CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-038

FINAL PRINTED LABELING
Dexmedetomidine HCl
Draft 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 C₁₅H₁₆N₂•HCl and the structural formula is:

\[
\begin{align*}
& \text{CH₃} \quad \text{CH₃} \\
& \quad \quad \text{CH₃} \\
& \text{N} \quad \text{H} \\
& \quad \quad \text{H} \\
\end{align*}
\]

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 alpha₂-adrenoceptor agonist with sedative properties. Alpha₂-selectivity was observed in animals following slow intravenous (IV) infusion of low and medium doses (10-300 mcg/kg). Both alpha₁ and alpha₂ 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 (t½) of approximately 6 minutes; a terminal elimination half-life (t½) of approximately 2 hours; and steady-state volume of distribution (Vₜ) of approximately 118 liters. Clearance is
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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>
<thead>
<tr>
<th>Parameter</th>
<th>Loading Infusion (min)/Total infusion duration (hrs)</th>
<th>10 min/12 hrs</th>
<th>10 min/24 hrs</th>
<th>10 min/24 hrs</th>
<th>35 min/24 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dexmedetomidine Target Concentration (ng/mL) /Dose (mcg/kg/hr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t1/2*, hour</td>
<td>0.3/0.17</td>
<td>1.78 ± 0.30</td>
<td>2.22 ± 0.59</td>
<td>2.23 ± 0.21</td>
<td>2.50 ± 0.61</td>
</tr>
<tr>
<td>CL, liter/hour</td>
<td>0.3/0.17</td>
<td>46.3 ± 8.3</td>
<td>43.1 ± 6.5</td>
<td>35.3 ± 6.8</td>
<td>36.5 ± 7.5</td>
</tr>
<tr>
<td>Vss, liter</td>
<td>0.3/0.17</td>
<td>88.7 ± 22.9</td>
<td>102.4 ± 20.3</td>
<td>93.6 ± 17.0</td>
<td>99.6 ± 17.8</td>
</tr>
<tr>
<td>Avg Css#, ng/mL</td>
<td>0.3/0.17</td>
<td>0.27 ± 0.05</td>
<td>0.27 ± 0.05</td>
<td>0.67 ± 0.10</td>
<td>1.37 ± 0.20</td>
</tr>
</tbody>
</table>

*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 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) 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-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 (41-55 years), and elderly (>65 years) subjects.

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

Renal Impairment
Dexmedetomidine pharmacokinetics \((C_{max}, T_{max}, AUC, t_{1/2}, CL, \text{ and } V_{ss})\) 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>
<thead>
<tr>
<th>Table 2: Ramsay Level of Sedation Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Score</strong></td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

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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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 randomized to placebo received significantly more midazolam
than patients randomized to dexmedetomidine (see Table 3).

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 3).

<table>
<thead>
<tr>
<th>Table 3: Midazolam Use As Rescue Medication During Intubation (ITT)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study One</td>
</tr>
<tr>
<td>Mean total dose of midazolam</td>
</tr>
<tr>
<td>Standard deviation</td>
</tr>
<tr>
<td>Categorized midazolam use</td>
</tr>
<tr>
<td>0mg</td>
</tr>
<tr>
<td>0-4 mg</td>
</tr>
<tr>
<td>&gt;4 mg</td>
</tr>
</tbody>
</table>

*ITT (intent-to-treat) population includes all randomized patients.
**ANOVA model with treatment and Center ***Chi-Square

A prospective secondary analysis assessed the dose of morphine sulfate administered to
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 a second study, 198 patients were randomized to receive placebo and 203 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 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 randomized to placebo received significantly more propofol than patients randomized to dexmedetomidine (see Table 4).

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 4).

<table>
<thead>
<tr>
<th>Study Two</th>
<th>Placebo N=198</th>
<th>Dexmedetomidine N=203</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean total dose (mg) of propofol</td>
<td>513 mg</td>
<td>72 mg</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>782 mg</td>
<td>249 mg</td>
<td></td>
</tr>
<tr>
<td>Categorized propofol use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0mg</td>
<td>47 (24%)</td>
<td>122 (60%)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>0-50 mg</td>
<td>30 (15%)</td>
<td>43 (21%)</td>
<td></td>
</tr>
<tr>
<td>&gt;50 mg</td>
<td>121 (61%)</td>
<td>38 (19%)</td>
<td></td>
</tr>
</tbody>
</table>

*ANOVA model with treatment and center  **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.

INDICATIONS AND USAGE
PRECEDEX is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. PRECEDEX should be administered by continuous infusion not to exceed 24 hours.

WARNINGS
PRECEDEX should be administered only by persons skilled in the management of patients in the intensive care setting. Due to the known pharmacological effects of PRECEDEX, patients should be continuously monitored while receiving PRECEDEX.
Clinically significant episodes of bradycardia and sinus arrest have been associated with PRECEDEX administration in young, healthy volunteers with high vagal tone or with different routes of administration, including rapid intravenous or bolus administration.

PRECAUTIONS

General
Some patients receiving PRECEDEX have been observed to be arousable and alert when stimulated. This alone should not be considered an evidence of lack of efficacy in the absence of other clinical signs and symptoms.

Reports of hypotension and bradycardia have been associated with PRECEDEX infusion. If medical intervention is required, treatment may include decreasing or stopping the infusion of PRECEDEX, increasing the rate of IV fluid administration, elevation of the lower extremities, and use of pressor agents. Because PRECEDEX has the potential to augment bradycardia induced by vagal stimuli, clinicians should be prepared to intervene. The intravenous administration of anticholinergic agents (eg, atropine) should be considered to modify vagal tone. In clinical trials, atropine or glycopyrrolate were effective in the treatment of most episodes of PRECEDEX-induced bradycardia. However, in some patients with significant cardiovascular dysfunction, more advanced resuscitative measures were required. Caution should be exercised when administering PRECEDEX to patients with advanced heart block.

Transient hypertension has been observed primarily during the loading dose in association with the initial peripheral vasoconstrictive effects of PRECEDEX. Treatment of the transient hypertension has generally not been necessary, although reduction of the loading infusion rate may be desirable.

PRECEDEX infusion should not be coadministered through the same IV catheter with blood or plasma since physical compatibility has not been established. Safety and effectiveness of dexmedetomidine have not been evaluated in infusions over 24 hours. Dexmedetomidine is not indicated for infusions lasting over 24 hours (see INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION).

Withdrawal
Although not specifically studied, if PRECEDEX is administered chronically and stopped abruptly, withdrawal symptoms similar to those reported for another alpha-2-adrenergic agent, clonidine, may result. These symptoms may include nervousness, agitation, and headaches, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma. PRECEDEX should not be administered for greater than 24 hours (see INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION).
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%.

Hepatic Impairment
Since dexmedetomidine clearance decreases with severity of hepatic impairment, dose reduction should be considered in patients with impaired hepatic function (see CLINICAL PHARMACOLOGY, Pharmacokinetics, DOSAGE AND ADMINISTRATION).

Drug Interactions

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

Anesthetics/Sedatives/Hypnotics/Opioids
Co-administration of PRECEDEX with anesthetics, sedatives, hypnotics, and opioids is likely to lead to an enhancement of effects. Specific studies have confirmed these effects with sevoflurane, 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 PRECEDEX, a reduction in dosage of PRECEDEX on the concomitant anesthetic, sedative, hypnotic or opioid may be required.

Neuromuscular Blockers
In one study of 10 healthy volunteers, administration of PRECEDEX for 45 minutes at a plasma concentration of 1 (one) ng/mL resulted in no clinically meaningful increases in the magnitude or neuromuscular blockade associated with rocuronium administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Animal carcinogenicity studies have not been performed with dexmedetomidine.

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). Dexmedetomidine was clastogenic in the in vitro human lymphocyte chromosome aberration test with, but not without, metabolic activation. Dexmedetomidine was also clastogenic in the in vivo mouse micronucleus test.
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Fertility in male or female rats was not affected after daily subcutaneous injections at
doses up to 54 mcg/kg (less than the maximum recommended human intravenous dose on
a mcg/m²² basis). Dexmedetomidine was dosed from 10 weeks prior to mating in males
and 3 weeks prior to mating and during mating in females.

Pregnancy: Teratogenic Effects. Pregnancy Category C
Teratogenic effects were not observed following administration of dexmedetomidine at
subcutaneous doses up to 200 mcg/kg in rats from day 5 to day 16 of gestation and
intravenous doses up to 96 mcg/kg in rabbits from day 6 to day 18 of gestation. The dose
in rats is approximately 2 times the maximum recommended human intravenous dose on
a mcg/m²² basis. The exposure in rabbits is approximately equal to that in humans at the
maximum recommended intravenous dose based on plasma area-under-the-curve values.
However, fetal toxicity, as evidenced by increased postimplantation losses and reduced
live pups, was observed in rats at a subcutaneous dose of 200 mcg/kg. The no-effect dose
was 20 mcg/kg (less than the maximum recommended human intravenous dose on a
mcg/m²² basis). In another reproductive study when dexmedetomidine was administered
subcutaneously to pregnant rats from gestation day 16 through nursing, it caused lower
pup weights at doses of 8 and 32 mcg/kg as well as fetal and embryocidal toxicity of
second generation offspring at a dose of 32 mcg/kg (less than the maximum
recommended human intravenous dose on a mcg/m²² basis). Dexmedetomidine also
produced delayed motor development in pups at a dose of 32 mcg/kg (less than the
maximum recommended human intravenous dose on a mcg/m²² basis). No such effects
were observed at a dose of 2 mcg/kg (less than the maximum recommended intravenous
dose on a mcg/m²² basis).

Placental transfer of dexmedetomidine was observed when radiolabeled
dexmedetomidine was administered subcutaneously to pregnant rats.

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 fetus.

Labor and Delivery
The safety of PRECEDEX during labor and delivery has not been studied. Therefore,
PRECEDEX is not recommended during labor and delivery, including cesarean section
deliveries.

Nursing Mothers
It is not known whether PRECEDEX is excreted in human milk. Radiolabeled
dexmedetomidine administered subcutaneously to lactating female rats was excreted in
milk. Because many drugs are excreted in human milk, caution should be exercised when
PRECEDEX is administered to a nursing woman.
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Pediatrics
There have been no clinical studies to establish the safety and efficacy of PRECEDEX in pediatric patients below 18 years of age. Therefore, PRECEDEX is not recommended for use in this population.

Geriatrics
A total of 531 subjects in the clinical studies were 65 years of age and over. A total of 129 subjects in the clinical studies 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 PRECEDEX. Therefore a dose reduction may be considered in patients over 65 years of age.

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.

ADVERSE REACTIONS
Adverse event information is derived from the placebo-controlled, continuous infusion trials of dexmedetomidine for sedation in the ICU setting in which 387 patients received PRECEDEX. Overall, the most frequently observed treatment-emergent adverse events included hypotension, hypertension, nausea, bradycardia, fever, vomiting hypoxia, tachycardia and anemia (see Table 5).

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Dexmedetomidine (N=387)</th>
<th>Placebo (N=379)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>30%</td>
<td>15%</td>
</tr>
<tr>
<td>Nausea</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Anemia</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Pain</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Pleural Effusion</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Infection</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Oliguria</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Pulmonary Edema</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Thirst</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
The treatment-emergent adverse events in Table 6 were reported in ≤1% of all dexametomidine-treated patients and are potentially clinically relevant.

<table>
<thead>
<tr>
<th>Body System</th>
<th>Preferred Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td>Fever, Hyperpyrexia, Hypovolemia, Light Anesthesia, Pain, Rigors</td>
</tr>
<tr>
<td>Cardiovascular Disorders, General</td>
<td>Blood pressure fluctuation, Heart disorder, Aggravated hypertension</td>
</tr>
<tr>
<td>Central and Peripheral Nervous System Disorders</td>
<td>Dizziness, Headache, Neuropathy, Neuritis, Speech disorder</td>
</tr>
<tr>
<td>Gastrointestinal System Disorders</td>
<td>Abdominal pain, Diarrhea, Vomiting</td>
</tr>
<tr>
<td>Heart Rate and Rhythm Disorders</td>
<td>Arrhythmia, Ventricular arrhythmia, AV block, Cardiac arrest, Extrasystoles, Atrial fibrillation, Heart block, T wave inversion, Tachycardia, Supraventricular tachycardia, Ventricular tachycardia</td>
</tr>
<tr>
<td>Liver and Biliary System Disorders</td>
<td>Increased GGT, Increased SGOT, Increased SGPT,</td>
</tr>
<tr>
<td>Metabolic and Nutritional Disorders</td>
<td>Acidosis, Respiratory acidosis, Hyperkalemia, Increased alkaline phosphatase, Thirst</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Agitation, Confusion, Delirium, Hallucination, Illusion, Somnolence</td>
</tr>
<tr>
<td>Red Blood Cell Disorders</td>
<td>Anemia</td>
</tr>
<tr>
<td>Respiratory System Disorders</td>
<td>Apnea, Bronchospasm, Dyspnea, Hypercapnia, Hypoventilation, Hypoxia, Pulmonary congestion</td>
</tr>
<tr>
<td>Skin and Appendages Disorders</td>
<td>Increased sweating</td>
</tr>
<tr>
<td>Vision Disorders</td>
<td>Photopsia, Abnormal vision</td>
</tr>
</tbody>
</table>

**DRUG ABUSE AND DEPENDENCE**

PRECEDEX (dexametomidine hydrochloride) is not a controlled substance.

The dependence potential of dexametomidine has not been studied in humans. However, since studies in rodents and primates have demonstrated that dexametomidine exhibits pharmacologic actions similar to those of clonidine, it is possible that PRECEDEX may produce a clonidine-like withdrawal syndrome upon abrupt discontinuation (See PRECAUTIONS, Withdrawal).

**OVERDOSAGE**

The tolerability of PRECEDEX was noted in one study in which healthy 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 AV block and second degree heart block. No hemodynamic compromise was noted with the AV block and the heart block resolved spontaneously within one minute.
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Draft Labeling

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Five patients received an overdose of PRECEDEX in the ICU sedation studies. Two of these patients had no symptoms reported; one patient received a 2 mcg/kg loading dose over 10 minutes (twice the recommended loading dose) and one patient received a maintenance infusion of 0.8 mcg/kg/hr. Two other patients who received a 2 mcg/kg loading dose over 10 minutes, experienced bradycardia and/or hypotension. One patient who received a loading bolus dose of undiluted PRECEDEX (19.4 mcg/kg), had cardiac arrest from which he was successfully resuscitated.

DOSAGE AND ADMINISTRATION
PRECEDEX should be administered using a controlled infusion device.

PRECEDEX dosing should be individualized and titrated to the desired clinical effect. For adult patients, PRECEDEX is generally initiated with a loading infusion of 1 (one) mcg/kg over 10 minutes, followed by a maintenance infusion of 0.2 to 0.7 mcg/kg/hr. The rate of the maintenance infusion should be adjusted to achieve the desired level of sedation. Dexmedetomidine is not indicated for infusions lasting longer than 24 hours.

PRECEDEX has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post-extubation. It is not necessary to discontinue PRECEDEX prior to extubation provided the infusion does not exceed 24 hours.

Dosage Adjustment
Dosage reductions may need to be considered for patients with renal or hepatic impairment (see CLINICAL PHARMACOLOGY, Pharmacokinetics & PRECAUTIONS, Hepatic Impairment).

Dilution Prior to Administration
PRECEDEX must be diluted in 0.9% sodium chloride solution 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 PRECEDEX and add to 48 mL of 0.9% Sodium Chloride injection to a total of 50 mL. Shake gently to mix well.

Administration With Other Fluids
Compatibility of PRECEDEX with coadministration of blood, serum, or plasma has not been established. PRECEDEX has been shown to be compatible when administered with the following intravenous fluids and drugs:
Lactated Ringers
5% dextrose in water, 0.9% sodium chloride in water, 20% mannitol, thiopental sodium, etomidate, vecuronium bromide, pancuronium bromide, succinylcholine, atracurium besylate, mivacurium chloride, glycopyrrolate bromide, phenylephrine HCl, atropine sulfate, midazolam, morphine sulfate, fentanyl citrate, and a plasma-substitute.

Handling Procedures
Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. Strict aseptic technique must always be maintained during handling of PRECEDEX. Ampules and vials are intended for single use only.

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

PRECEDEX must be diluted in 0.9% sodium chloride solution to achieve the required concentrations prior to administration. Preparation of solutions is the same, whether for the loading or maintenance infusion (see DOSAGE AND ADMINISTRATION).

HOW SUPPLIED
PRECEDEX (dexmedetomidine hydrochloride injection), 100 mcg/mL as the base is available in 2 mL clear glass vials and 2 mL clear glass ampules.

2 mL vial (NDC XXXX-XXXX-XX)
2 mL ampule (NDC XXXX-XXXX-XX)

Store at controlled room temperature, 25°C (77°F) with excursions allowed from 15° to 30°C (59° to 86°F).
Manufactured and Distributed by:
Abbott Laboratories
North Chicago, IL 60064

Licensed from:
Orion Corporation
Espoo, Finland

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