DATA SHEET

1. PRODUCT NAME

Dexmedetomidine-Teva (Dexmedetomidine hydrochloride) (100 micrograms/mL) concentrate for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dexmedetomidine-Teva is a sterile, non-pyrogenic solution suitable for intravenous infusion.
The active ingredient in Dexmedetomidine-Teva is dexmedetomidine as hydrochloride.

Each 2 mL of Dexmedetomidine-Teva contains 236 micrograms of dexmedetomidine hydrochloride (equivalent to 200 micrograms dexmedetomidine base) and 18 mg of sodium chloride in water for injections. The solution is preservative-free and contains no additives or chemical stabilisers.

Dexmedetomidine-Teva is presented in a 2 mL vial, and must be diluted prior to use.

For a full list of excipients, see **Section 6.1.**

3. PHARMACEUTICAL FORM

Concentrate for infusion.

Dexmedetomidine-Teva (dexmedetomidine hydrochloride) 100 micrograms/mL is supplied clear, colourless isotonic solution with a pH 4.5 – 7.0. Dexmedetomidine-Teva is presented in 2 mL vial and must be diluted prior to use.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ICU Sedation
For sedation of initially intubated patients during treatment in an intensive care setting. The use of Dexmedetomidine-Teva by continuous infusion in these patients should not exceed 24 hours.

Procedural Sedation
For sedation of non-intubated 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 is generally initiated with a loading infusion of 1 (one) microgram/kg over 10 to 20 minutes, if needed. The use of dexmedetomidine 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/hr*. 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/hr 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/hr or higher. Dosages as low as 0.05 microgram/kg/hr have been used in clinical studies. Patients receiving dexmedetomidine have been observed to be rousable and alert when stimulated. This is an expected component of dexmedetomidine sedation and should not be considered a lack of efficacy in the absence of other clinical signs and symptoms.

*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.

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

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 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 should generally be initiated at 0.6

microgram/kg/hr and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 microgram/kg/hr for all procedures. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation.

Following the loading dose in awake fibreoptic intubation, a fixed maintenance dose of 0.7 microgram/kg/hr should be used.

A dose reduction should be considered in patients with impaired hepatic function and in patients over 65 years of age.

Children

The safety and efficacy of dexmedetomidine has not been studied in children.

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 medicine before administration, see **6.6 Special precautions for disposal and other handling**.

4.3 Contraindications

Dexmedetomidine is contraindicated in patients with a known hypersensitivity to dexmedetomidine.

4.4 Special warnings and precautions for use

Drug Administration

Dexmedetomidine should be administered only by persons skilled in the management of patients in the intensive care or operating room setting. Continuous electrocardiogram (ECG), blood pressure, and oxygen saturation monitoring are recommended during infusion of dexmedetomidine. Dexmedetomidine may cause reduced lacrimation. Lubrication of the patient's eyes should be considered when administering dexmedetomidine to avoid corneal dryness.

Dexmedetomidine 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 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. If medical intervention is required, treatment may include decreasing or stopping the infusion of dexmedetomidine, 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 agent (e.g., glycopyrronium bromide (glycopyrrolate), atropine) should be considered to modify vagal tone. In clinical trials, glycopyrronium bromide (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 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, coadministration 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.

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: Withdrawal symptoms were not seen after discontinuation of short term infusions of dexmedetomidine (< 6 hrs).

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 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/hr were not associated with significant adrenocortical suppression.

Hyperthermia

Dexmedetomidine may induce hyperthermia that may be resistant to traditional cooling methods. Dexmedetomidine 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 Dose and method of administration**).

Paediatric Use

Safety and efficacy of dexmedetomidine in children below 18 years of age have not been established for procedural or ICU sedation. Therefore, dexmedetomidine is not recommended in this 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.

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.

ICU Sedation

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 **4.8 Undesirable effects**).

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

Procedural Sedation

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 PRECEDEX-treated patients 65 years or older (71.9%) and 75 years or older (73.5%) as compared to patients <65 years (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 section 4.2).

4.5 Interaction with other medicines and other forms of interaction

General: *In vitro* studies indicate that clinically relevant cytochrome P450 mediated drug interactions are unlikely.

Anesthetics/Sedatives/Hypnotics/Opioids: Co-administration of dexmedetomidine is likely to lead to an enhancement of effects with anesthetics, 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.

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.

Pregnancy

Category B1[1]: Radiolabelled dexmedetomidine administered subcutaneously to female rats on gestation day 18 crossed the placental barrier to foetal 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, foetal 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 foetal body weight or embryo foetal 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 should be used during pregnancy only if the potential benefits justify the potential risk to the foetus. 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 foetus.

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

Labor and Delivery
The safety of dexmedetomidine in labor 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.

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

[1] Category B1: Drugs which have been taken by only 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 foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage

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/hr (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% 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/hr (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% > 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 Special warnings and precautions**).

***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/hr (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% > 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		
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. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypotension and bradycardia were the most common adverse reactions associated with the use of dexmedetomidine during post approval use of the drug.

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

Body System	Preferred Term
Body as a Whole	Fever, Hyperpyrexia, Hypovolaemia, Light anaesthesia, Pain, Rigors
Cardiovascular Disorders, General	Blood pressure fluctuation, Heart disorder, Hypertension, Hypotension, Myocardial infarction
Central and Peripheral Nervous System Disorders	Dizziness, Headache, Neuralgia, Neuritis, Speech disorder, Convulsion
Gastrointestinal System Disorders	Abdominal pain, Diarrhoea, Vomiting, Nausea
Heart Rate and Rhythm Disorders	Arrhythmia, Ventricular arrhythmia, Bradycardia, Hypoxia, AV block, Cardiac arrest, Extrasystoles, Atrial fibrillation, Heart block, T wave inversion, Tachycardia, Supraventricular tachycardia, Ventricular tachycardia
Liver and Biliary System Disorders	Increased gamma-glutamyl transpeptidase, Hepatic function abnormal, Hyperbilirubinaemia, Increased alanine transaminase, Increased aspartate aminotransferase
Metabolic and Nutritional Disorders	Acidosis, Respiratory acidosis, Hyperkalaemia, Increased alkaline phosphatase, Thirst, Hypoglycaemia, hypernatraemia
Psychiatric Disorders	Agitation, Confusion, Delirium, Hallucination, Illusion
Red Blood Cell Disorders	Anaemia
Renal disorders	Urea increased, Oliguria, polyuria
Respiratory System Disorders	Apnoea, Bronchospasm, Dyspnoea, Hypercapnia, Hypoventilation, Hypoxia, Pulmonary congestion
Skin and Appendages Disorders	Increased sweating
Vascular disorders	Haemorrhage
Vision Disorders	Photopsia, Abnormal vision

Dependence

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

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://nzphvc.otago.ac.nz/reporting/

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.

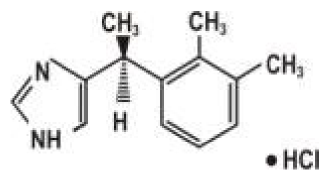
Of five patients reported with overdose of dexmedetomidine in the Phase II/III ICU sedation studies, two had no symptoms reported; one patient received a 2microgram/kg loading dose over 10 minutes (twice the recommended loading dose) and one patient received a maintenance infusion of 0.8microgram/kg/hr.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

Pharmacotherapeutic group: Psycholeptics, other hypnotics and sedatives, ATC code: N05CM18

Mechanism of action

Dexmedetomidine is a relatively selective alpha $_2$-adrenoreceptor agonist with a broad range of 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 intravenous (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 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.

Two of 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 patients were randomised to receive placebo and 178 to receive dexmedetomidine by intravenous infusion at a dose of 0.4 microgram/kg/hr (with allowed adjustment between 0.2 and 0.7 microgram/kg/hr) 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)

Study One

	Placebo N=175	dexmedetomidine N=178	p-value
Mean total dose (mg) of midazolam Standard deviation	19 mg 53 mg	5 mg 19 mg	0.011*
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 patients were randomised to receive placebo and 203 to receive dexmedetomidine by intravenous infusion at a dose of 0.4 microgram/kg/hr (with allowed adjustment between 0.2 and 0.7 microgram/kg/hr) 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)

Study Two

	Placebo N=198	Dexmedetomidine N=203	p-value
Mean total dose (mg) of propofol Standard deviation	513 mg 782 mg	72 mg 249 mg	<0.0001*
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.

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/hr. The maintenance infusion of study drug could be titrated from 0.2 microgram/kg/hr to 1 microgram/kg/hr 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 score >2 (Table 5) during AFOI. Patients were randomised to receive a dexmedetomidine loading infusion of 1 microgram/kg or placebo (normal saline) given over 10 minutes followed by a fixed maintenance infusion of 0.7 microgram/kg/hr. 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 >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	r9.7	<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)	1
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.

5.3 Pharmacokinetic properties

Following intravenous administration of dexmedetomidine, dexmedetomidine exhibits the following pharmacokinetic characteristics: rapid distribution phase with a distribution half-life ($t_{½}$ a) of about six minutes; terminal elimination half-life ($t_{½}$) approximately two hours; steady-state volume of distribution (Vss) approximately 118 liters. Clearance has an estimated value of about 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/hr 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/hr (target concentration of 0.3 ng/mL) for 12 and 24 hours, 0.33 microgram/kg/hr (target concentration of 0.6 ng/mL) for 24 hours, and 0.70 microgram/kg/hr (target concentration of 1.25 ng/mL) for 24 hours.

Table 10: Mean ± SD Pharmacokinetic Parameters

	Loading Infusion (min)/Total infusion duration (hrs)			
	10 min/12 hrs	**10 min/24 hrs**	**10 min/24 hrs**	**35 min/24 hrs**
	Dexmedetomidine Target Concentration (ng/mL) and Dose (microgram/kg/hr)			
	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
Vss, litre	88.7 ± 22.9	102.4 ± 20.3	93.6 ± 17.0	99.6 ± 17.8
AvgCss†, 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.
† Avg Css = Average steady-state concentration of dexmedetomidine.
(2.5 - 9 hour samples for 12 hour infusion and 2.5 - 18 hour samples for 24 hour infusions).

Distribution
The steady-state volume of distribution (Vss) of dexmedetomidine is approximately 118 liters. Dexmedetomidine protein binding was assessed in the plasma of normal healthy male and female volunteers. The average protein binding was 94% and was constant across the different concentrations tested. Protein binding was similar in males and females. The fraction of dexmedetomidine that was bound to plasma proteins was statistically significantly decreased in subjects with hepatic impairment compared 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 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-hydroxy dexmedetomidine, the glucuronide of 3-hydroxy dexmedetomidine, and 3-carboxy dexmedetomidine; and *N*-methylation of dexmedetomidine to generate 3-hydroxy *N*-methyl dexmedetomidine, 3-carboxy *N*-methyl dexmedetomidine, and *N*-methyldexmedetomidine *O*-glucuronide.

Elimination

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 radiolabeled 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-hydroxy dexmedetomidine, the glucuronide of 3-hydroxy dexmedetomidine, and 3-carboxylic acid dexmedetomidine together represented approximately 14% of the dose in urine. *N*-methylation of dexmedetomidine to form 3-hydroxy *N*-methyl dexmedetomidine, 3-carboxy *N*-methyl dexmedetomidine, and *N*-methyl *O*-glucuronide dexmedetomidine 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

Gender

No difference in dexmedetomidine pharmacokinetics due to gender was observed.

Elderly (>65 years)

The pharmacokinetic profile of dexmedetomidine 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 and Adolescents:

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

Renal Impairment

Dexmedetomidine pharmacokinetics (C_{max}, T_{max}, AUC, $t_{½}$, CL, and V_{ss}) were not different in subjects with severe renal impairment (Cr Cl: <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 Dose and method of administration**).

Hepatic Impairment

In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values were lower than in healthy subjects. The mean clearance values for subjects 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 Dose and method of administration**).

5.4 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). 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.

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. Dexmedetomidine-Teva must not be mixed with other medicinal products.

6.3 Shelf life

24 months

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

6.4 Special precautions for storage

Store in the original container. No special storage conditions are needed.
Store below 25°C.

For storage conditions after dilution, see section 6.3.

6.5 Nature and contents of container

Available in 2mL glass vials

6.6 Special precautions for disposal and other handling

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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

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

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

Dexmedetomidine 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 bromide, phenylephrine hydrochloride.

Vials are intended for single patient use only.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Teva Pharma (New Zealand) Limited
PO Box 128 244
Remuera
Auckland, New Zealand, 1541
Toll Free Number: 0800 800 097

9. DATE OF FIRST APPROVAL

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