

Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Precidex Injection

2. Qualitative and quantitative composition

Each ml contains:

Dexmedetomidine (as Dexmedetomidine HCl)...100mcg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Clear and colorless solution

4. Clinical particulars

4.1 Therapeutic indications

Precidex (Dexmedetomidine Injection USP) is indicated for:

- Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting.
- Sedation of non-intubated patients prior to and/or during surgical and other procedures.

4.2 Posology and method of administration

DOSAGE AND

ADMINISTRATION

- Individualize and titrate Precidex (Dexmedetomidine Injection USP) dosing to desired clinical effect.
- Administer Precidex (Dexmedetomidine Injection USP) using a controlled infusion device.
- Dilute ampoule contents in 0.9% sodium chloride solution to achieve required concentration (4 mcg/ml) prior to administration.

For Intensive Care Unit Sedation: Generally initiate at 1 mcg/kg over 10 minutes, followed by a maintenance infusion of 0.2 to 0.7 mcg/kg/hr.

For Procedural Sedation: Generally initiate at 1 mcg/kg over 10 minutes, followed by a maintenance infusion initiated at 0.6 mcg/kg/hr and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 mcg/kg/hr.

Alternative Doses: Recommended for patients over 65 years of age and awake fiberoptic intubation patients is 0.5 mcg/kg over 10 minutes

For patients with impaired hepatic function: a dose reduction should be considered

Preparation of Solution

Strict aseptic technique must always be maintained during handling of Precidex (Dexmedetomidine Injection USP). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Precidex (Dexmedetomidine Injection USP), Concentrate, 200 mcg/2ml (100 mcg/ml) Precidex Injection must be diluted in 0.9% Sodium Chloride solution to achieve required concentration (4 mcg/ml) prior to administration.

Preparation of solutions is the same, whether for the loading dose or maintenance infusion. To prepare the infusion, withdraw 2 ml of Precidex (Dexmedetomidine Injection USP) and add to 48 ml of 0.9% Sodium Chloride injection to a total of 50 ml. Shake gently to mix well.

Precidex (Dexmedetomidine Injection USP) has been shown to be compatible when administered with the following intravenous fluids:

- 0.9% Sodium Chloride in water
- 5% Dextrose in water
- 20% Mannitol
- Lactated Ringer's solution
- 100 mg/ml Magnesium Sulfate solution
- 0.3% Potassium Chloride solution

4.3 Contraindications

Known hypersensitivity to Dexmedetomidine or any of the excipients.

4.4 Special warnings and precautions for use

Monitoring

Precidex is intended for use in an intensive care setting, operating room and during diagnostic procedures. The use in other environments is not recommended. All patients should have continuous cardiac monitoring during Precidex infusion. Respiration should be monitored in non-intubated patients due to the risk of respiratory depression and in some case apnoea. The time to recovery after the use of dexmedetomidine was reported to be approximately one hour. When used in an outpatient setting close monitoring should continue for at least one hour (or longer based on the patient condition), with medical supervision continued for at least one further hour to ensure the safety of the patient.

General precautions

Precidex should not be given as a bolus dose and in the ICU a loading dose is not recommended. Users should therefore be ready to use an alternative sedative for acute control of agitation or during procedures, especially during the first few hours of

treatment. During procedural sedation a small bolus of another sedative may be used if a rapid increase in sedation level is required.

Some patients receiving Precidex 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.

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

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

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

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

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

When Precidex is used in an outpatient setting patients should normally be discharged into the care of a suitable third party. Patients should be advised to refrain from driving or other hazardous tasks and where possible to avoid the use of other agents that may sedate (e.g, benzodiazepines, opioids, alcohol) for a suitable period of time based on observed effects of dexmedetomidine, the procedure, concomitant medications, the age and the condition of the patient.

Caution should be exercised when administering dexmedetomidine to elderly patients. Elderly patients over 65 years of age may be more prone to hypotension with the administration of dexmedetomidine, including a loading dose, for procedures. A dose reduction should be considered.

Cardio-vascular effects and precautions

Dexmedetomidine reduces heart rate and blood pressure through central sympatholysis but at higher concentrations causes peripheral vasoconstriction leading to hypertension. Dexmedetomidine is therefore not suitable in patients with severe cardiovascular instability.

Caution should be exercised when administering dexmedetomidine to patients with pre-existing bradycardia. Data on the effects of Precidex in patients with heart rate <60 are very limited and particular care should be taken with such patients. Bradycardia does not normally require treatment, but has commonly responded to anti-cholinergic medicine or dose reduction where needed. Patients with high physical fitness and slow resting heart rate may be particularly sensitive to bradycardic effects of alpha-2 receptor agonists and cases of transient sinus arrest have been reported. Also cases of cardiac arrest, often preceded by bradycardia or atrioventricular block, have been reported

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

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

Transient hypertension has been observed primarily during the loading dose in association with the peripheral vasoconstrictive effects of dexmedetomidine and a loading dose is not recommended in ICU sedation. Treatment of hypertension has generally not been necessary but decreasing the continuous infusion rate may be advisable.

Local vasoconstriction at higher concentration may be of greater significance in patients with ischaemic heart disease or severe cerebrovascular disease who should be monitored closely. Dose reduction or discontinuation should be considered in a patient developing signs of myocardial or cerebral ischaemia.

Caution is advised when administering dexmedetomidine together with spinal or epidural anaesthesia due to possible increased risk of hypotension or bradycardia.

Patients with hepatic impairment

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

Patients with neurological disorders

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

Other

Alpha-2 agonists have rarely been associated with withdrawal reactions when stopped abruptly after prolonged use. This possibility should be considered if the patient develops agitation and hypertension shortly after stopping dexmedetomidine.

Dexmedetomidine may induce hyperthermia that may be resistant to traditional cooling methods. Dexmedetomidine treatment should be discontinued in the event of a sustained unexplained fever and is not recommended for use in malignant hyperthermia-sensitive patients. Precidex contains less than 1 mmol sodium (23 mg) per ml.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Co-administration of dexmedetomidine with anaesthetics, sedatives, hypnotics, and opioids is likely to lead to an enhancement of effects, including sedative, anaesthetic and cardiorespiratory effects. Specific studies have confirmed enhanced effects with isoflurane, propofol, alfentanil, and midazolam.

No pharmacokinetic interactions between dexmedetomidine and isoflurane, propofol, alfentanil and midazolam have been demonstrated. However, due to possible pharmacodynamic interactions, when co-administered with dexmedetomidine, a reduction in dosage of dexmedetomidine or the concomitant anaesthetic, sedative, hypnotic or opioid may be required.

Inhibition of CYP enzymes including CYP2B6 by dexmedetomidine has been studied in human liver microsome incubations. In vitro study suggests that interaction potential in

vivo exists between dexmedetomidine and substrates with dominant CYP2B6 metabolism.

Induction of dexmedetomidine *in vitro* was observed on CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP3A4, and induction *in vivo* cannot be excluded. The clinical significance is unknown.

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

Pregnancy

There are no or limited amount of data from the use of dexmedetomidine in pregnant women.

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

Breastfeeding

Dexmedetomidine is excreted in human milk, however levels will be below the limit of detection by 24 hours following treatment discontinuation. A risk to infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue dexmedetomidine therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

In the rat fertility study, dexmedetomidine had no effect on male or female fertility. No human data on fertility are available.

4.7 Effects on ability to drive and use machines

Patients should be advised to refrain from driving or other hazardous tasks for a suitable period of time after receiving Precidex for procedural sedation.

4.8 Undesirable effects

Precidex (Dexmedetomidine Injection USP) can cause low or high blood pressure, slowing of the heartbeat, and dry mouth. If Precidex (Dexmedetomidine Injection USP) is given in an infusion for more than 6 hours, it is important to report to your doctor any nervousness, agitation, and headaches that may occur for up to 48 hours. Additionally, you should report symptoms that may occur within 48 hours after you are given Precidex (Dexmedetomidine Injection USP) such as: weakness, confusion, excessive sweating, weight loss, abdominal pain, salt cravings, diarrhea, constipation, dizziness or lightheadedness. Report immediately any pounding or unusual heartbeat, or respiratory difficulty.

After exposure to Precidex (Dexmedetomidine Injection USP) you should contact your physician or anaesthesiologist if you have any of the following reactions:

Hypotension (low blood pressure), Hypertension (high blood pressure), Bradycardia (slow heart beat), Tachycardia (fast heart beat), Dry mouth uncommon effects like Nervousness, Headaches, Agitation, Weakness Confusion, Excessive sweating, Weight loss, Abdominal pain, Salt cravings, Diarrhea, Constipation, Dizziness/ Lightheadedness

and Respiratory difficulty.

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions to the National Regulatory Authority.

4.9 Overdose

Symptoms

Several cases of dexmedetomidine overdose have been reported both in the clinical trial and the post-marketing data. The reported highest infusion rates of dexmedetomidine in these cases have reached up to 60 µg/kg/h for 36 minutes and 30 µg/kg/h for 15 minutes in a 20-month-old child and in an adult, respectively. The most common adverse reactions reported in conjunction with overdose include bradycardia, hypotension, hypertension, oversedation, respiratory depression and cardiac arrest.

Management

In cases of overdose with clinical symptoms, dexmedetomidine infusion should be reduced or stopped. Expected effects are primarily cardiovascular and should be treated as clinically indicated. At high concentration hypertension may be more prominent than hypotension. In clinical studies, cases of sinus arrest reversed spontaneously or responded to treatment with atropine and glycopyrrolate. Resuscitation was required in isolated cases of severe overdose resulting in cardiac arrest.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

Dexmedetomidine is a selective alpha-2 receptor agonist with a broad range of pharmacological properties. It has a sympatholytic effect through decrease of the release of noradrenaline in sympathetic nerve endings. The sedative effects are mediated through decreased firing of locus coeruleus, the predominant noradrenergic nucleus, situated in the brainstem. Dexmedetomidine has analgesic and anaesthetic/analgesic-sparing effects. The cardiovascular effects depend on the dose; with lower infusion rates the central effects dominate leading to decrease in heart rate and blood pressure. With higher doses, peripheral vasoconstricting effects prevail leading to an increase in systemic vascular resistance and blood pressure, while the bradycardic effect is further emphasized. Dexmedetomidine is relatively free from respiratory depressive effects when given as monotherapy to healthy subjects.

Sedation of adult ICU (Intensive Care Unit) patients

In placebo-controlled trials in a post-operative ICU population previously intubated and sedated with midazolam or propofol, Precidex significantly reduced the requirement for both rescue sedative (midazolam or propofol) and opioids during sedation for up to 24 hours. Most dexmedetomidine patients required no additional sedative treatment. Patients could be successfully extubated without stopping the Precidex infusion. Studies from outside the ICU have confirmed that Precidex can be administered safely to patients without endotracheal intubation provided adequate monitoring is in place.

Dexmedetomidine was similar to midazolam (Ratio 1.07; 95% CI 0.971, 1.176) and

propofol (Ratio 1.00; 95% CI 0.922, 1.075) on the time in target sedation range in a predominantly medical population requiring prolonged light to moderate sedation (RASS 0 to -3) in the ICU for up to 14 days, reduced the duration of mechanical ventilation compared to midazolam and reduced the time to extubation compared to midazolam and propofol. Compared to both propofol and midazolam, patients were more easily roused, more cooperative and better able to communicate whether or not they had pain. Dexmedetomidine treated patients had more frequent hypotension and bradycardia but less tachycardia than those receiving midazolam and more frequent tachycardia but similar hypotension to propofol-treated patients. Delirium measured by the CAM-ICU scale was reduced in a study compared to midazolam and delirium-related adverse events were lower on dexmedetomidine compared to propofol. Those patients who withdrew due to insufficient sedation were switched to either propofol or midazolam. The risk of insufficient sedation was increased in patients who were difficult to sedate with standard care immediately prior to switching.

Evidence of paediatric efficacy was seen in a dose-controlled ICU study in a largely post-operative population aged 1 month to ≤ 17 years. Approximately 50% of patients treated with dexmedetomidine did not require rescue addition of midazolam during a median treatment period of 20.3 hours, not exceeding 24 hours. Data on treatment for > 24 hours is not available. Data in new-born infants (28 – 44 weeks gestation) is very limited and restricted to low doses (≤ 0.2 mcg/kg/h). New-born infants may be particularly sensitive to the bradycardic effects of Precidex in the presence of hypothermia and in conditions of heart rate-dependent cardiac output.

In double blind comparator-controlled ICU studies the incidence of cortisol suppression in patients treated with dexmedetomidine (n=778) was 0.5% compared with 0% in patients treated with either midazolam (n=338) or propofol (n=275). The event was reported as mild in 1 and moderate in 3 cases.

Procedural/awake sedation

The safety and efficacy of dexmedetomidine for sedation of non-intubated patients prior to and/or during surgical and diagnostic procedures was evaluated in two randomized, double-blind, placebo-controlled multicentre clinical trials.

• Study 1 randomized patients undergoing elective surgeries/procedures under monitored anaesthesia care and local/regional anaesthesia to receive a loading infusion of dexmedetomidine either 1 $\mu\text{g/kg}$ (n=129) or 0.5 $\mu\text{g/kg}$ (n=134), or placebo (normal saline; n=63) given over 10 minutes and followed by a maintenance infusion started at 0.6 $\mu\text{g/kg/h}$. The maintenance infusion of study drug could be titrated from 0.2 $\mu\text{g/kg/h}$ to 1 $\mu\text{g/kg/h}$. The proportion of patients that achieved the targeted sedation level (Observer's Assessment of Alertness/Sedation Scale ≤ 4) without need for rescue midazolam was 54% of the patients receiving dexmedetomidine 1 $\mu\text{g/kg}$ and 40% of the patients receiving dexmedetomidine 0.5 $\mu\text{g/kg}$ compared to 3% of patients receiving the placebo. The risk difference in proportion of subjects randomized to dexmedetomidine 1 $\mu\text{g/kg}$ group and dexmedetomidine 0.5 $\mu\text{g/kg}$ group not requiring rescue midazolam was 48% (95% CI: 37 % - 57%) and 40% (95% CI: 28 % - 48%), respectively compared placebo. The median (range) midazolam rescue dose was 1.5 (0.5-7.0) mg in the dexmedetomidine 1.0 $\mu\text{g/kg}$ group, 2.0 (0.5-8.0) mg in the dexmedetomidine 0.5 $\mu\text{g/kg}$ group, and 4.0 (0.5-14.0) mg in the placebo group. The difference in means in dose of rescue midazolam in dexmedetomidine 1 $\mu\text{g/kg}$ and dexmedetomidine 0.5 $\mu\text{g/kg}$ group compared to placebo was -3.1 mg (95% CI: -3.8 - -2.5) and -2.7 mg (95% CI: -3.3 - -2.1), respectively favoring dexmedetomidine.

The median time to first rescue dose was 114 minutes in the dexmedetomidine 1.0 µg/kg group, 40 minutes in the dexmedetomidine 0.5 µg/kg group, and 20 minutes in the placebo group.

• Study 2 randomized patients undergoing awake fiberoptic intubation under topical anaesthesia to receive a loading infusion of dexmedetomidine 1 µg/kg (n=55) or placebo (normal saline) (n=50) given over 10 minutes and followed by a fixed maintenance infusion of 0.7 µg/kg/h. To maintain a Ramsay Sedation Scale ≥ 2 53% of the patients receiving dexmedetomidine did not require midazolam rescue vs. 14% of patients receiving placebo. The risk difference in proportion of subjects randomised to dexmedetomidine not requiring rescue midazolam was 43% (95% CI: 23 % - 57%) compared placebo. The mean midazolam rescue dose was 1.1 mg in the dexmedetomidine group, and 2.8 mg in the placebo group. The difference in means in dose of rescue midazolam was -1.8 mg (95% CI: -2.7 - - 0.86) favouring dexmedetomidine.

5.2 Pharmacokinetic properties

The pharmacokinetics of dexmedetomidine has been assessed following short term IV administration in healthy volunteers and long-term infusion in ICU population.

Distribution

Dexmedetomidine exhibits a two-compartment disposition model. In healthy volunteers it exhibits a rapid distribution phase with a central estimate of the distribution half-life ($t_{1/2\alpha}$) of about 6 minutes. The mean estimate of the terminal elimination half-life ($t_{1/2}$) is approximately 1.9 to 2.5 h (min 1.35, max 3.68 h) and the mean estimate of the steady-state volume of distribution (V_{ss}) is approximately 1.16 to 2.16 l/kg (90 to 151 litres). Plasma clearance (Cl) has a mean estimated value of 0.46 to 0.73 l/h/kg (35.7 to 51.1 l/h). The mean body weight associated with these V_{ss} and Cl estimates was 69 kg. Plasma pharmacokinetics of dexmedetomidine is similar in the ICU population following infusion >24 h. The estimated pharmacokinetic parameters are: $t_{1/2}$ approximately 1.5 hours, V_{ss} approximately 93 litres and Cl approximately 43 l/h. The pharmacokinetics of dexmedetomidine is linear in the dosing range from 0.2 to 1.4 µg/kg/h and it does not accumulate in treatments lasting up to 14 days.

Dexmedetomidine is 94% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0.85 to 85 ng/ml. Dexmedetomidine binds to both human serum albumin and Alpha-1-acid glycoprotein with serum albumin as the major binding protein of dexmedetomidine in plasma.

Biotransformation and Elimination

Dexmedetomidine is eliminated by extensive metabolism in the liver. There are three types of initial metabolic reactions; direct N-glucuronidation, direct N-methylation and cytochrome P450 catalysed oxidation. The most abundant circulating dexmedetomidine metabolites are two isomeric N-glucuronides. Metabolite H-1, N-methyl 3-hydroxymethyl dexmedetomidine O-glucuronide, is also a major circulating product of dexmedetomidine biotransformation. Cytochrome P-450 catalyses the formation of two minor circulating metabolites, 3-hydroxymethyl dexmedetomidine produced by hydroxylation at the 3-methyl group of dexmedetomidine and H-3 produced by oxidation in the imidazole ring. Available data suggest that the formation of the oxidised metabolites is mediated by several CYP forms (CYP2A6, CYP1A2, CYP2E1, CYP2D6 and CYP2C19). These metabolites have negligible pharmacological activity.

Following IV administration of radiolabeled dexmedetomidine an average 95% of

radioactivity was recovered in the urine and 4% in the faeces after nine days. The major urinary metabolites are the two isomeric N-glucuronides, which together accounted for approximately 34% of the dose and N-methyl 3-hydroxymethyl dexmedetomidine O-glucuronide that accounted for 14.51% of the dose. The minor metabolites dexmedetomidine carboxylic acid, 3-hydroxymethyl dexmedetomidine and its O-glucuronide individually comprised 1.11 to 7.66% of the dose. Less than 1% of unchanged parent drug was recovered in the urine. Approximately 28% of the urinary metabolites are unidentified minor metabolites.

Special Populations

No major pharmacokinetic differences have been observed based on gender or age.

Dexmedetomidine plasma protein binding is decreased in subjects with hepatic impairment compared with healthy subjects. The mean percentage of unbound dexmedetomidine in plasma ranged from 8.5% in healthy subjects to 17.9% in subjects with severe hepatic impairment. Subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C) had decreased hepatic clearance of dexmedetomidine and prolonged plasma elimination $t_{1/2}$. The mean plasma clearance values of unbound dexmedetomidine for subjects with mild, moderate, and severe hepatic impairment were 59%, 51% and 32% of those observed in the normal healthy subjects, respectively. The mean

$t_{1/2}$ for the subjects with mild, moderate or severe hepatic impairment was prolonged to 3.9, 5.4, and 7.4 hours, respectively. Although dexmedetomidine is administered to effect, it may be necessary to consider initial/maintenance dose reduction in patients with hepatic impairment depending on the degree of impairment and the response.

The pharmacokinetics of dexmedetomidine in subjects with severe renal impairment (creatinine clearance <30 ml/min) is not altered relative to healthy subjects.

Data in new-born infants (28 - 44 weeks gestation) to children 17 years of age are limited. Dexmedetomidine half-life in children (1 months to 17 years) appears similar to that seen in adults, but in new-born infants (under 1 month) it appears higher. In the age groups 1 months to 6 years, body weight-adjusted plasma clearance appeared higher but decreased in older children. Body weight-adjusted plasma clearance in new-born infants (under 1 month) appeared lower (0.9 l/h/kg) than in the older groups due to immaturity. The available data is summarized in the following table;

Age	N	Mean (95% CI)	
		Cl (l/h/kg)	$t_{1/2}$ (h)
Under 1 month	28	0.93	4.47

		(0.76, 1.14)	(3.81, 5.25)
1 to < 6 months	14	1.21 (0.99, 1.48)	2.05 (1.59, 2.65)
6 to < 12 months	15	1.11 (0.94, 1.31)	2.01 (1.81, 2.22)
12 to < 24 months	13	1.06 (0.87, 1.29)	1.97 (1.62, 2.39)
2 to < 6 years	26	1.11 (1.00, 1.23)	1.75 (1.57, 1.96)
6 to < 17 years	28	0.80 (0.69, 0.92)	2.03 (1.78, 2.31)

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxicity.

In the reproductive toxicity studies, dexmedetomidine had no effect on male or female fertility in the rat, and no teratogenic effects were observed in the rat or rabbit. In the rabbit study intravenous administration of the maximum dose, 96 µg/kg/day, produced exposures that are similar to those observed clinically. In the rat, subcutaneous administration at the maximum dose, 200 µg/kg/day, caused an increase in embryofetal death and reduced the fetal body weight. These effects were associated with clear maternal toxicity. Reduced fetal body weight was noted also in the rat fertility study at dose 18 µg/kg/day and was accompanied with delayed ossification at dose 54 µg/kg/day. The observed exposure levels in the rat are below the clinical exposure range.

6. Pharmaceutical particulars

6.1 List of

excipients

Sodium

chloride

Water for

injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products. Compatibility studies have shown potential for adsorption of dexmedetomidine to some types of natural rubber. Although dexmedetomidine is dosed to effect, it is advisable to use components with synthetic or coated natural rubber gaskets.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at temperature below 30°C away from light.

6.5 Nature and contents of container

2ml clear glass USP type I ampoule, further packed in bleach board pack containing 02 ampoules with PVC tray and insert.

6.6 Special precautions for disposal and other handling

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

7. Marketing authorisation holder

Brookes Pharma Private Limited

58 & 59,

Sector 15, Korangi Industrial Area, Karachi-Pakistan

8. Marketing authorisation number(s)

H2022/CTD8293/17780

9. Date of first authorisation/renewal of the authorisation

2022 September 12

10. Date of revision of the text

2022 September 12