NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Dexmedetomidine-AFT 200 micrograms/ 2 mL Concentrate for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 mL of Dexmedetomidine-AFT contains 236 micrograms of dexmedetomidine hydrochloride (equivalent to 200 microgram dexmedetomidine).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dexmedetomidine-AFT (dexmedetomidine hydrochloride) 200 microgram/2 mL is supplied as a clear, colourless, isotonic solution with a pH of 4.5 to 7.0.

Dexmedetomidine-AFT is presented in 2 mL ampoules and must be diluted prior to use.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ICU (intensive care unit) sedation

For sedation of initially adult intubated patients during treatment in an intensive care setting. The use of Dexmedetomidine-AFT 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 hydrochloride 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 administration in young, healthy volunteers with high vagal tone or with different routes of administration including rapid intravenous or bolus administration of dexmedetomidine.

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

ICU sedation

Initiation

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

The use of a loading dose of dexmedetomidine was associated with an increased rate of adverse events, 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 section 4.4 and 5.2)

Dexmedetomidine-AFT has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post-extubation. It is not necessary to discontinue Dexmedetomidine-AFT 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, Dexmedetomidine-AFT 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 Dexmedetomidine-AFT 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.

Paediatrics use

The safety and efficacy of dexmedetomidine has not been established in paediatric patients (see section 4.4).

Administration

A controlled infusion device should be used to administer dexmedetomidine.

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

Vials are intended for single patient use only.

For instructions on dilution of the product before administration, see section 6.6.

4.3 Contraindications

Dexmedetomidine-AFT is contraindicated in patients with a known hypersensitivity to dexmedetomidine, or any of the excipients contained in Dexmedetomidine-AFT (see section 6.1).

4.4 Special warnings and precautions for use

Drug administration

Dexmedetomidine hydrochloride is for hospital use only. Dexmedetomidine-AFT 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 Dexmedetomidine-AFT. Dexmedetomidine may cause reduced lacrimation. Lubrication of the patient's eyes should be considered when administering dexmedetomidine to avoid corneal dryness.

Dexmedetomidine-AFT 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 Dexmedetomidine-AFT 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 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 Dexmedetomidine-AFT, increasing the rate of IV fluid administration, elevation of the lower extremities, and the 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 Dexmedetomidine-AFT 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

Some patients receiving dexmedetomidine have been observed to be arousable and alert when stimulated. This alone should not be considered as evidence of lack of efficacy in the absence of other clinical signs and symptoms.

Withdrawal

Although not specifically studied, if dexmedetomidine is administered chronically and stopped abruptly, withdrawal symptoms similar to those reported for another α_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).

Dependence

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

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

Dexmedetomidine-AFT may induce hyperthermia that may be resistant to traditional cooling methods. Dexmedetomidine-AFT should be discontinued and hyperthermia should be managed with conventional medical measures.

Hepatic impairment

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

Risk of Mortality

Use of dexmedetomidine greater than 24 hours has been associated with an increased mortality in critically ill adult ICU patients 63.7 years of age and younger compared to usual care (see section 5.1 – Clinical efficacy and safety).

Seizures

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

Paediatric use

The safety and efficacy of dexmedetomidine in paediatric patients below 18 years of age have not been established for procedural or ICU sedation. Therefore, Dexmedetomidine-AFT is not recommended in this population.

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 pharmacodynamic properties-clinical trial).

4.5 Interaction with other medicines and other forms of interaction

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.

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 – 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

[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.

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 α_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 both animal and human published studies. The limited available information on dexmedetomidine use during pregnancy is not sufficient to inform a drug-associated risk of birth defects or miscarriage. Dexmedetomidine should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

It has been reported that prenatal exposure to dexmedetomidine may be associated with some degree of functional impairment at birth in some neonates.

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 has been associated with a longer time to clinical recovery and extubation compared with other anaesthetic agents.

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 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 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 section 4.4).

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**	**Placebo n = 113**
	n (%)	**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		

Body System/ Adverse Event	Dexmedetomidine n = 318	Placebo n = 113
	n (%)	n(%)
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. Table 4 lists adverse drug reactions (ADRs) within each standard System Organ Class (SOC).

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

Body System	Preferred Term
Metabolic and nutritional disorders	Hypovolaemia, acidosis, hyperkalaemia, hypoglycaemia
Surgical and medical procedures	Light anaesthesia
General disorders and administration site conditions	Chills, thirst, oedema peripheral
Nervous system disorders	Dizziness, neuralgia, neuritis, speech disorder, convulsion

Body System	Preferred Term
Investigations	Electrocardiogram t wave inversion, gammaglutamyltransferase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood urea increased
Cardiac disorders	Cardiac disorder, myocardial infarction, arrhythmia, ventricular arrhythmia, atrioventricular block, cardiac arrest, extrasystoles, supraventricular tachycardia, ventricular tachycardia, sinus tachycardia
Hepatobiliary disorders	Hepatic function abnormal, hyperbilirubinaemia
Psychiatric disorders	Confusion, delirium, hallucination, illusion
Blood and lymphatic system disorders	Anaemia
Renal disorders	Polyuria
Respiratory, thoracic and mediastinal disorders	Respiratory acidosis, apnoea, bronchospasm, dyspnoea, hypercapnia, hypoventilation, pulmonary congestion, pulmonary oedema, wheezing
Skin and subcutaneous tissue disorders	Hyperhidrosis
Vascular Disorders	Haemorrhage, blood pressure fluctuation
Eye disorders	Photopsia, visual impairment

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 professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

The tolerability of dexmedetomidine was noted in one study in which healthy 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.

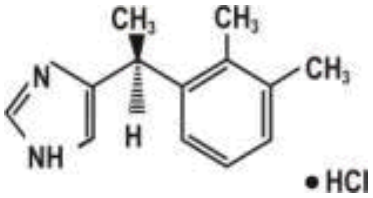
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON

(0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 CAS registry number for Dexmedetomidine hydrochloride is CAS-145108-58-3. The structural formula is:



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.

Mechanism of action

Dexmedetomidine is a relatively selective α_2-adrenoreceptor agonist with a broad range of pharmacologic properties.

The sedative actions of dexmedetomidine are believed to be mediated primarily by post-synaptic α2-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. α2-selectivity was observed in animals following slow IV infusion of low and medium doses (10-300 microgram/kg). Both α1 and α2 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.

Pharmacodynamics

In a study in healthy volunteers (N = 10), respiratory rate and oxygen saturation remained within normal limits and there was no evidence of respiratory depression when dexmedetomidine was administered by intravenous infusion at doses within the recommended dose range (0.2-0.7 mcg/kg/hr). The safety and efficacy of dexmedetomidine has been evaluated in four randomized, double-blind, placebo-controlled multicentre clinical trials in 1185 adult patients.

Clinical efficacy and safety

ICU sedation

Two randomised, double-blind, parallel-group, placebo-controlled multicentre clinical trials in a surgical intensive care unit (ICU) 754 patients being treated. 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) 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 a Ramsay sedation 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 a Ramsay sedation score of ≥3 during intubation without the use of additional rescue medication. A significantly greater percentage of patients in the dexmedetomidine group maintained a Ramsay sedation 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)

	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 a Ramsay sedation 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 a Ramsay sedation score of ≥3 without receiving any propofol rescue (see Table 7).

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

	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**

	Placebo n=198	Dexmedetomidine n=203	p-value
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 0.89mg/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.

In a controlled clinical trial, dexmedetomidine was compared to midazolam for ICU sedation exceeding 24 hours duration. Dexmedetomidine was not shown to be superior to midazolam for the primary efficacy endpoint, the percent of time patients were adequately sedated (81% versus 81%).

Sedation practice in intensive care evaluation (SPICE) III study

In a published randomized controlled trial (Sedation Practice in Intensive Care Evaluation (SPICE) III trial) of 3904 critically ill adult ICU patients, dexmedetomidine was used as primary sedative and compared with usual care.

There was no overall significant difference in the primary outcome of 90-day mortality between the dexmedetomidine and usual care group (mortality 29.1% in both groups). In exploratory subgroup analyses, dexmedetomidine was associated with a decreased mortality in patients with age greater than the median age of 63.7 years (risk difference -4.4; 95% confidence interval -8.7 to -0.1) compared to usual care. Conversely, dexmedetomidine was associated with an increased mortality in patients with age less than or equal to the median age of 63.7 years (risk difference 4.4; 95% confidence interval 0.8 to 7.9) compared to usual care.

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.

The significance of these findings is unknown, but they should be weighed against the expected clinical benefit of dexmedetomidine compared to alternative sedatives in patients less than or equal to 63.7 years old.

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 section 4.4).

Consideration should be given to lower initial loading and maintenance doses in patients over 65 years of age and careful monitoring for the development of hypotension when up titrating the maintenance dose (see sections 4.2 and 5.2).

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 dexmedetomidine 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 a Ramsay sedation score >2 (Table 5) 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 a Ramsay sedation score >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]**	**% Not Requiring Midazolam Rescue**	**Confidenc[e] Interval on the Difference Vs. Placebo**	**Mean (Sd) Total Dose (Mg) of Rescue Midazolam Required**	**Confidenc[b] Intervals of the Mean Rescue Dose**
Study 1	Dexmedetomidine 0.5 microgram/kg	134	40	<0.001	1.4 (1.69)	-2.7 (-3.4, -2.0)
	Dexmedetomidine 1 microgram/kg	129	54	<0.001	0.9 (1.51)	-3.1 (-3.8, -2.5)
	placebo	63	3	–	4.1 (3.02)	–
Study 2	Dexmedetomidine 1 microgram/kg	55	53	<0.001	1.1 (1.5)	-1.8 (-2.7, -0.9)
	placebo	50	14	–	2.9 (3.0)	–

a. Based on ITT population defined as all randomized and treated patients.

b. Normal approximation to the binomial with continuity correction.

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 72%) and 75 years or older (74%) as compared to patients below 65 years of age (47%). A reduced loading dose of 0.5 mcg/kg given over 10 minutes is recommended and a reduction in the maintenance infusion should be considered for patients greater than 65 years of age.

Paediatric population

Three pivotal studies in ICU sedation did not meet their primary efficacy endpoint, and the safety data were insufficient to fully characterise the safety profile of dexmedetomidine. One open-label ICU sedation study conducted in Japanese patients did meet its primary efficacy endpoint.

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

The safety profile of dexmedetomidine 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.

5.2 Pharmacokinetic properties

Following intravenous administration of Dexmedetomidine-AFT, dexmedetomidine exhibits the following pharmacokinetic parameters: rapid distribution phase with a distribution half-life ($t_{½}$) of approximately six minutes; terminal elimination half-life ($t_{½}$) approximately two hours; steady-state volume of distribution (V_{ss}) approximately 118 litres. Clearance (CL) has an estimated value of 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

Parameter	**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)			
	0.3/0.17	**0.3/0.17**	**0.6/0.33**	**1.25/0.70**
$t_{1/2}$*, 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
Avg C_{ss}†, ng/mL	0.27 ± 0.05	0.27 ± 0.05	0.67 ± 0.10	1.37 ± 0.20

* Presented as harmonic mean and pseudo standard deviation.

† Mean Css = Average steady-state concentration of dexmedetomidine. The mean Css was calculated based on post-dose sampling from 2.5-9 hour samples for 12 hour infusion and 2.5-18 hour samples for 24 hour infusion.

The loading doses for each of the above indicated groups were 0.5, 0.5, 1 and 2.2 mcg/kg, respectively.

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.

Biotransformation

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.

Elimination

The terminal elimination half-life (t½) 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.

Special populations

Male and female patients

No difference in dexmedetomidine pharmacokinetics due to gender was observed.

Elderly (over 65 years)

The pharmacokinetic profile of dexmedetomidine was not altered by age. There were no differences in the pharmacokinetics of dexmedetomidine hydrochloride in young (18-40 years), middle age (41-65 years), and elderly (>65 years) subjects. 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 and adolescents

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

Patients with impairment

Dexmedetomidine 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 section 4.2).

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 is dosed to effect, it may be necessary to consider dose reduction depending on the degree of hepatic impairment (see section 4.2).

Drug Interaction

In vitro studies did not demonstrate evidence for clinically relevant cytochrome P450-mediated drug interactions

5.3 Preclinical safety data

Carcinogenicity

Animal carcinogenicity studies have not been performed with dexmedetomidine.

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). Dexmedetomidine was clastogenic in the in vitro human lymphocyte chromosome aberration test with, but not without, rat S9 metabolic activation. In contrast, dexmedetomidine was not clastogenic in the in vitro human lymphocyte chromosome aberration test with or without human S9 metabolic activation. Although dexmedetomidine was clastogenic in an *in vivo* mouse micronucleus test in NMRI mice, there was no evidence of clastogenicity in CD-1 mice.

Impairment of fertility

Fertility in male or female rats was not affected after daily subcutaneous injections of dexmedetomidine at doses up to 54 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m^2 basis) administered from 10 weeks prior to mating in males, and 3 weeks prior to mating and during mating in females.

Animal toxicology and/or pharmacology

There were no differences in the adrenocorticotropic hormone (ACTH)-stimulated cortisol response in dogs following a single dose of dexmedetomidine compared to saline control. However, after continuous subcutaneous infusions of dexmedetomidine at 3 mcg/kg/hr and 10 mcg/kg/hr for one week in dogs (exposures estimated to be within the clinical range), the ACTH-stimulated cortisol response was diminished by approximately 27% and 40%, respectively, compared to saline-treated control animals indicating a dose-dependent adrenal suppression.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, Hydrochloric Acid, Sodium Hydroxide, Water for injections.

6.2 Incompatibilities

Compatibility of dexmedetomidine with co-administration of blood, serum, or plasma has not been established. Dexmedetomidine-AFT must not be mixed with other medicinal products.

Dexmedetomidine has been shown to be incompatible when administered with amphotericin B and

diazepam.

Compatibility with natural rubber

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

6.3 Shelf life

36 months.

After dilution: To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2 ° C-8 °C for not more than 24 hours.

6.4 Special precautions for storage

Store below 30 °C. For storage conditions after dilution of the medicine, see section 6.3.

6.5 Nature and contents of container

Available in 2 mL glass ampoule.

6.6 Special precautions for disposal and other handling

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

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Dexmedetomidine-AFT must be diluted with 0.9% sodium chloride injection to achieve required concentration (4 microgram/mL) prior to administration.

Preparation of infusion solutions is the same, whether for the loading dose or maintenance.

To prepare the infusion, withdraw 2 mL of dexmedetomidine hydrochloride concentrate for infusion solution and add to 48 mL of 0.9% sodium chloride to total 50 mL. Shake gently to mix well. Use as soon as practicable after dilution to reduce microbiological hazard. If storage is necessary, hold at 2 °C -8 °C for not more than 24 hours. Parenteral products should be inspected visually for particulate matter and discolouration prior to administration.

Dexmedetomidine-AFT has been shown to be compatible when administered with the following intravenous fluids: Lactated Ringers, 5% Glucose in Water, 0.9% Sodium Chloride in Water, 20% Mannitol in Water.

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.

7. MEDICINE SCHEDULE

Prescription Only Medicine.

8. SPONSOR

AFT Pharmaceuticals Limited
PO Box 33-203
Takapuna
Auckland 0740
Phone: 0800 423 823

9. DATE OF FIRST APPROVAL

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