procedures. (1.2)

DOSAGE AND ADMINISTRATION

- Individualize and titrate Precedex dosing to desired clinical effect. (2.1)
- Administer Precedex using a controlled infusion device. (2.1)
- Dilute vial contents in 0.9% sodium chloride solution to achieve required concentration (4 mcg/mL) prior to administration. (2.4)

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. (2.2)

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. (2.2)

DOSAGE FORMS AND STRENGTHS

Precedex Injection, Concentrate, 200 mcg/2 mL (100 mcg/mL) in a glass vial. (3)

Precedex Injection 200 mcg/50 mL (4 mcg/mL) in a 50 mL glass bottle. (3)

Precedex Injection 400 mcg/100 mL (4 mcg/mL) in a 100 mL glass bottle. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Monitoring: Continuously monitor patients while receiving Precedex. (5.1)
- Bradycardia and Sinus Arrest: Have occurred in young healthy volunteers with high vagal tone or with different routes of administration, e.g., rapid intravenous or bolus administration. (5.2)
- Hypotension and Bradycardia: May necessitate medical intervention. May be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic hypertension, and in the elderly. Use with caution in patients with advanced heart block or severe ventricular dysfunction. (5.2)
- Co-administration with Other Vasodilators or Negative Chronotropic Agents: Use with caution due to additive pharmacodynamic effects. (5.2)
- Transient Hypertension: Observed primarily during the loading dose. Consider reduction in loading infusion rate. (5.3)
- Arousability: Patients can become aroused/alert with stimulation; this alone should not be considered as lack of efficacy. (5.4)
- Prolonged exposure to dexmedetomidine beyond 24 hours may be associated with tolerance and tachyphylaxis and a dose-related increase in adverse events. (5.6)

ADVERSE REACTIONS

- The most common adverse reactions (incidence greater than 2%) are hypotension, bradycardia, and dry mouth. (6.1)
- Adverse reactions associated with infusions greater than 24 hours in duration include ARDS, respiratory failure, and agitation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Hospira, Inc. at 1-800-441-4100 or electronically at ProductComplaintsPP@hospira.com, or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

Anesthetics, Sedatives, Hypnotics, Opioids: Enhancement of pharmacodynamic effects. Reduction in dosage of Precedex or the concomitant medication may be required. (7.1)

USE IN SPECIFIC POPULATIONS

- Geriatric Patients: Dose reduction should be considered. (2.2, 2.3, 5.1, 8.5)
- Hepatic Impairment: Dose reduction should be considered. (2.1, 2.2, 2.3, 5.7, 8.6)
- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing Mothers: Caution should be exercised when administered to a nursing woman. (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 09/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Guidelines

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

2.2 Dosage Information

Table 1: Dosage Information

INDICATION	DOSAGE AND ADMINISTRATION
Initiation of Intensive Care Unit Sedation	**For adult patients:** a loading infusion of 1 mcg/kg over 10 minutes. **For patients being converted from alternate sedative therapy:** a loading dose may not be required [*see Dosage and Administration: Maintenance of Intensive Care Unit Sedation (2.2)*]. **For patients over 65 years of age:** a dose reduction should be considered [*see Use in Specific Populations (8.5)*]. **For patients with impaired hepatic-function:** a dose reduction should be considered [*see Use in Specific Populations (8.6)*, *Clinical Pharmacology (12.3)*].
Maintenance of Intensive Care Unit Sedation	**For adult patients:** 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. **For patients over 65 years of age:** a dose reduction should be considered [*see Use in Specific Populations (8.5)*]. **For patients with impaired hepatic function:** a dose reduction should be considered [*see Use in Specific Populations (8.6)*, *Clinical Pharmacology (12.3)*].
Initiation of Procedural Sedation	**For adult patients:** a loading infusion of 1 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 patients:** a loading infusion of 1 mcg/kg over 10 minutes. **For patients over 65 years of age:** a loading infusion of 0.5 mcg/kg over 10 minutes [*see Use in Specific Populations (8.5)*]. **For patients with impaired hepatic function:** a dose reduction should be considered [*see Use in Specific Populations (8.6)*, *Clinical Pharmacology (12.3)*].
Maintenance of Procedural Sedation	**For adult patients:** the maintenance infusion is generally 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. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation. **For awake fiberoptic intubation patients:** a maintenance infusion of 0.7 mcg/kg/hr is recommended until the endotracheal tube is secured. **For patients over 65 years of age:** a dose reduction should be considered [*see Use in Specific Populations (8.5)*]. **For patients with impaired hepatic function:** a dose reduction should be considered [*see Use in Specific Populations (8.6)*, *Clinical Pharmacology (12.3)*].

2.3 Dosage Adjustment

Due to possible pharmacodynamic interactions, a reduction in dosage of Precedex or other concomitant anesthetics, sedatives, hypnotics or opioids may be required when co-administered [*see Drug Interactions (7.1)*].

Dosage reductions may need to be considered for patients with hepatic impairment, and geriatric patients [*see Warnings and Precautions (5.7)*, *Use in Specific Populations (8.6)*, *Clinical Pharmacology (12.3)*].

2.4 Preparation of Solution

Strict aseptic technique must always be maintained during handling of Precedex.

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

Precedex Injection, Concentrate, 200 mcg/2 mL (100 mcg/mL)

Precedex 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 Precedex and add to 48 mL of 0.9% sodium chloride injection to a total of 50 mL. Shake gently to mix well.

Precedex Injection, 200 mcg/50 mL (4 mcg/mL) and 400 mcg/100 mL (4 mcg/mL)

Precedex Injection is supplied in glass containers containing a premixed, ready to use dexmedetomidine hydrochloride solution in 0.9% sodium chloride in water. No further dilution of these preparations are necessary.

2.5 Administration with Other Fluids

Precedex infusion should not be co-administered through the same intravenous catheter with blood or plasma because physical compatibility has not been established.

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

Precedex 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

2.6 Compatibility with Natural Rubber

Compatibility studies have demonstrated the potential for absorption of Precedex 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.

receiving Precedex.

5.2 Hypotension,

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5.3 Transient Hyp

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5.4 Arousability

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5.5 Withdrawal
Intensive Care

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Procedural Se

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5.6 Tolerance and

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5.7 Hepatic Impai

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6 ADVERSE REA

6.1 Clinical Studie

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Use of Precede

- Hypotens
- Transient

Most common
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hypotension, bradycar

Intensive Care

Adverse reactio
Precedex for sedation
Precedex. The mean to
was 0.5 mcg/kg/hr (ra
(range: 0.2 to 157.2). T
of age, 77% male and
at an incidence of >2%
hypotension, bradycar

	abnormal, hyperbilirubinemia, alanine transaminase, aspartate aminotransferase
Metabolic and Nutritional Disorders	Acidosis, respiratory acidosis, hyperkalemia, increased alkaline phosphatase, thirst, hypoglycemia
Psychiatric Disorders	Agitation, confusion, delirium, hallucination, illusion
Red Blood Cell Disorders	Anemia
Renal Disorders	Blood urea nitrogen increased, oliguria
Respiratory System Disorders	Apnea, bronchospasm, dyspnea, hypercapnia, hypoventilation, hypoxia, pulmonary congestion
Skin and Appendages Disorders	Increased sweating
Vascular Disorders	Hemorrhage
Vision Disorders	Photopsia, abnormal vision

7 DRUG INTERACTIONS

7.1 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 Precedex 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 or the concomitant anesthetic, sedative, hypnotic or opioid may be required.

7.2 Neuromuscular Blockers

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of Precedex use in pregnant women. In an *in vitro* human placenta study, placental transfer of dexmedetomidine occurred. In a study in the pregnant rat, placental transfer of dexmedetomidine was observed when radiolabeled dexmedetomidine was administered subcutaneously. Thus, fetal exposure should be expected in humans, and Precedex should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

Teratogenic effects were not observed in rats following subcutaneous administration of dexmedetomidine during the period of fetal organogenesis (from gestation day 5 to 16) with doses up to 200 mcg/kg (representing a dose approximately equal to the maximum recommended human intravenous dose based on body surface area) or in rabbits following intravenous administration of dexmedetomidine during the period of fetal organogenesis (from gestation day 6 to 18) with doses up to 96 mcg/kg (representing approximately half the human exposure at the maximum recommended dose based on plasma area under the time-curve comparison). However, fetal toxicity, as evidenced by increased post-implantation losses and reduced live pups, was observed in rats at a subcutaneous dose of 200 mcg/kg. The no-effect dose in rats was 20 mcg/kg (representing a dose less than the maximum recommended human intravenous dose based on a body surface area comparison). In another reproductive toxicity study when dexmedetomidine was administered subcutaneously to pregnant rats at 8 and 32 mcg/kg (representing a dose less than the maximum recommended human intravenous dose based on a body surface area comparison) from gestation day 16 through weaning, lower offspring weights were observed. Additionally, when offspring of the 32 mcg/kg group were allowed to mate, elevated fetal and embryocidal toxicity and delayed motor development was observed in second generation offspring.

8.2 Labor and Delivery

The safety of Precedex during labor and delivery has not been studied.

8.3 Nursing Mothers

It is not known whether Precedex is excreted in human milk. Radio-labeled 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.

8.4 Pediatric Use

The efficacy, safety, and pharmacokinetics of Precedex in pediatric patients less than 18 years of age have not been established. Therefore, Precedex should not be used in this population.

8.5 Geriatric Use

Intensive Care Unit Sedation

A total of 729 patients in the clinical studies were 65 years of age and over. A total of 200 patients 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 [*see Warnings and Precautions (5.2)*]. Therefore a dose reduction may be considered in patients over 65 years of age [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

Procedural Sedation

A total of 131 patients in the clinical studies were 65 years of age and over. A total of 47 patients were 75 years of age and over. Hypotension occurred in a higher incidence in Precedex-treated patients 65 years or older (72%) and 75 years or older (74%) as compared to patients <65 years (47%). A reduced loading dose of 0.5 mcg/kg given over 10 minutes is recommended and a reduction in the maintenance infusion should be considered for patients greater than 65 years of age.

8.6 Hepatic Impairment

Since Precedex clearance decreases with increasing severity of hepatic impairment, dose reduction should be considered in patients with impaired hepatic function [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

9 DRUG ABUSE AND DEPENDENCE

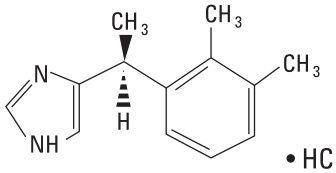
9.1 Controlled Substance

Precedex (dexmedetomidine hydrochloride) is not a controlled substance.

Five patients received an overdose of Precedex in the intensive care unit 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.

11 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. Precedex has a molecular weight of 236.7 and the empirical formula is $C_{13}H_{16}N_2 \cdot HCl$ 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 mL of Precedex Injection, Concentrate contains 118 mcg of dexmedetomidine hydrochloride equivalent to 100 mcg of dexmedetomidine and 9 mg of sodium chloride in water. Each mL of Precedex Injection contains 4.72 mcg of dexmedetomidine hydrochloride equivalent to 4 mcg dexmedetomidine and 9 mg of sodium chloride in water. The solution is preservative-free and contains no additives or chemical stabilizers.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 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 Precedex was administered by intravenous infusion at doses within the recommended dose range (0.2–0.7 mcg/kg/hr).

12.3 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 Precedex 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.

Table 8: Mean ± SD Pharmacokinetic Parameters

	Loading Infusion (min)/Total Infusion Duration (hrs)			
	10 min/12 hrs	10 min/24 hrs	10 min/24 hrs	35 min/24 hrs
	Precedex Target Plasma Concentration (ng/mL) and Dose (mcg/kg/hr)			
Parameter	**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 C_{ss} #, 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.

\# Mean C_{ss} = Average steady-state concentration of Precedex. The mean C_{ss} was calculated based on post-dose sampling from 2.5 to 9 hours samples for 12 hour infusion and post-dose sampling from 2.5 to 18 hours for 24 hour infusions.
The loading doses for each of the above indicated groups were 0.5, 0.5, 1 and 2.2 mcg/kg, respectively.

Dexmedetomidine pharmacokinetic parameters after Precedex maintenance doses of 0.2 to 1.4 mcg/kg/hr for >24 hours were similar to the PK parameters after Precedex 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 Precedex 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 Precedex were observed. The potential for protein binding displacement of phenytoin, warfarin, ibuprofen, propranolol, theophylline and digoxin by Precedex was explored *in vitro* and none of these compounds appeared to be significantly displaced by Precedex.

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13 NONCLINICAL

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14 CLINICAL STU

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