CENTER FOR DRUG EVALUATION AND RESEARCH

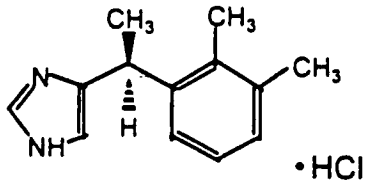
Application Number 21-038

FINAL PRINTED LABELING

PRECEDEX™
DEXMEDETOMIDINE HYDROCHLORIDE Injection

DESCRIPTION

PRECEDEX™ (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. The empirical formula is $C_{13}H_{16}N_2 \bullet HCl$ 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. PRECEDEX is supplied as a clear, colorless, isotonic solution with a pH of 4.5 to 7.0. Each 1 mL of PRECEDEX contains 118 mcg of dexmedetomidine HCl (equivalent to 100 mcg dexmedetomidine base) and 9 mg of sodium chloride in water. The solution is preservative-free and contains no additives or chemical stabilizers.

CLINICAL PHARMACOLOGY

General

Dexmedetomidine is a relatively selective alpha$_2$-adrenoceptor agonist with sedative properties. Alpha$_2$-selectivity was observed in animals following slow intravenous (IV) infusion of low and medium doses (10-300 mcg/kg). Both alpha$_1$ and alpha$_2$ activity was observed following slow IV infusion of high doses (≥1000 mcg/kg) or with rapid IV administration.

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 PRECEDEX was administered by IV infusion at doses within the recommended dose range (0.2-0.7 mcg/kg).

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 kinetics in the dosage range of 0.2 to 0.7 µg/kg/hr when administered by IV infusion for up to 24 hours. Table 1 shows the main pharmacokinetic parameters when PRECEDEX was infused (after appropriate loading doses) at maintenance infusion rates of 0.17 µg/kg/hr (target concentration of 0.3 ng/mL) for 12 and 24 hours, 0.33 µg/kg/hr (target concentration of 0.6 ng/mL) for 24 hours, and 0.70 µg/kg/hr (target concentration of 1.25 ng/mL) for 24 hours.

Table 1: Mean ± SD Pharmacokinetic Parameters.

Parameter	Loading Infusion (min)/Total infusion duration (hrs)			
	10 min/12 hrs	10 min/24hrs	10 min/24 hrs	35 min/24 hrs
	Dexmedetomidine Target Concentration (ng/mL) /Dose (mcg/kg/hr)			
	0.3/0.17	0.3/0.17	0.6/0.33	1.25/0.70
$t_{1/2}$*, hour	1.78 ± 0.30	2.22 ± 0.59	2.23 ± 0.21	2.50 ± 0.61
CL, liter/hour	46.3 ± 8.3	43.1 ± 6.5	35.3 ± 6.8	36.5 ± 7.5
V_{ss}, liter	88.7 ± 22.9	102.4 ± 20.3	93.6 ± 17.0	99.6 ± 17.8
Avg Css#, 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 (V_{SS}) 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 by dexmedetomidine was explored *in vitro* and none of these compounds appeared to be significantly displaced by dexmedetomidine.

Metabolism

Dexmedetomidine undergoes almost complete biotransoformation 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) 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-methyl O-glucuronide dexmedetomidine.

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 IV 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-glucoronidation 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.

Pediatrics

The pharmacokinetic profile of dexmedetomidine has not been studied in pediatric patients.

Renal Impairment

Dexmedetomidine pharmacokinetics (C_{max}, T_{max}, AUC, $t_{1/2}$, CL, and V_{SS}) were not significantly different in subjects with severe renal impairment (creatinine clearance <30 mL/min) compared to healthy subjects. However, the pharmacokinetics of the

metabolites of dexmedetomidine have not been evaluated in patients with impaired renal function. Since the majority of metabolites are excreted in the urine, it is possible that the metabolites may accumulate upon long-term infusions in patients with impaired renal function (See PRECAUTIONS, Geriatrics, DOSAGE AND ADMINISTRATION).

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 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 PRECEDEX is dosed to effect, it may be necessary to consider dose reduction in patients with hepatic impairment (see PRECAUTIONS, Hepatic Impairment and DOSAGE AND ADMINISTRATION).

Clinical Trials

The safety and efficacy of PRECEDEX has been evaluated in two randomized, double-blind, parallel-group, placebo-controlled multicenter clinical trials in 754 patients being treated in a surgical intensive care unit (ICU). All patients were initially intubated and received mechanical ventilation. These trials evaluated the sedative properties of dexmedetomidine by comparing the amount of rescue medication (midazolam in one trial and propofol in the second) required to achieve a specified level of sedation (using the standardized Ramsay sedation scale) between PRECEDEX 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 2.

Table 2: 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 randomized to receive placebo and 178 to receive dexmedetomidine by intravenous infusion at a dose of 0.4 mcg/kg/hr (with allowed adjustment between 0.2 and 0.7 mcg/kg/hr) following an initial loading infusion of 1 (one) mcg/kg 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

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