

Renal and Urinary Disorders	Oliguria, polyuria
Respiratory Thoracic and Mediastinal Disorders	Apnea, bronchospasm, dyspnea, hypercapnia, hypoventilation, hypoxia, pulmonary congestion, respiratory acidosis
Skin and Subcutaneous Tissue Disorders	Hyperhidrosis, pruritus, rash, urticaria
Surgical and Medical Procedures	Light anesthesia
Vascular Disorders	Hemorrhage, blood pressure fluctuation, hypertension, hypotension

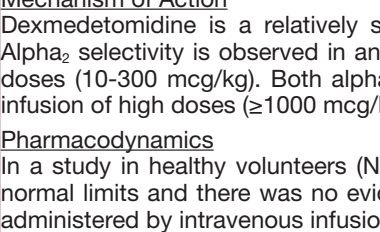
4.9 Overdose

The tolerability of Dexmedetomidine was studied in one study in which healthy adult subjects were administered doses at and above the recommended dose of 0.2 to 0.7 mcg/kg/hr. The maximum blood concentration achieved in this study was approximately 13 times the upper boundary of the therapeutic range. The most notable effects observed in two subjects who achieved the highest doses were first degree atrioventricular block and second-degree heart block. No hemodynamic compromise was noted with the atrioventricular block and the heart block resolved spontaneously within one minute.

5. Pharmacological properties

Dexmedetomidine (dexmedetomidine hydrochloride) injection is a sterile, nonpyrogenic solution suitable for intravenous infusion following dilution. Dexmedetomidine hydrochloride is the S-enantiomer of medetomidine and is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride.

Dexmedetomidine has a molecular weight of 236.7 and the empirical formula is C₁₃H₁₆N₂HCl and the structural formula is:



Dexmedetomidine hydrochloride is a white or almost white powder that is freely soluble in water and has a pKa of 7.1. Its partition coefficient in-octanol: water at pH 7.4 is 2.89. Dexmedetomidine injection is supplied as a clear, colorless, isotonic solution with a pH of 4.5 to 7.0. Each mL contains 118 mcg of dexmedetomidine hydrochloride equivalent to 100 mcg (0.1 mg) of dexmedetomidine and 9 mg of sodium chloride in water and is to be used after dilution. The solution is preservative free and contains no additives or chemical stabilizers.

Mechanism of Action

Dexmedetomidine is a relatively selective alpha₂-adrenergic agonist with sedative properties. Alpha₂ selectivity is observed in animals following slow intravenous infusion of low and medium doses (10-300 mcg/kg). Both alpha₁ and alpha₂ activity is observed following slow intravenous infusion of high doses (≥1000 mcg/kg) or with rapid intravenous administration.

Pharmacodynamics

In a study in healthy volunteers (N=10), respiratory rate and oxygen saturation remained within normal limits and there was no evidence of respiratory depression when Dexmedetomidine was administered by intravenous infusion at doses within the recommended dose range (0.2 - 0.7 mcg/kg/hr).

Pharmacokinetics

Following intravenous administration, dexmedetomidine exhibits the following pharmacokinetic parameters: a rapid distribution phase with a distribution half-life (t_{1/2}) of approximately 6 minutes; a terminal elimination half-life (t_{1/2}) of approximately 2 hours; and steady-state volume of distribution (V_{ss}) of approximately 118 liters. Clearance is estimated to be approximately 39 L/h. The mean body weight associated with this clearance estimate was 72 kg.

Dexmedetomidine exhibits linear pharmacokinetics in the dosage range of 0.2 to 0.7 mcg/kg/hr when administered by intravenous infusion for up to 24 hours.

Table 8 shows the main pharmacokinetic parameters when Dexmedetomidine was infused (after appropriate loading doses) at maintenance infusion rates of 0.17 mcg/kg/hr (target plasma concentration of 0.3 ng/mL) for 12 and 24 hours, 0.33 mcg/kg/hr (target plasma concentration of 0.6 ng/mL) for 24 hours, and 0.70 mcg/kg/hr (target plasma concentration of 1.25 ng/mL) for 24 hours.

Dexmedetomidine pharmacokinetic parameters after Dexmedetomidine maintenance doses of 0.2 to 1.4 mcg/kg/hr for >24 hours were similar to the PK parameters after Dexmedetomidine maintenance dosing for <24 hours in other studies. The values for clearance (CL), volume of distribution (V), and t_{1/2} were 39.4 L/hr, 152 L, and 2.67 hours, respectively.

Distribution

The steady-state volume of distribution (V_{ss}) of dexmedetomidine was approximately 118 liters. Dexmedetomidine protein binding was assessed in the plasma of normal healthy male and female subjects. The average protein binding was 94% and was constant across the different plasma concentrations tested. Protein binding was similar in males and females. The fraction of Dexmedetomidine that was bound to plasma proteins was significantly decreased in subjects with hepatic impairment compared to healthy subjects.

The potential for protein binding displacement of dexmedetomidine by fentanyl, ketorolac, theophylline, digoxin and lidocaine was explored *in vitro*, and negligible changes in the plasma protein binding of Dexmedetomidine were observed. The potential for protein binding displacement of phenytoin, warfarin, ibuprofen, propranolol, theophylline and digoxin by Dexmedetomidine was explored *in vitro* and none of these compounds appeared to be significantly displaced by Dexmedetomidine.

Metabolism

Dexmedetomidine undergoes almost complete biotransformation with very little unchanged dexmedetomidine excreted in urine and feces. 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 with a minor role of CYP1A2, CYP2E1, CYP2D6 and CYP2C19) of dexmedetomidine to generate 3-hydroxydexmedetomidine, the glucuronide of 3-hydroxy-dexmedetomidine, and 3-carboxydexmedetomidine; and N methylation of dexmedetomidine to generate 3-hydroxy N-methyl dexmedetomidine, 3-carboxy N-methyl-dexmedetomidine, and dexmedetomidine-N-methyl Oglucuronide.

Elimination

The terminal elimination half-life (t_{1/2}) 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 intravenous administration of radiolabeled dexmedetomidine, was recovered in the urine and 4% in the feces. 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.

Gender

There was no observed difference in Dexmedetomidine pharmacokinetics due to gender.

Geriatrics

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

Hepatic Impairment

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

Drug Interactions

In vitro studies: *In vitro* studies in human liver microsomes demonstrated no evidence of cytochrome P450 mediated drug interactions that are likely to be of clinical relevance.

6. Pharmaceutical particulars

6.1 List of excipients Sodium chloride Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

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

4 years

6.4 Special precautions for storage

Store below 30°C

After dilution

Chemical, physical and microbiological in-use stability has been demonstrated for 48 hours at 25 °C.

From a microbiological point of view, the product should be used immediately.

6.5 Nature and contents of container

2ml Type I colourless glass ampoules (with filling volumes of 2ml)

Pack sizes

25 x 2 ml ampoules

6.6 Special precautions for disposal and other handling

Ampoules and vials are intended for single patient use only.

Preparation of solution

Dexmedetomidine EVER Pharma can be diluted in glucose 50 mg/ml (5%), Ringers, mannitol or sodium chloride 9 mg/ml (0.9%) solution for injection to achieve the required concentration of either 4 micrograms/ml or 8 micrograms/ml prior to administration. Please see below in tabulated form the volumes needed to prepare the infusion.

In case the required concentration is 4 micrograms/ml:

Volume of Dexmedetomidine EVER Pharma 100 micrograms/ml concentrate for solution for infusion	Volume of diluent	Total volume of infusion
2 ml	48 ml	50 ml
4 ml	96 ml	100 ml
10 ml	240 ml	250 ml
20 ml	480 ml	500 ml

In case the required concentration is 8 micrograms/ml:

Volume of Dexmedetomidine EVER Pharma 100 micrograms/ml concentrate for solution for infusion	Volume of diluent	Total volume of infusion
4 ml	46 ml	50 ml
8 ml	92 ml	100 ml
20 ml	230 ml	250 ml
40 ml	460 ml	500 ml

The solution should be shaken gently to mix well.

Dexmedetomidine EVER Pharma should be inspected visually for particulate matter and discoloration prior to administration.

Dexmedetomidine EVER Pharma has been shown to be compatible when administered with the following intravenous fluids and medicinal products:

Lactated Ringers, 5% glucose solution, sodium chloride 9 mg/ml (0.9%) solution for injection, mannitol 200 mg/ml (20%), thiopental sodium, etomidate, vecuronium bromide, pancuronium bromide, succinylcholine, atracurium besylate, mivacurium chloride, rocuronium bromide, glycopyrrolate bromide, phenylephrine HCl, atropine sulfate, dopamine, noradrenaline, dobutamine, midazolam, morphine sulfate, fentanyl citrate, and a plasma-substitute.

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

Manufacturer

EVER Pharma Jena GmbH
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Product Registration Holder

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Date of revision

26-May-2025



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Layout Management



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