dexmedetomidine decreases sympathetic nervous system activity, hypotension and/or bradycardia may be expected to be more pronounced in hypovolaemic patients and in those with diabetes mellitus or chronic hypertension and in elderly patients.

In situations where other vasodilators or negative chronotropic agents are administered, co-administration of dexmedetomidine could have an additive pharmacodynamic effect and should be administered with caution.

Clinical events of bradycardia or hypotension may be potentiated when dexmedetomidine is used concurrently with propofol or midazolam. Therefore, consider a reduction in the dose of midazolam or propofol.

Elderly patients over 65 years of age, or diabetic patients, are more prone to hypotension with the administration of dexmedetomidine. All episodes either spontaneously reversed or were treated with standard therapy.

Transient Hypertension

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

Arousability

Patients receiving PRECEDEX READY TO USE have been observed to be rousable and alert when stimulated. This is an expected component of PRECEDEX READY TO USE sedation and should not be considered a lack of efficacy in the absence of other clinical signs and symptoms.

Withdrawal

Although not specifically studied, if dexmedetomidine is administered chronically and stopped abruptly, withdrawal symptoms similar to those reported for another alpha-$_2$-adrenergic agent, clonidine, may result. These symptoms include nervousness, agitation, and headaches, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma. Dexmedetomidine should not be administered for greater than 24 hours.

Procedural Sedation: In adult subjects, withdrawal symptoms were not seen after discontinuation of short-term infusions of dexmedetomidine (<6 h).

Adrenal Insufficiency

Dexmedetomidine had no effect on ACTH-stimulated cortisol release in dogs after a single dose; however, after the subcutaneous (SC) infusion of dexmedetomidine for one week, the cortisol response to ACTH was diminished by approximately 40%. In a clinical study, prolonged infusions of dexmedetomidine at doses up to 1.4 microgram/kg/h were not associated with significant adrenocortical suppression.

Hyperthermia

PRECEDEX READY TO USE may induce hyperthermia that may be resistant to traditional cooling methods. PRECEDEX READY TO USE should be discontinued and hyperthermia should be managed with conventional medical measures.

Use in Hepatic Impairment

Since dexmedetomidine clearance decreases with increasing severity of hepatic impairment, dose reductions should be considered in patients with impaired hepatic function **(see 4.2 Dose and method of administration).**

Risk of Mortality in ICU patients ≤ 65 years old

Use of dexmedetomidine greater than 24 hours has been associated with an increased mortality in critically ill adult ICU patients 65 years of age and younger compared to usual care (see **5.1 Pharmacodynamic properties – Clinical trials**).

Seizures

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

Incompatibility

Precedex has been shown to be incompatible when administered with the following drugs: amphotericin B, diazepam (see **6.2 Incompatibilities)**.

Use in the Elderly

Dexmedetomidine is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in elderly patients, and it may be useful to monitor renal function (see **5.1 Pharmacodynamic properties – Clinical trials**).

Paediatric Use

The safety of dexmedetomidine in paediatric patients below 18 years of age has not been sufficiently established for procedural or ICU sedation. Therefore, PRECEDEX READY TO USE is not recommended in this population (see **4.2 Dose and method of administration** and **5.1 Pharmacodynamic Properties – Clinical trials**).

Effects on Laboratory Tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Anaesthetics/Sedatives/Hypnotics/Opioids: Co-administration of dexmedetomidine is likely to lead to an enhancement of effects with anaesthetics, sedatives, hypnotics, and opioids. Specific studies have confirmed these effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam. No pharmacokinetic interactions between dexmedetomidine and isoflurane, propofol, alfentanil, and midazolam were demonstrated. However, due to pharmacodynamic effects, when co-administered with dexmedetomidine, a reduction in dosage with these agents may be required.

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

Drugs with Cardiovascular Activities: The possibility of enhanced hypotensive and bradycardic effects should be considered in patients receiving other medicinal products causing these effects, for example beta blockers, although additional effects in an interaction study with esmolol were modest.

Cytochrome P450: *In vitro* studies indicate that clinically relevant cytochrome P450 mediated drug interactions are unlikely. PRECEDEX READY TO USE has shown strongest properties for inhibition of CYP2D6, CYP3A4 and CYP2B6. Use caution during concomitant

administration of PRECEDEX READY TO USE with other medicines metabolized by CYP2D6, CYP3A4 and CYP2B6 enzymes.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Dexmedetomidine did not affect reproductive capacity or fertility in male or female rats after daily subcutaneous injections at doses up to 54 microgram/kg/day for 10 weeks prior to mating in males and 3 weeks prior to mating and during mating in females. Systemic exposure ($AUC_{0\text{-}24h}$) at this dose level was less than anticipated at the maximum recommended human dose of 17.8 microgram/kg.

Use in pregnancy

Category B1[1]. Radiolabelled dexmedetomidine administered subcutaneously to female rats on gestation day 18 crossed the placental barrier to fetal tissue. Teratogenic effects were not observed following administration of dexmedetomidine at subcutaneous doses up to 200 microgram/kg/day in rats or IV doses up to 96 microgram/kg/day in rabbits. Systemic exposure ($AUC_{1\text{-}24h}$) at these dose levels was 3 to 5 times greater than those in humans at the maximum recommended dose of 17.8 microgram/kg. In rats, fetal and pup body weights were reduced at SC doses ≥6 microgram/kg/day, post-implantation loss was increased at 200 microgram/kg/day, and perinatal mortality was increased at SC doses ≥18 microgram/kg/day. These findings are consistent with those of clonidine, another $alpha_2$-adrenoreceptor agonist. Dexmedetomidine has no effect on fetal body weight or embryo fetal viability at IV doses as high as 96 microgram/kg/day in rabbits. Dexmedetomidine also produced delayed motor development in rat pups at a dose of 32 microgram/kg (less than the maximum recommended human intravenous dose). No such effects were observed at a dose of 2 microgram/kg.

There are no adequate and well-controlled studies in pregnant women. Dexmedetomidine has been shown to cross the placental barrier in human published studies. It has been reported that prenatal exposure to dexmedetomidine may be associated with some degree of functional impairment at birth in some neonates. Dexmedetomidine should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

Labour and Delivery: The safety of dexmedetomidine in labour and delivery has not been studied and is, therefore, not recommended for obstetrics, including caesarean section deliveries. Perioperative administration of dexmedetomidine in pregnant women receiving general anaesthesia for elective caesarean section was associated with a longer time to clinical recovery and extubation compared with remifentanil.

Use in lactation

Dexmedetomidine is excreted in human milk, but no studies assessing the effects of dexmedetomidine in breastfed children and on milk production have been performed. The developmental and health benefits of breastfeeding should be considered along with the

[1] Category B1: Drugs which have been taken only by a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects in the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

mother's clinical need for dexmedetomidine and any potential adverse effects on the breastfed child from dexmedetomidine.

A lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk for 24 hours after receiving dexmedetomidine in order to minimise potential drug exposure to a breastfed neonate.

Radiolabelled dexmedetomidine administered subcutaneously to lactating female rats was distributed to, but did not accumulate in, milk.

4.7 Effects on ability to drive and use machines

Patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery or signing legal documents, may be impaired for some time after sedation.

4.8 Adverse effects (undesirable effects)

ICU Sedation

Adverse event information derived from the placebo-controlled, continuous infusion trials of dexmedetomidine for sedation in the surgical ICU setting in which 387 patients received dexmedetomidine. In these studies, the mean total dose was 7.06 microgram/kg (SD = 2.86), mean dose per hour was 0.51 microgram/kg/h (SD = 0.39) and the mean duration of infusion of 15.6 hours (range: 0.17 to 29.08). The population was between 19 to 83 years of age, 43% over 65 years of age, 73% male and 97% Caucasian. Overall, the most frequently observed treatment-emergent adverse events included hypotension, hypertension, nausea, bradycardia, fever, vomiting, hypoxia, tachycardia and anaemia (see Table 1).

Table 1: Treatment-Emergent Adverse Events Occurring in >1% of All Dexmedetomidine-Treated Patients in the Randomised Placebo-controlled Continuous Infusion ICU Sedation Studies

Adverse Event	Randomised Dexmedetomidine (N=387)	Placebo (N=379)
Hypotension	28%	13%
Hypertension	16%	18%
Nausea	11%	9%
Bradycardia	7%	3%
Fever	5%	4%
Vomiting	4%	6%
Atrial Fibrillation	4%	3%
Hypoxia	4%	4%
Tachycardia	3%	5%
Haemorrhage	3%	4%
Anaemia	3%	2%
Dry Mouth	3%	1%
Rigors	2%	3%
Agitation	2%	3%
Hyperpyrexia	2%	3%
Pain	2%	2%
Hyperglycaemia	2%	2%
Acidosis	2%	2%

Pleural Effusion	2%	1%
Oliguria	2%	<1%
Thirst	2%	<1%

Adverse event information derived from the midazolam-controlled, continuous infusion trial of dexmedetomidine for sedation in a predominantly medical ICU setting in which 244 patients received dexmedetomidine for long-term sedation. Treatment-emergent adverse events occurring at an incidence of >5% are provided in Table 2. The mean total dose was 72.5 microgram/kg (range: 0.1 to 489.9), mean dose per hour was 0.83 microgram/kg/h (range: 0.18 to 1.54) and the mean duration of infusion of 3.4 days (range: 0.02 to 15.6). The population was between 18 to 89 years of age, 46% over 65 years of age, 51% male and 79% Caucasian. The most frequent adverse events for this population were hypotension, tachycardia, bradycardia and systolic hypertension (see **4.4 Special warnings and precautions for use**).

Table 2: Treatment-Emergent Adverse Events Occurring in ≥5% of Dexmedetomidine- or Midazolam-Treated Patients in the Randomised Active Comparator Continuous Infusion Long-Term ICU Sedation Study

Variable	**Dexmedetomidine (n=244)**	**Midazolam (n=122)**
Cardiac disorders		
Bradycardia[3]	103 (42.2%)	23 (18.9%)
Bradycardia requiring intervention	12 (4.9%)	1 (0.8%)
Tachycardia[4]	62 (25.4%)	54 (44.3%)
Tachycardia requiring intervention	24 (9.8%)	12 (9.8%)
Vascular disorders		
Diastolic Hypertension	30 (12.3%)	18 (14.8%)
Systolic Hypertension	69 (28.3%)	51 (41.8%)
Hypertension[2]	26 (10.7%)	18 (14.8%)
Hypertension requiring intervention†	46 (18.9%)	36 (29.5%)
Hypotension[1]	137 (56.1%)	68 (55.7%)
Hypotension requiring intervention	69 (28.3%)	33 (27.0%)
General Disorders and Administrative Site		
Generalised oedema	5 (2.0%)	7 (5.7%)
Pyrexia	18 (7.4%)	3 (2.5%)
Metabolism and nutrition disorders		
Hyperglycaemia	16 (6.6%)	2 (1.6%)
Hypoglycaemia	13 (5.3%)	7 (5.7%)
Hypokalaemia	23 (9.4%)	16 (13.1%)
Hypomagnesaemia	3 (1.2%)	8 (6.6%)
Gastrointestinal disorders		
Constipation	15 (6.1%)	7 (5.7%)
Psychiatric Disorders		
Agitation	17 (7.0%)	7 (5.7%)

†Includes any type of hypertension.

1. Hypotension was defined in absolute terms as Systolic blood pressure of <80 mmHg or Diastolic blood pressure of <50 mmHg or in relative terms as ⩽30% lower than pre-study drug infusion value.
2. Hypertension was defined in absolute terms as Systolic blood pressure >180 mmHg or Diastolic blood pressure of >100 mmHg or in relative terms as ⩾30% higher than pre-study drug infusion value.
3. Bradycardia was defined in absolute terms as <40 bpm or in relative terms as ⩽30% lower than pre-study drug infusion value.
4. Tachycardia was defined in absolute terms as >120 bpm or in relative terms as ⩾30% greater than pre-study drug infusion value.

The following adverse events occurred between 2 and 5% for dexmedetomidine and midazolam, respectively: anaemia (2.9%, 4.1%), thrombocytopaenia (0.8%, 2.5%), atrial fibrillation (2.0%,

3.3%), abdominal distension (4.1%, 1.6%), abdominal pain (1.2%, 3.3%), diarrhoea (4.9%, 4.1%), nausea (4.1%, 1.6%), vomiting (2.0%, 4.9%), peripheral oedema (4.1%, 4.9%), pneumonia (1.2%, 4.9%), sepsis (2.5%, 2.5%), septic shock (1.6%, 2.5%), urinary tract infection (0, 3.3%), haemoglobin decreased (0, 2.5%), urine output decreased (2.0%, 3.3%), electrolyte imbalance (0.8%, 2.5%), fluid overload (1.6%, 4.1%), hypernatraemia (2.5%, 1.6%), hypophosphataemia (2.5%, 1.6%), headache (2.0%, 0.8%), anxiety (2.5%, 0), oliguria (0.4%, 2.5%), renal failure acute (2.5%, 0.8%), acute respiratory distress syndrome (2.5%, 0.8%), pharyngolaryngeal pain (2.5%, 4.9%), pleural effusion (2.9%, 2.5%), respiratory failure (4.5%, 3.3%), decubitus ulcer (1.2%, 4.9%), and rash (0.8%, 2.5%).

Procedural Sedation

Adverse event information is derived from the two primary phase 3 trials for procedural sedation in which 318 patients received dexmedetomidine. The mean total dose was 1.6 microgram/kg (range: 0.5 to 6.7), mean dose per hour was 1.3 microgram/kg/h (range: 0.3 to 6.1) and the mean duration of infusion of 1.5 hours (range: 0.1 to 6.2). The population was between 18 to 93 years of age, 30% over 65 years of age, 52% male and 61% Caucasian.

Treatment-emergent adverse events occurring at an incidence of >2% are provided in Table 3. The majority of the adverse events were assessed as mild in severity. The most frequent adverse events were hypotension, bradycardia, and dry mouth. Pre-specified criteria for the vital signs to be reported as Adverse Events are footnoted below the table. Respiratory depression and hypoxia was similar in the dexmedetomidine and placebo groups when evaluated against the pre-specified criteria. The incidence of absolute respiratory depression and hypoxia was less in the dexmedetomidine -treated patients than the placebo patients (3.04% vs 12.7%) in the MAC trial.

Table 3: Adverse Events with an Incidence >2% - Primary Phase 3 Procedural Sedation Population

Body System/ Adverse Event	**Dexmedetomidine N = 318** n (%)	**Placebo N = 113** n (%)
Vascular disorders		
Hypotension[1]	173 (54.4%)	34 (30.1%)
Hypertension[2]	41 (12.9%)	27 (23.9%)
Respiratory, thoracic and mediastinal disorders		
Respiratory depression[5]	117 (36.8%)	36 (31.9%)
Hypoxia[6]	7 (2.2%)	3 (2.7%)
Bradypnea	5 (1.6%)	5 (4.4%)
Cardiac disorders		
Bradycardia[3]	45 (14.2%)	4 (3.5%)
Tachycardia[4]	17 (5.3%)	19 (16.8%)
Gastrointestinal disorders		
Nausea	10 (3.1%)	2 (1.8%)
Dry mouth	8 (2.5%)	1 (0.9%)

1. Hypotension was defined in absolute and relative terms as Systolic blood pressure of <80 mmHg or ⩽30% lower than pre-study drug infusion value, or Diastolic blood pressure of <50 mmHg

2. Hypertension was defined in absolute and relative terms as Systolic blood pressure >180 mmHg or ⩾30% higher than pre-study drug infusion value or Diastolic blood pressure of >100 mmHg.

3. Bradycardia was defined in absolute and relative terms as <40 bpm or ⩽30% lower than pre-study drug infusion value.

4. Tachycardia was defined in absolute and relative terms as >120 bpm or ⩾30% greater than pre-study drug

infusion value.

5. Respiratory Depression was defined in absolute and relative terms as RR<8 bpm or >25% decrease from baseline

6. Hypoxia was defined in absolute and relative terms as SpO2 <90% or 10% decrease from baseline

Post-marketing Experience

The adverse reactions that have been identified during post approval use of dexmedetomidine are provided in Table 4.

Hypotension and bradycardia were the most common adverse reactions associated with the use of dexmedetomidine during post approval use of the drug. The following table lists adverse drug reactions (ADRs) within each standard System Organ Class (SOC).

Table 4: Adverse Events Experienced During Post Approval Use of Dexmedetomidine

System Organ Class	**Adverse Drug Reactions**
Metabolism and nutrition disorders	Hypovolaemia, acidosis, hyperkalaemia, hypocalcaemia
Surgical and medical procedures	Light anaesthesia
General disorders and administration site conditions	Chills, thirst, oedema peripheral
Vascular disorders	Blood pressure fluctuation, haemorrhage
Cardiac disorder	Cardiovascular disorder, myocardial infarction, arrhythmia, ventricular arrhythmia, atrioventricular block, cardiac arrest, extrasystoles, supraventricular tachycardia, ventricular tachycardia, sinus tachycardia
Nervous system disorders	Dizziness, neuralgia, neuritis, speech disorder, convulsion
Investigations	Electrocardiogram t wave inversion, gamma-glutamyltransferase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood urea increased
Hepatobiliary disorders	Hepatic function abnormal, hyperbilirubinaemia
Respiratory, thoracic and mediastinal disorders	Respiratory acidosis, apnoea, bronchospasm, dyspnoea, hypercapnia, hypoventilation, pulmonary congestion, pulmonary oedema, wheezing
Psychiatric disorders	Confusion, delirium, hallucination, illusion
Skin and subcutaneous tissue disorders	Hyperhidrosis
Eye disorders	Photopsia, visual impairment
Blood and lymphatic system disorders	Anaemia

Renal and urinary disorders	Polyuria

Dependence

The dependence potential of dexmedetomidine has not been studied in humans.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 Overdose

The tolerability of dexmedetomidine was noted in one study in which healthy adult subjects achieved plasma concentrations from 1.8 up to 13 times the upper boundary of the therapeutic range. The most notable effects observed in two subjects who achieved the highest plasma concentrations were 1st degree AV block and 2nd degree heart block. No haemodynamic compromise was noted with the AV block and the heart block resolved spontaneously within one minute.

Of five adult patients reported with overdose of dexmedetomidine in the Phase II/III ICU sedation studies, two had no symptoms reported; one patient received a 2 microgram/kg loading dose over 10 minutes (twice the recommended loading dose) and one patient received a maintenance infusion of 0.8 microgram/kg/h. Two other patients who received a 2 microgram/kg loading dose over 10 minutes experienced bradycardia with or without hypotension. One patient, who received a loading bolus dose of undiluted (100 microgram/mL) dexmedetomidine (19.4 microgram/kg), had cardiac arrest from which he was successfully resuscitated.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, other hypnotics and sedatives.

Mechanism of action

Dexmedetomidine is a relatively selective alpha$_2$-adrenoreceptor agonist with sedative pharmacologic properties.

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 was observed in animals following slow IV infusion of low and medium doses (10-300 microgram/kg). Both alpha$_1$ and alpha$_2$ activity was observed following slow IV

infusion of high doses (≥1000 microgram/kg) or with rapid IV administration. Dexmedetomidine has a low affinity for beta adrenergic, muscarinic, dopaminergic and serotonin receptors.

Clinical trials

The following clinical trials have been conducted on **dexmedetomidine hydrochloride 100 micrograms/mL concentrated injection diluted to 4 micrograms/mL**.

ICU Sedation

Two randomised, double-blind, parallel-group, placebo-controlled multicentre clinical trials included 754 adult patients being treated in a surgical intensive care unit (ICU). All patients were initially intubated and received mechanical ventilation.

These trials evaluated the sedative properties of dexmedetomidine by comparing the amount of rescue medication (midazolam in one trial and propofol in the second) required to achieve a specified level of sedation (using the standardised Ramsay Sedation Scale, RSS) between dexmedetomidine and placebo from onset of treatment to extubation or to a total treatment duration of 24 hours. The Ramsay Level of Sedation Scale is displayed in Table 5.

Table 5: Ramsay Level of Sedation Scale

Clinical Score	Level of Sedation Achieved
6	Asleep, no response
5	Asleep, sluggish response to light glabellar tap or loud auditory stimulus
4	Asleep, but with brisk response to light glabellar tap or loud auditory stimulus
3	Patient responds to commands
2	Patient cooperative, oriented, and tranquil
1	Patient anxious, agitated, or restless

In the first study, 175 adult patients were randomised to receive placebo and 178 to receive dexmedetomidine by intravenous infusion at a dose of 0.4 microgram/kg/h (with allowed adjustment between 0.2 and 0.7 microgram/kg/h) following an initial loading infusion of 1 (one) microgram/kg IV over 10 minutes. The study drug infusion rate was adjusted to maintain an RSS score of ≥3. Patients were allowed to receive "rescue" midazolam as needed to augment the study drug infusion. In addition, morphine sulfate was administered for pain as needed. The primary outcome measure for this study was the total amount of rescue medication (midazolam) needed to maintain sedation as specified while intubated. Patients randomised to placebo received significantly more midazolam than patients randomised to dexmedetomidine (see Table 6).

A second prospective primary analysis assessed the sedative effects of dexmedetomidine by comparing the percentage of patients who achieved an RSS score of ≥3 during intubation without the use of additional rescue medication. A significantly greater percentage of patients in the dexmedetomidine group maintained an RSS score of ≥3 without receiving any midazolam rescue compared to the placebo group (see Table 6).

Table 6: Midazolam use as rescue medication during intubation (ITT)

	Study One		
	Placebo N=175	Dexmedetomidine N=178	p-value
Mean total dose (mg) of midazolam	19 mg	5 mg	0.0011*

Standard deviation	53 mg	19 mg	
Categorised midazolam use			
0 mg	43 (25%)	108 (61%)	<0.001**
0-4 mg	34 (19%)	36 (20%)	
>4 mg	98 (56%)	34 (19%)	

ITT (intent-to-treat) population includes all randomised patients.
*ANOVA model with treatment centre. **Chi-square

A prospective secondary analysis assessed the dose of morphine sulfate administered to patients in the dexmedetomidine and placebo groups. On average, dexmedetomidine-treated patients received less morphine sulfate for pain than placebo-treated patients (0.47 versus 0.83 mg/h). In addition, 44% (79 of 178 patients) of dexmedetomidine patients received no morphine sulfate for pain versus 19% (33 of 175 patients) in the placebo group.

In the second study, 198 adult patients were randomised to receive placebo and 203 to receive dexmedetomidine by intravenous infusion at a dose of 0.4 microgram/kg/h (with allowed adjustment between 0.2 and 0.7 microgram/kg/h) following an initial loading infusion of 1 (one) microgram/kg IV over 10 minutes. The study drug infusion was adjusted to maintain an RSS score of ≥3. Patients were allowed to receive "rescue" propofol as needed to augment the study drug infusion. In addition, morphine sulfate was administered as needed for pain. The primary outcome measure for this study was the total amount of rescue medication (propofol) needed to maintain sedation as specified while intubated.

Patients randomised to placebo received significantly more propofol than patients randomised to dexmedetomidine (see Table 7).

A significantly greater percentage of patients in the dexmedetomidine group compared to the placebo group maintained an RSS score of ≥3 without receiving any propofol rescue (see Table 7).

Table 7: Propofol use as rescue medication during intubation (ITT)

	Study Two		
	Placebo N=198	Dexmedetomidine N=203	p-value
Mean total dose (mg) of propofol	513 mg	72 mg	<0.0001*
Standard deviation	782 mg	249 mg	
Categorised propofol use			
0 mg	47 (24%)	122 (60%)	<0.001**
0-50 mg	30 (15%)	43 (21%)	
>50 mg	121 (61%)	38 (19%)	

*ANOVA model with treatment centre. **Chi-square

A prospective secondary analysis assessed the dose of morphine sulfate administered to patients in the dexmedetomidine and placebo groups. On average, dexmedetomidine-treated patients received less morphine sulfate for pain than placebo-treated patients (0.43 versus 0.89 mg/h). In addition, 41% (83 of 203 patients) of dexmedetomidine patients received no morphine sulfate for pain versus 15% (30 of 198 patients) in the placebo group.

Mortality in ICU patients ≤ 65 years old

In the SPICE III pragmatic randomised controlled trial of 3904 critically ill adult ICU patients dexmedetomidine was used as primary sedative and compared with usual care. There was no overall difference in 90-day mortality between the dexmedetomidine and usual care group (mortality 29.1% in both groups), but a heterogeneity of effect from age on mortality was observed. Dexmedetomidine was associated with an increased mortality in the age-group ≤ 65

years (odds ratio 1.26; 95% credibility interval 1.02 to 1.56) compared to alternative sedatives. While the mechanism is unclear, this heterogeneity of effect on mortality from age was most prominent in patients admitted for reasons other than post-operative care, and increased with increasing APACHE II scores and with decreasing age. These findings should be weighed against the expected clinical benefit of dexmedetomidine compared to alternative sedatives in younger patients.

In the published study, exposure to dexmedetomidine was greater than 24 hours with a median duration of treatment of 2.56 days (interquartile range, 1.10 to 5.23). The administration of dexmedetomidine was continued as clinically required for up to 28 days after randomization (see **4.4 Special warnings and precautions for use**).

ICU Sedation - Elderly

A total of 729 patients in the clinical studies were 65 years of age and over. A total of 200 patients were 75 years of age and over. In patients greater than 65 years of age, a higher incidence of bradycardia and hypotension was observed following administration of dexmedetomidine (**see 4.4 Special warnings and precautions for use**).

Consideration should be given to lower initial loading and maintenance doses in patients over65 years of age and careful monitoring for the development of hypotension when up titrating the maintenance dose (see **4.2 Dose and method of administration**).

Procedural Sedation

The safety and efficacy of dexmedetomidine for sedation of non-intubated patients prior to and/or during surgical and other procedures was evaluated in two randomised, double-blind, placebo-controlled multicentre clinical trials. Study 1 evaluated the sedative properties of dexmedetomidine in patients having a variety of elective surgeries/procedures performed under monitored anaesthesia care. Study 2 evaluated dexmedetomidine in patients undergoing awake fibreoptic intubation (AFOI) prior to a surgical or diagnostic procedure.

In Study 1, the sedative properties of dexmedetomidine were evaluated by comparing the percent of patients not requiring rescue midazolam to achieve a specified level of sedation using the standardised Observer's Assessment of Alertness/Sedation Scale between dexmedetomidine and placebo. The Observer's Assessment of Alertness/Sedation Scale (Table 8).

Table 8: Observer's Assessment of Alertness/Sedation (OAA/S)

Assessment Categories				
Responsiveness	**Speech**	**Facial Expression**	**Eyes**	**Composite Score**
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	5 (alert)
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	Few recognizable words	--	--	2

Does not respond to mild prodding or shaking	--	--	--	1 (deep sleep)

Patients were randomised to receive a loading infusion of either dexmedetomidine 1 microgram/kg or dexmedetomidine 0.5 microgram/kg, or placebo (normal saline) given over 10 minutes and followed by a maintenance infusion started at 0.6 microgram/kg/h. The maintenance infusion of study drug could be titrated from 0.2 microgram/kg/h to 1 microgram/kg/h to achieve the targeted sedation score (OAA/S ≤4). Patients were allowed to receive rescue midazolam as needed to achieve and/or maintain an OAA/S <4. After achieving the desired level of sedation, a local or regional anaesthetic block was performed. Demographic characteristics were similar between the dexmedetomidine and placebo groups. Efficacy results showed that dexmedetomidine was significantly more effective than placebo when used to sedate non-intubated patients requiring monitored anaesthesia care during surgical and other procedures (Table 9).

In Study 2, the sedative properties of dexmedetomidine were evaluated by comparing the percent of patients requiring rescue midazolam to achieve or maintain a specified level of sedation using the Ramsay Sedation Scale (RSS) score >2 (Table 2) during AFOI. Patients were randomised to receive a loading infusion of dexmedetomidine 1 microgram/kg or placebo (normal saline) given over 10 minutes and followed by a fixed maintenance infusion of 0.7 microgram/kg/h. After achieving the desired level of sedation, topicalisation of the airway occurred. Patients were allowed to receive rescue midazolam as needed to achieve and/or maintain an RSS score of >2. Demographic characteristics were similar between the dexmedetomidine and placebo groups.

Table 9: Key Efficacy Results of Procedural Sedation Studies

Study	Loading Infusion Treatment Arm	Number of Patients Enrolled[a]/Completed[b]	% Requiring midazolam rescue	p value (dexmedetomidine vs placebo)	Mean (SD) Total Dose (mg) of Rescue midazolam Required	p value (dexmedetomidine vs placebo)
Study 1	Dexmedetomidine 0.5 microgram/kg	134/125	59.7	<0.001	1.4 (1.69)	<0.001
	Dexmedetomidine 1 microgram/kg	129/118	45.7	<0.001	0.9 (1.51)	<0.001
	placebo	63/57	96.8	–	4.1 (3.02)	–
Study 2	Dexmedetomidine 1 microgram/kg	55/51	47.3	<0.001	1.07 (1.541)	<0.001
	placebo	50/46	86.0	–	2.85 (3.014)	–

Notes:

a Based on ITT population.

b For Study 1, "completed" = both study drug infusion and post-treatment period. For Study 2, "completed" = 24 hour follow-up.

Procedural Sedation - Elderly

A total of 131 patients in the clinical studies were 65 years of age and over. A total of 47 patients were 75 years of age and over. Hypotension occurred at a higher incidence in dexmedetomidine-treated patients 65 years or older (71.9%) and 75 years or older (73.5%) as compared to patients below 65 years of age (46.8%). The loading dose may be omitted or

reduced and a reduction in the maintenance infusion should be considered for patients greater than 65 years of age (see **4.2 Dose and method of administration**).

Paediatric studies

A US double-blind and two open-label studies in ICU sedation did not meet their primary efficacy endpoint, and the safety data were insufficient to fully characterise the safety profile of PRECEDEX.

One open-label ICU sedation study conducted in Japanese patients did meet its primary efficacy endpoint.

The safety profile of PRECEDEX in these studies was generally similar to that of adults, although increased frequencies of adverse events of bradycardia, hypotension, and respiratory depression were seen in the Japan ICU sedation study.

One open-label study conducted in paediatric patients for procedural sedation also did not meet its efficacy endpoint.

5.2 Pharmacokinetic properties

Following intravenous administration, dexmedetomidine exhibits the following pharmacokinetic parameters: a rapid distribution phase with a distribution half-life ($t_{½}$) of approximately six minutes; a terminal elimination half-life ($t_{½}$) of approximately two hours; and steady-state volume of distribution (V_{ss}) of approximately 118 litres. Clearance (CL) is estimated to be approximately 39 L/h. The mean body weight associated with this clearance estimate was 72 kg.

Dexmedetomidine exhibits linear kinetics in the dosage range of 0.2 to 0.7 microgram/kg/h when administered by IV infusion for up to 24 hours. Table 10 shows the main pharmacokinetic parameters when dexmedetomidine was infused (after appropriate loading doses) at maintenance infusion rates of 0.17 microgram/kg/h (target plasma concentration of 0.3 ng/mL) for 12 and 24 hours, 0.33 microgram/kg/h (target plasma concentration of 0.6 ng/mL) for 24 hours, and 0.70 microgram/kg/h (target plasma concentration of 1.25 ng/mL) for 24 hours.

Table 10: Mean ± SD Pharmacokinetic Parameters				
	Loading Infusion (min)/Total infusion duration (h)			
	10 min/12 h	**10 min/24 h**	**10 min/24 h**	**35 min/24 h**
	Dexmedetomidine Target Concentration (ng/mL) and Dose (microgram/kg/h)			
Parameter	**0.3/0.17**	**0.3/0.17**	**0.6/0.33**	**1.25/0.70**
$t_{½}$*, hour	1.78 ± 0.30	2.22 ± 0.59	2.23 ± 0.21	2.50 ± 0.61
CL, litre/hour	46.3 ± 8.3	43.1 ± 6.5	35.3 ± 6.8	36.5 ± 7.5
V_{ss}, litre	88.7 ± 22.9	102.4 ± 20.3	93.6 ± 17.0	99.6 ± 17.8
Mean C_{ss}#, ng/mL	0.27 ± 0.05	0.27 ± 0.05	0.67 ± 0.10	1.37 ± 0.20

Abbreviations: $t_{½}$ = half-life, CL = clearance, V_{ss} = steady state volume of distribution.
* Presented as harmonic mean and pseudo standard deviation.
# Mean C_{ss} = Average steady-state concentration of dexmedetomidine. The mean C_{ss} was calculated based on post-dose sampling from 2.5 to 9 hours samples for 12 hour infusion and 2.5 to 18 hours samples for 24 hour infusions.

Distribution

The steady-state volume of distribution (V_{ss}) of dexmedetomidine is approximately 118 litres. Dexmedetomidine protein binding was assessed in the plasma of normal healthy male and female subjects. The average protein binding was 94% and was constant across the different plasma 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 to healthy subjects. The potential for protein binding displacement of dexmedetomidine by fentanyl, ketorolac, theophylline, digoxin and lidocaine was explored *in vitro*, and negligible changes in the plasma protein binding of dexmedetomidine were observed. The potential for protein binding displacement of phenytoin, warfarin, ibuprofen, propranolol, theophylline and digoxin by dexmedetomidine was explored *in vitro* and none of these compounds appeared to be significantly displaced by dexmedetomidine.

Metabolism

Dexmedetomidine undergoes almost complete biotransformation with very little unchanged dexmedetomidine excreted in urine and faeces. Biotransformation involves both direct glucuronidation as well as cytochrome P450 mediated metabolism. The major metabolic pathways of dexmedetomidine are: direct *N*-glucuronidation to inactive metabolites; aliphatic hydroxylation (mediated primarily by CYP2A6) of dexmedetomidine to generate 3-hydroxydexmedetomidine, the glucuronide of 3-hydroxydexmedetomidine, and 3-carboxydexmedetomidine; and *N*-methylation of dexmedetomidine to generate 3-hydroxy-*N*-methyldexmedetomidine, 3-carboxy-*N*-methyldexmedetomidine, and *N*-methyldexmedetomidine-*O*-glucuronide.

Excretion

The terminal elimination half-life ($t_{½}$) of dexmedetomidine is approximately 2 hours and clearance is estimated to be approximately 39 L/h. A mass balance study demonstrated that after nine days an average of 95% of the radioactivity, following IV administration of radiolabelled dexmedetomidine, was recovered in the urine and 4% in the faeces. No unchanged dexmedetomidine was detected in the urine. Approximately 85% of the radioactivity recovered in the urine was excreted within 24 hours after the infusion. Fractionation of the radioactivity excreted in urine demonstrated that products of *N*-

glucuronidation accounted for approximately 34% of the cumulative urinary excretion. In addition, aliphatic hydroxylation of parent drug to form 3-hydroxydexmedetomidine, the glucuronide of 3-hydroxydexmedetomidine, and 3-carboxydexmedetomidine together represented approximately 14% of the dose in urine. *N*-methylation of dexmedetomidine to form 3-hydroxy-*N*-methyldexmedetomidine, 3-carboxy-*N*-methyldexmedetomidine, and *N*-methyldexmedetomidine-*O*-glucuronide accounted for approximately 18% of the dose in urine. The *N*-methyl metabolite itself was a minor circulating component and was undetected in urine. Approximately 28% of the urinary metabolites have not been identified.

Specific Populations

Patients with Hepatic Impairment

In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values for dexmedetomidine hydrochloride were lower than in healthy subjects. The mean clearance values for patients with mild, moderate, and severe hepatic impairment were 74%, 64% and 53% of those observed in the normal healthy subjects, respectively. Mean clearances for free drug were 59%, 51% and 32% of those observed in the normal healthy subjects, respectively.

Although dexmedetomidine hydrochloride is dosed to effect, it may be necessary to consider dose reduction depending on the degree of hepatic impairment (see **4.2 Dose and method of administration**).

Patients with Renal Impairment

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

In view of the limited toxicological data and the potential for higher plasma metabolite concentrations in patients with severe renal impairment, caution is advised with prolonged dosing in such patients (see **4.2 Dose and method of administration**).

Male and Female Patients

There was no observed difference in dexmedetomidine hydrochloride pharmacokinetics due to gender.

Elderly

The pharmacokinetic profile of dexmedetomidine hydrochloride was not altered by age. However, as with many drugs, the elderly may be more sensitive to the effects of dexmedetomidine. In clinical trials, there was a higher incidence of bradycardia and hypotension in elderly patients.

Children

The pharmacokinetic profile of dexmedetomidine hydrochloride has not been studied in children.

5.3 Preclinical safety data

Genotoxicity

Dexmedetomidine was not mutagenic *in vitro*, in either the bacterial reverse mutation assay (*E coli* and *Salmonella typhimurium*) or the mammalian cell forward mutation assay (mouse

lymphoma). In a mouse micronucleus study, dexmedetomidine was not cytotoxic to bone marrow and did not increase the numbers of micronucleated PCEs at any dose tested, both in animals maintained at room temperature and in those kept warm. In addition, dexmedetomidine did not induce chromosomal aberrations in cultured human peripheral blood lymphocytes in the absence or presence of an exogenous metabolic activation system comprised of a human S9 homogenate.

Carcinogenicity

Animal carcinogenicity studies have not been performed with dexmedetomidine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections

6.2 Incompatibilities

Compatibility of dexmedetomidine with co-administration of blood, serum, or plasma has not been established. PRECEDEX READY TO USE must not be mixed with other medicinal products.Precedex has been shown to be incompatible when administered with the following drugs: amphotericin B, diazepam (see **4.4 Special warnings and precautions for use)**.

Compatibility with Natural Rubber

Compatibility studies have demonstrated the potential for absorption of Precedex to some types of natural rubber.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Store in the original container.

6.5 Nature and contents of container

Available in 20 mL glass vials, and 50 mL or 100 mL glass bottles, as follows:

80 micrograms/20 mL (AUST R 234022). Available in cartons containing 10 vials.
200 micrograms/50 mL (AUST R 234023). Available in cartons containing 20 bottles.
400 micrograms/100 mL (AUST R 234024). Available in cartons containing 10 bottles.

6.6 Special precautions for disposal

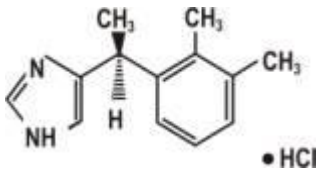
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Dexmedetomidine hydrochloride is a white or almost white powder, freely soluble in water and its pKa is 7.1. The partition coefficient in octanol: water at pH 7.84 is 2.89.

Chemical structure

Dexmedetomidine hydrochloride is chemically described as (+)-4-(S)-[1-(2, 3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride and has a molecular weight of 236.7 and the empirical formula is C13H16N2•HCl. The structural formula is:



CAS number

CAS-145108-58-3

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

09 December 2015

10. DATE OF REVISION

17 November 2023

Summary table of changes

Section Changed	Summary of new information
4.4	Addition of warning on mortality rates differences in critically ill patients

5.1	Inclusion of clinical trial SPICE III study