Emidex

Dexmedetomidine

EMIDEX 100MCG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

Composition:
Each ml contains 118mcg of dexmedetomidine hydrochloride equivalent to 100mcg dexmedetomidine

DESCRIPTION
A clear, colourless solution filled in a clear glass vial, when examined under suitable condition visibly, it is free from foreign particles.

Description after dilution: A clear, colourless solution.
Emidex has been shown to be compatible when administered the following intravenous fluids: 0.9% Sodium Chloride (NaCL) in water, 5% dextrose in water, 20% mannitol and lactated ringer's solution.

CLINICAL PHARMACOLOGY

Pharmacodynamics
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 emphasised. Dexmedetomidine is relatively free from respiratory depressive effects when given as monotherapy to healthy individuals.

Pharmacokinetics

Distribution
Dexmedetomidine exhibits a two-compartment disposition model. 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 (Vss) 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 Vss 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, Vss 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 individual with hepatic impairment. Individuals with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C) will have decreased hepatic clearance of dexmedetomidine and prolonged plasma elimination $t_{1/2}$. 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 severe renal impairment (creatinine clearance <30 ml/min) is not altered. 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.

INDICATIONS

Intensive Care Unit Sedation
Dexmedetomidine Injection is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Dexmedetomidine Injection should be administered by continuous infusion not to exceed 24 hours. Dexmedetomidine Injection has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post-extubation. It is not necessary to discontinue Dexmedetomidine Injection prior to extubation.

Procedural Sedation
Dexmedetomidine Injection is indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures.

DOSAGE AND ADMINISTRATION

Dosing Guidelines
Dexmedetomidine injection dosing should be individualized and titrated to desired clinical response.
Dexmedetomidine injection is not indicated for infusions lasting longer than 24 hours.
Dexmedetomidine injection should be administered using a controlled infusion device.

Dosage Information
Table 1: Dosage Information

INDICATION	DOSAGE AND ADMINISTRATION
Initiation of Intensive Care Unit Sedation	**For adult patients:** a loading infusion of one mcg/kg over 10 minutes. **For patients over 65 years of age:** a dose reduction should be considered. **For adult patients with impaired hepatic or renal function:** a dose reduction should be considered.
Maintenance of Intensive Care Unit Sedation	**For adult patients:** a maintenance infusion of 0.2 to 0.7 mcg/kg/hour. The rate of the maintenance infusion should be adjusted to achieve the desired level of sedation. **For patients over 65 years of age:** a dose reduction should be considered. **For adult patients with impaired hepatic or renal function:** a dose reduction should be considered.
Initiation of Procedural Sedation	**For adult patients:** a loading infusion of one mcg/kg over 10 minutes. For less invasive procedures such as ophthalmic surgery, a loading infusion of 0.5 mcg/kg given over 10 minutes may be suitable. **For awake fiberoptic intubation in adult patients:** a loading infusion of one mcg/kg over 10 minutes. **For patients over 65 years of age:** a loading infusion of 0.5 mcg/kg over 10 minutes. **For adult patients with impaired hepatic or renal function:** a dose reduction should be considered.
Maintenance of Procedural Sedation	**For adult patients:** the maintenance infusion is generally initiated at 0.6 mcg/kg/hour and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 mcg/kg/hour. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation. **For awake fiberoptic intubation in adult patients:** a maintenance infusion of 0.7 mcg/kg/hour is recommended until the endotracheal tube is secured. **For patients over 65 years of age:** a dose reduction should be considered. **For adult patients with impaired hepatic or renal function:** a dose reduction should be considered.

Dosage Adjustment
Due to possible pharmacodynamic interactions, a reduction in dosage of dexmedetomidine injection or other concomitant anesthetics, sedatives, hypnotics or opioids may be required when co-administered.
Dosage reductions may need to be considered for adult patients with hepatic or renal impairment, and geriatric patients.

Instruction for use
Preparation of Solution
Dexmedetomidine injection must be diluted with 0.9% sodium chloride injection to achieve required concentration (4 mcg/mL) prior to administration. Preparation of solutions is the same, whether for the loading dose or maintenance infusion.

Strict aseptic technique must always be maintained during handling of Dexmedetomidine injection.

To prepare the infusion, withdraw 2 mL of dexmedetomidine injection, and add to 48 mL of 0.9% sodium chloride injection to a total of 50 mL. Shake gently to mix well.

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

Administration with Other Fluids
Dexmedetomidine injection infusion should not be co-administered through the same intravenous catheter with blood or plasma because physical compatibility has not been established.

Dexmedetomidine injection has been shown to be incompatible when administered with the following drugs: amphotericin B, diazepam.

Emidex 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,

Compatibility with Natural Rubber
Compatibility studies have demonstrated the potential for absorption of dexmedetomidine injection to some types of natural rubber. Although dexmedetomidine injection is dosed to effect, it is advisable to use administration components made with synthetic or coated natural rubber gaskets.

ROUTE OF ADMINISTRATION
For Intravenous Use.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.
Advanced heart block (grade 2 or 3) unless paced.
Uncontrolled hypotension.
Acute cerebrovascular conditions.

WARNINGS AND PRECAUTION

Monitoring
Dexmedetomidine is intended for use in an intensive care setting and use in other environments is not recommended. All patients should have continuous cardiac monitoring during Dexmedetomidine infusion. Respiration should be monitored in non-intubated patients due to the risk of respiratory depression and in some case apnoea.

General precautions
Since Dexmedetomidine should not be administered by loading or bolus dose, users should be ready to use an alternative sedative for acute control of agitation or during procedures, especially during the first few hours of treatment.

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.

Dexmedetomidine should not be used as an 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.

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 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 or with severe cardiovascular instability.

Caution should be exercised when administering dexmedetomidine to patients with pre-existing bradycardia. Data on the effects of Dexmedetomidine 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.

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. 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.

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.

It is not known whether dexmedetomidine is safe to use in malignant hyperthermia-sensitive individuals therefore it is not recommended. Dexmedetomidine treatment should be discontinued in the event of a sustained unexplained fever.

DRUG INTERACTIONS

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.

PREGNANCY AND LACTATION

Pregnancy
There are no or limited amount of data from the use of dexmedetomidine in pregnant women. Dexmedetomidine is not recommended during pregnancy and in women of childbearing potential not using contraception.

Lactation
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
Fertility study in rats did not reveal any effect of dexmedetomidine on male or female fertility.

SIDE EFFECTS
The most frequently reported adverse reactions with dexmedetomidine are hypotension, hypertension and bradycardia.

Tabulated list of adverse reactions

Table 1. Adverse reactions

Metabolism and nutrition disorders	
Common:	Hyperglycaemia, hypoglycaemia
Uncommon:	Metabolic acidosis, hypoalbuminaemia
Psychiatric disorders	
Common:	Agitation
Uncommon:	Hallucination
Cardiac disorders	
Very common:	Bradycardia*
Common:	Myocardial ischaemia or infarction, tachycardia
Uncommon:	Atrioventricular block first degree, cardiac output decreased
Vascular disorders	
Very common:	Hypotension*, hypertension*
Respiratory, thoracic and mediastinal disorders	
Common:	Respiratory depression
Uncommon:	Dyspnoea, apnoea
Gastrointestinal disorders	
Common:	Nausea, vomiting, dry mouth
Uncommon:	Abdominal distension
General disorders and administration site conditions	
Common:	Withdrawal syndrome, hyperthermia
Uncommon:	Drug ineffective, thirst

* See section on Description of selected adverse reactions

Description of selected adverse reactions
Clinically significant hypotension or bradycardia should be treated as described in section warning and precaution. Bradycardia has occasionally led to sinus arrest or pause.

The symptoms responded to leg raising and anticholinergics such as atropine or glycopyrrolate. In isolated cases bradycardia has progressed to periods of asystole in patients with pre-existing bradycardia. Hypertension has been associated with the use of a loading dose and this reaction can be reduced by avoiding such a loading dose or reducing the infusion rate or size of the loading dose.

OVERDOSAGE

The most common adverse reactions reported in conjunction with overdose included bradycardia, hypotension, over sedation, somnolence and cardiac arrest.

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. 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

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

STORAGE

Store below 30ºC
Storage condition after dilution: Store at room temperature (<30°C) up to 48 hours.

SHELF LIFE

24 months
After dilution: Store at room temperature (<30°C) up to 48 hours.

PACKAGING AVAILABLE:

Pack size: 25 units of 2mL Single Dose Vial
Dexmedetomidine Injection, 200 mcg/2 mL (100 mcg/mL) is available in 2 mL Type 1 clear glass vials. The strength is based on the dexmedetomidine base. Vials are intended for single dose only.

MANUFACTURED BY

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MAL NO.:

MAL21036022AZ

REVISION DATE:

08/06/2022