HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use dexmedetomidine hydrochloride safely and effectively. See full prescribing information for Precedex.

Precedex (dexmedetomidine hydrochloride) injection
For intravenous infusion following dilution
Initial U.S. Approval: 1999

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Dosing Information (2.2)	09/2010
Dosage and Administration, Administration with Other Fluids (2.5)	09/2010
Warnings and Precautions (5)	09/2010
Adverse Reactions, Clinical Studies Experience (6.1)	09/2010
Use in Special Populations, Pregnancy (8 1)	09/2010
Clinical Pharmacology, Pharmacokinetics (12.3)	09/2010
Animal Toxicology and/or Pharmacology (13.2)	09/2010
Clinical Studies, Intensive Care Unit Sedation (14.1)	09/2010

----------INDICATIONS AND USAGE----------

Precedex is a relatively selective alpha$_2$-adrenergic agonist indicated for:

- Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Administer Precedex by continuous infusion not to exceed 24 hours. (1.1)
- Sedation of non-intubated patients prior to and/or during surgical and other 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 one 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 one 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----------

200 mcg/2 mL (100 mcg/mL) in a glass vial (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 1-888-441-4100 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, 5.6, 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)

Revised: 09/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Intensive Care Unit Sedation

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.

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.

1.2 Procedural Sedation

Precedex is indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures.

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 up to one 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 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 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 [*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 (5.6), Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

2.4 Preparation of Solution

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.

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

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.

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

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

- 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.

3 DOSAGE FORMS AND STRENGTHS

200 mcg/2 mL (100 mcg/mL) in a glass vial

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Drug Administration

Precedex should be administered only by persons skilled in the management of patients in the intensive care or operating room setting. Due to the known pharmacological effects of Precedex, patients should be continuously monitored while receiving Precedex.

5.2 Hypotension, Bradycardia, and Sinus Arrest

Clinically significant episodes of bradycardia and sinus arrest have been reported with Precedex administration in young, healthy volunteers with high vagal tone or with different routes of administration including rapid intravenous or bolus administration.

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 intravenous 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 (e.g., glycopyrrolate, atropine) should be considered to modify vagal tone. In clinical trials, glycopyrrolate or atropine 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 and/or severe ventricular dysfunction. Because Precedex decreases sympathetic nervous system activity, hypotension and/or bradycardia may be expected to be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic hypertension and in elderly patients.

In clinical trials where other vasodilators or negative chronotropic agents were co-administered with Precedex an additive pharmacodynamic effect was not observed. Nonetheless, caution should be used when such agents are administered concomitantly with Precedex.

5.3 Transient Hypertension

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.

5.4 Arousability

Some patients receiving Precedex 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.

5.5 Withdrawal

Intensive Care Unit Sedation

With administration up to 7 days, regardless of dose, 12 (5%) Precedex subjects experienced at least 1 event

experienced at least 1 event 24 to 48 hours after end of study drug. The most common events were nausea, vomiting, and agitation.

Tachycardia and hypertension requiring intervention in the 48 hours following study drug discontinuation occurred at frequencies of <5%. If tachycardia and/or hypertension occurs after discontinuation of Precedex supportive therapy is indicated.

Procedural Sedation

Withdrawal symptoms were not seen after discontinuation of short term infusions of Precedex (<6 hours).

5.6 Tolerance and Tachyphylaxis

Use of dexmedetomidine beyond 24 hours has been associated with tolerance and tachyphylaxis and a dose-related increase in adverse reactions [see Adverse Reactions (6.1)].

5.7 Hepatic Impairment

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

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

Use of Precedex has been associated with the following serious adverse reactions:

- Hypotension, bradycardia and sinus arrest *[see Warnings and Precautions (5.2)]*
- Transient hypertension *[see Warnings and Precautions (5.3)]*

Most common treatment-emergent adverse reactions, occurring in greater than 2% of patients in both Intensive Care Unit and procedural sedation studies include hypotension, bradycardia and dry mouth.

Intensive Care Unit Sedation

Adverse reaction information is derived from the continuous infusion trials of Precedex for sedation in the Intensive Care Unit setting in which 1007 patients received Precedex. The mean total dose was 7.4 mcg/kg (range: 0.8 to 84.1), mean dose per hour was 0.5 mcg/kg/hr (range: 0.1 to 6.0) and the mean duration of infusion of 15.9 hours (range: 0.2 to 157.2). The population was between 17 to 88 years of age, 43% $\geq$ 65 years of age, 77% male and 93% Caucasian. Treatment-emergent adverse reactions occurring at an incidence of >2% are provided in Table 2. The most frequent adverse reactions were hypotension, bradycardia and dry mouth. *[see Warnings and Precautions (5.2)]*.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.