

PRODUCT MONOGRAPH



PRECEDEX™

Dexmedetomidine Hydrochloride for Injection

100 mcg/mL in a 2 mL glass vial

Dexmedetomidine (supplied as dexmedetomidine hydrochloride)

Alpha₂-adrenergic agonist

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PRECEDEX™

Dexmedetomidine Hydrochloride for Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
IV infusion	Parenteral injection, 100 mcg/mL in a 2 mL vial	Sodium Chloride 0.9%

INDICATIONS AND CLINICAL USE

Precedex™ (Dexmedetomidine Hydrochloride for Injection) is indicated for:

- **Intensive Care Unit Sedation**

Precedex™ is indicated for sedation of initially intubated and mechanically ventilated post-surgical patients during treatment in an intensive care setting by continuous intravenous infusion. The Precedex™ infusion must not 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. After extubation, the dose of Precedex™ should be reduced by half. The mean time of continued infusion is approximately 6.6 hours.

- **Conscious Sedation**

Precedex™ is indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures by continuous intravenous infusion for the following procedures:

- Monitored Anesthesia Care (MAC) with an adequate nerve block and/or local infiltration; and
- Awake Fiberoptic Intubation (AFI) with adequate topical preparation of the upper airway with local lidocaine formulations.

Due to insufficient safety and efficacy data, Precedex™ is not recommended for use in procedures other than the two listed above.

Geriatrics (> 65 years of age): Dosage adjustment in this population is recommended (see **Dosage and Administration**).

Pediatrics: There have been no clinical studies to establish the safety and efficacy of Precedex™ in pediatric patients younger than 18 years of age. Therefore, Precedex™ should not be used in this population.

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **Dosage Forms, Composition and Packaging** section of the product monograph.

WARNINGS AND PRECAUTIONS

General

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™.

Cardiovascular

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 situations where other vasodilators or negative chronotropic agents are administered, co-administration of Precedex™ could have an additive pharmacodynamic effect and should be administered with caution.

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 dose infusion rate may be desirable.

Dependence/Tolerance

Precedex™ is not a controlled substance. The dependence potential of Precedex™ has not been studied in humans.

Endocrine and Metabolism

The available evidence is inadequate to confirm if dexmedetomidine is associated with significant adrenocortical suppression. The adequacy of the adrenocortical function should be individually assessed and managed.

Hepatic/Biliary/Pancreatic

Since Precedex™ clearance decreases with severity of hepatic impairment, dose reduction should be considered in patients with impaired hepatic function.

Renal

Precedex™ 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. (See **Dosage and Administration**)

Peri-Operative Considerations

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.

Withdrawal

Intensive Care Unit

Precedex™ is indicated only for sedation of initially intubated and mechanically ventilated post-operative patients recovering in a post-operative care unit or an intensive care unit. During the use of Precedex™ in an intensive care setting, the patients must be monitored continuously, particularly for their cardiovascular safety indicators.

If Precedex™ were to be administered for more than 24 hours and stopped abruptly, withdrawal symptoms similar to those reported for other alpha-2-adrenergic agents may result. These symptoms include nervousness, agitation, and headaches, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma. Precedex™ infusion must not exceed 24 hours.

Conscious Sedation

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

Patient Counselling Information

Precedex™ is indicated for short-term intravenous sedation. Dosage must be individualized and titrated to the desired clinical effect. Blood pressure, heart rate and oxygen levels will be monitored both continuously during the infusion of Precedex™ and as clinically appropriate after discontinuation.

- When Precedex™ is infused for more than 6 hours, patients should be informed to report nervousness, agitation, and headaches that may occur for up to 48 hours.
- Additionally, patients should be informed to report symptoms that may occur within 48 hours after the administration of Precedex™ such as: weakness, confusion, excessive sweating, weight loss, abdominal pain, salt cravings, diarrhea, constipation, dizziness or light-headedness.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. Precedex™ 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 Women: It is not known whether Precedex™ is excreted in human milk. Radio-labeled Precedex™ 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.

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™ should not be used in this population.

Geriatrics: Precedex™ 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.

Intensive Care Unit Sedation

A total of 849 patients in the clinical studies were 65 years of age and over. A total of 242 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™. Therefore a dose reduction should be considered in patients over 65 years of age (**see Dosage and Administration**).

Conscious 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%). Pre-specified criteria for the vital signs to be reported as adverse reactions are footnoted below Table 3 (see **Adverse Reactions**). 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 (see **Dosage and Administration**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

- Hypotension, bradycardia and sinus arrest (see **Warnings and Precautions**),
- Transient hypertension (see **Warnings and Precautions**).

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

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Intensive Care Unit Sedation

Adverse event information derived from the placebo-controlled, continuous infusion trials of Precedex™ for sedation in the surgical intensive care unit setting in which 387 patients received Precedex™. In these studies, the mean total dose was 7.06 mcg/kg (SD = 2.86), mean dose per hour was 0.51 mcg/kg/hr (SD = 0.39) and the mean duration of infusion of 15.6 hours (range: 0.17 to 29.08). Midazolam or propofol was used as the rescue medication for patients on Precedex™ or placebo. The population was between 19 to 83 years of age, 43% ≥ 65 years of age, 73% male and 97% Caucasian. Overall, the most frequently observed treatment-emergent adverse events included hypotension, hypertension, nausea, bradycardia, fever, vomiting, hypoxia, tachycardia and anemia (see Table 1).

Table 1: Treatment-Emergent Adverse Events Occurring in >1% Of All Dexmedetomidine-Treated Patients in the Randomized Placebo-controlled Continuous Infusion Short-Term Intensive Care Unit Sedation Studies			
Adverse Event	Randomized Dexmedetomidine* (N=387)	Placebo with Midazolam Rescue (N=181)	Placebo with Propofol Rescue (N=198)
Hypotension	28%	15%	10%
Hypertension	16%	13%	23%
Nausea	11%	9%	10%
Bradycardia	7%	3%	2%
Fever	5%	6%	4%
Vomiting	4%	6%	6%
Atrial Fibrillation	4%	4%	3%
Hypoxia	4%	5%	3%
Tachycardia	3%	7%	3%
Hemorrhage	3%	6%	4%
Anemia	3%	4%	1%
Dry Mouth	3%	2%	<1%
Rigors	2%	3%	4%
Agitation	2%	3%	3%
Hyperpyrexia	2%	3%	2%
Pain	2%	3%	1%
Hyperglycemia	2%	3%	1%
Acidosis	2%	<1%	3%
Pleural Effusion	2%	<1%	2%
Oliguria	2%	1%	<1%
Thirst	2%	<1%	<1%

* Data combined from studies conducted in post-surgical patients recovering in an ICU setting.

Conscious Sedation

Adverse event information is derived from the two trials for conscious sedation in which 318 patients received Precedex™. Midazolam was used as the rescue medication for patients on Precedex™ or placebo. The mean total dose was 1.6 mcg/kg (range: 0.5 to 6.7), mean dose per hour was 1.3 mcg/kg/hr (range: 0.3 to 6.1) and the mean duration of infusion of 1.5 hours (range: 0.1 to 6.2). The population was between 18 to 93 years of age, 30% ≥ 65 years of age, 52% male and 61% Caucasian.

Treatment-emergent adverse events occurring at an incidence of >2% are provided in Table 2. The most frequent adverse events were hypotension, bradycardia, and dry mouth. Pre-specified

criteria for the vital signs to be reported as adverse reactions are footnoted below the table. The decrease in respiratory rate and hypoxia was similar between Precedex™ and comparator groups in both studies.

Table 2: Adverse Events with an Incidence > 2% - Conscious Sedation Population

Body System/ Adverse Event	Precedex™ N = 318	Placebo N = 113
	n (%)	n (%)
Vascular disorders		
Hypotension ¹	173 (54%)	34 (30%)
Hypertension ²	41 (13%)	27 (24%)
Respiratory, thoracic and mediastinal disorders		
Respiratory depression ⁵	117 (37%)	36 (32%)
Hypoxia ⁶	7 (2%)	3 (3%)
Bradypnea	5 (2%)	5 (4%)
Cardiac disorders		
Bradycardia ³	45 (14%)	4 (4%)
Tachycardia ⁴	17 (5%)	19 (17%)
Gastrointestinal disorders		
Nausea	10 (3%)	2 (2%)
Dry mouth	8 (3%)	1 (1%)

¹ Hypotension was defined in absolute and relative terms as Systolic blood pressure of <80 mmHg or ≤30% lower than pre-study drug infusion value, or Diastolic blood pressure of <50 mmHg

² Hypertension was defined in absolute and relative terms as Systolic blood pressure >180 mmHg or ≥30% higher than pre-study drug infusion value or Diastolic blood pressure of >100 mmHg.

³ Bradycardia was defined in absolute and relative terms as <40 bpm or ≤30% lower than pre-study drug infusion value.

⁴ Tachycardia was defined in absolute and relative terms as >120 bpm or ≥30% greater than pre-study drug infusion value.

⁵ Respiratory Depression was defined in absolute and relative terms as respiratory rate (RR) <8 bpm or >25% decrease from baseline

⁶ Hypoxia was defined in absolute and relative terms as SpO₂ < 90% or 10% decrease from baseline

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post approval use of Precedex™. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypotension and bradycardia were the most common adverse reactions associated with the use of Precedex™ during post approval use of the drug.

Table 3: Adverse Events Experienced During Post approval Use of Precedex™	
Body System	Preferred Term
Body as a Whole	Fever, hyperpyrexia, hypovolemia, light anesthesia, pain, rigors
Cardiovascular Disorders, General	Blood pressure fluctuation, heart disorder, hypertension, hypotension, myocardial infarction
Central and Peripheral Nervous System Disorders	Dizziness, headache, neuralgia, neuritis, speech disorder, convulsion
Gastrointestinal System Disorders	Abdominal pain, diarrhea, vomiting, nausea
Heart Rate and Rhythm Disorders	Arrhythmia, ventricular arrhythmia, bradycardia, hypoxia, atrioventricular block, cardiac arrest, extrasystoles, atrial fibrillation, heart block, t wave inversion, tachycardia, supraventricular tachycardia, ventricular tachycardia
Liver and Biliary System Disorders	Increased gamma-glutamyl transpeptidase, hepatic function abnormal, hyperbilirubinemia, increased alanine transaminase, increased 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

DRUG INTERACTIONS

Drug-Drug Interactions

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.

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 of neuromuscular blockade associated with rocuronium administration.

Cytochrome P-450

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Precedex™ should be used in only facilities adequately staffed and equipped for anesthesia, resuscitation, and cardiovascular monitoring.
- Precedex™ dosing should be individualized and titrated to the desired clinical response.
- Precedex™ is not indicated for infusions lasting longer than 24 hours.
- Precedex™ should be administered using a controlled infusion device with adequate precision.

Recommended Dose and Dosage Adjustment

Intensive Care Unit Sedation

- Precedex™ is indicated for post-surgical patients in an intensive care setting, e.g. in Post Anesthesia Care Unit or Intensive Care Unit.
- An assessment of the level of sedation and the need for Precedex™ should precede the initiation of Precedex.
- Another intravenous sedative (e.g. midazolam or propofol) may be added if Precedex™ provides inadequate sedation at the highest recommended dose level.
- The need for Precedex™ continuous infusion post-extubation must be assessed individually. If the continuous infusion is needed post-extubation, the infusion speed should be reduced by half. The mean time of continued infusion is approximately 6.6 hours.

- Precedex™ use should not exceed 24 hours in an ICU setting.

A dose reduction for both the loading and maintenance infusions should be considered in patients with impaired hepatic or renal function and in patients over 65 years of age.

Initiation

For adult patients, Precedex™ is generally initiated with a loading infusion of up to one mcg/kg over 10 to 20 minutes, if needed.

For patients being converted from alternate sedative therapy a loading dose may not be required.

Maintenance

Adult patients will generally require 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.

Conscious Sedation

- Based on the Ramsay and Observer's Assessment of Alertness/Sedation Scales, the loading infusion provides clinically effective onset of sedation 10 to 15 minutes after start of infusion.
- For use in Monitored Anesthesia Care, an adequate nerve block and/or local infiltration should be used.
- For Awake Fiberoptic Intubation, the upper airway should be topicalized with proper lidocaine formulations.

Initiation

For adult patients, Precedex™ is generally initiated with a loading infusion of one mcg/kg over 10 minutes.

For patients over 65 years of age or those undergoing less invasive procedures such as ophthalmic surgery, a loading infusion of 0.5 mcg/kg over 10 minutes may be suitable.

Maintenance

The maintenance infusion of Precedex™ 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.

Following the load in awake fiberoptic intubation, a fixed maintenance dose of 0.7 mcg/kg/hr is recommended until the endotracheal tube is secured.

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.

A dose reduction for both the loading and maintenance infusions should be considered in patients with impaired hepatic or renal function and in patients over 65 years of age.

Administration

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.

Compatibility with Other Fluids

Precedex™ has been shown to be compatible when administered with the following intravenous fluids: Lactated Ringers, 5% Glucose in Water, 0.9% Sodium Chloride in Water, 20% Mannitol in Water.

Dexmedetomidine has been found to be compatible with water solutions of the following drugs when administered via Y-site injections: thiopental sodium, vecuronium bromide, pancuronium bromide, glycopyrrolate bromide, phenylephrine hydrochloride.

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.

Incompatibilities

Precedex™ infusion should not be co-administered through the same IV catheter with blood, serum, 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.

OVERDOSAGE

The tolerability of Precedex™ was studied 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 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.

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

General

Precedex™ is a relatively selective α_2 -adrenergic agonist with sedative properties. α_2 selectivity is observed in animals following slow intravenous infusion of low and medium doses (10–300 mcg/kg). Both α_1 and α_2 activity is observed following slow intravenous infusion of high doses (≥ 1000 mcg/kg) or with rapid intravenous 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 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 4 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 4: Mean ± SD Pharmacokinetic Parameters				
Parameter	Loading Infusion (min)/Total infusion duration (hrs)			
	10 min/12 hrs	10 min/24 hrs	10 min/24 hrs	35 min/24 hrs
	Dexmedetomidine Target Concentration (ng/mL) and 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 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.

Avg C_{ss} = 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 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) 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 dexmedetomidine-N-methyl O-glucuronide.

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.

Special Populations and Conditions

Pediatrics:

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

Geriatrics:

The pharmacokinetic profile of Precedex™ was not altered by age. There were no differences in the pharmacokinetics of Precedex™ in young (18 – 40 years), middle age (41 – 65 years), and elderly (>65 years) subjects. However, in clinical trials an increased incidence of adverse events was observed in the elderly, and a dose reduction for both the loading and maintenance infusions should be considered in patients over 65 years of age. **(See Dosing and Administration)**

Gender: There was no observed difference in Precedex™ pharmacokinetics due to gender.

Hepatic Impairment: In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values for Precedex™ 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. In clinical trials an increased incidence of adverse events was observed in these patients, and a dose reduction for both the loading and maintenance infusions should be considered in patients with impaired hepatic function. **(See Dosing and Administration)**

Renal Impairment: Precedex™ pharmacokinetics (C_{max} , T_{max} , AUC, $t_{1/2}$, CL, and V_{ss}) were not significantly different in patients with severe renal impairment (creatinine clearance: <30 mL/min) compared to healthy subjects. Precedex™ 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 reduce the dose and monitor renal function. **(See Dosing and Administration)**

Concomitant Opioid Use: In Intensive Care Unit, 41-44% of Precedex™ treated patients received no morphine sulfate for pain versus 15-19% in the placebo-treated patients.

In conscious sedation, 39.6-56.6% of Precedex™ treated patients received no fentanyl for pain versus 11.1% of placebo-treated patients.

STORAGE AND STABILITY

Store at controlled room temperature, 25°C (77°F) with excursions allowed from 15 to 30°C (59 to 86°F). [See USP.]

DOSAGE FORMS, COMPOSITION AND PACKAGING

Precedex™ (dexmedetomidine hydrochloride for Injection) is a sterile, nonpyrogenic solution suitable for intravenous infusion following dilution.

Each 1 mL of Precedex™ contains 118 mcg of dexmedetomidine hydrochloride equivalent to 100 mcg dexmedetomidine and 9 mg of sodium chloride in water. The solution is preservative-free and contains no additives or chemical stabilizers.

Precedex™ (Dexmedetomidine Hydrochloride for Injection), 100 mcg/mL as the base is available in 2 mL clear glass vials (200 mcg/2 mL). Vials are intended for single use only.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

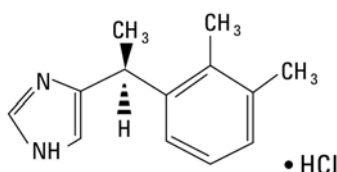
Proper name: dexmedetomidine hydrochloride

Chemical name: (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazolemonohydrochloride.

Molecular formula: $C_{13}H_{16}N_2 \cdot HCl$

Molecular mass: 236.7

Structural formula:



Physicochemical properties: Dexmedetomidine hydrochloride is a white or almost white powder that is freely soluble in water and has a pKa of 7.1. Precedex™ is supplied as a clear, colorless, isotonic solution with a pH of 4.5 to 7.0.

CLINICAL TRIALS

The safety and efficacy of Precedex™ has been evaluated in four randomized, double-blind, placebo-controlled multicenter clinical trials in 1185 patients. The studies for use in an ICU setting were conducted for use for less than 24 hours.

Study results

Intensive Care Unit Sedation

Two randomized, double-blind, parallel-group, placebo-controlled multicenter clinical trials included 754 patients being treated in a surgical intensive care unit. All patients were initially intubated and received mechanical ventilation. These trials evaluated the sedative properties of Precedex™ 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 5.

Table 5: Ramsay 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 Precedex™ 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 one mcg/kg intravenous 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 needed to augment the study drug infusion. In addition, morphine sulfate was administered for pain as needed.

The prospective primary analysis assessed the sedative effects of Precedex™ 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 Precedex™ group maintained a Ramsay sedation score of ≥ 3 without receiving any midazolam rescue compared to the placebo group (see Table 6).

Table 6: Midazolam use as rescue medication during intubation (ITT)			
Study One			
	Placebo N=175	Precedex™ N=178	p-value
Categorized midazolam use			
0 mg	43 (25%)	108 (61%)	<0.001**
0-4 mg	34 (19%)	36 (20%)	
>4 mg	98 (56%)	34 (19%)	

ITT (intent-to-treat) population includes all randomized patients.

**Chi-square

In a second study, 198 patients were randomized to receive placebo and 203 to receive Precedex™ 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 one mcg/kg intravenous 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.

A significantly greater percentage of patients in the Precedex™ group compared to the placebo group maintained a Ramsay sedation score of ≥ 3 without receiving any propofol rescue (see Table 7).

Table 7: Propofol use as rescue medication during intubation (ITT)			
Study Two			
	Placebo N=198	Precedex™ N=203	p-value
Categorized propofol use			
0 mg	47 (24%)	122 (60%)	<0.001**
0-50 mg	30 (15%)	43 (21%)	
>50 mg	121 (61%)	38 (19%)	

**Chi-square

Conscious Sedation

The safety and efficacy of Precedex™ for sedation of non-intubated patients prior to and/or during surgical and other procedures was evaluated in two randomized, double-blind, placebo-controlled multicenter clinical trials. Study 1 evaluated the sedative properties of Precedex™ in patients having a variety of elective surgeries/procedures performed under monitored anesthesia care. Study 2 evaluated Precedex™ in patients undergoing awake fiberoptic intubation prior to a surgical or diagnostic procedure.

In Study 1, the sedative properties of Precedex™ were evaluated by comparing the percent of patients not requiring rescue midazolam to achieve a specified level of sedation using the standardized Observer’s Assessment of Alertness/Sedation Scale (Table 8).

Table 8: Observer’s Assessment of Alertness/Sedation

Assessment Categories				
<u>Responsiveness</u>	<u>Speech</u>	<u>Facial Expression</u>	<u>Eyes</u>	<u>Composite Score</u>
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	5 (alert)
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	Few recognizable words	--	--	2
Does not respond to mild prodding or shaking	--	--	--	1 (deep sleep)

Patients were randomized to receive a loading infusion of either Precedex™ 1 mcg/kg, 0.5 mcg/kg, or placebo (normal saline) given over 10 minutes and followed by a maintenance infusion started at 0.6 mcg/kg/hr. The maintenance infusion of study drug could be titrated from 0.2 mcg/kg/hr to 1 mcg/kg/hr to achieve the targeted sedation score (Observer’s Assessment of Alertness/Sedation Scale \leq 4). Patients were allowed to receive rescue midazolam as needed to achieve and/or maintain an Observer’s Assessment of Alertness/Sedation Scale \leq 4. After achieving the desired level of sedation, a local or regional anesthetic block was performed. Demographic characteristics were similar between the Precedex™ and comparator groups. Efficacy results showed that Precedex™ was more effective than the comparator group when used to sedate non-intubated patients requiring monitored anesthesia care during surgical and other procedures (See Table 9).

In Study 2 the sedative properties of Precedex™ were evaluated by comparing the percent of patients requiring rescue midazolam to achieve or maintain a specified level of sedation using the Ramsay Sedation Scale score \geq 2 (Table 5). Patients were randomized to receive a loading infusion of Precedex™ of 1 mcg/kg or placebo (normal saline) given over 10 minutes and followed by a fixed maintenance infusion of 0.7 mcg/kg/hr. After achieving the desired level of sedation, topicalization of the airway was carried out with lidocaine formulations. Patients were allowed to receive rescue midazolam as needed to achieve and/or maintain an Ramsay Sedation Scale \geq 2. Demographic characteristics were similar between the Precedex™ and comparator groups. For efficacy results see Table 9.

Table 9: Key Efficacy Results of Conscious Sedation Studies

Study	Treatment Arm	No. of Patients Enrolled ^a	% Not Requiring midazolam rescue	Confidence ^b interval on the difference vs. placebo	Mean (SD) Total Dose (mg) of Rescue midazolam Required	Confidence ^b intervals of the mean rescue dose
Study 1	Precedex™ 0.5 mcg/kg	134	40	37 (27,48)	1.4 (1.7)	-2.7 (-3.4, -2.0)
	Precedex™ 1 mcg/kg	129	54	51 (40,62)	0.9 (1.5)	-3.1 (-3.8, -2.5)
	PBO	63	3	–	4.1 (3.0)	–
Study 2	Precedex™ 1 mcg/kg	55	53	39 (20,57)	1.1 (1.5)	-1.8 (-2.7, -0.9)
	PBO	50	14	–	2.9 (3.01)	–

Notes:

^a Based on ITT population defined as all randomized and treated

^b Normal approximation to the binomial with continuity correction.

DETAILED PHARMACOLOGY

Primary Pharmacodynamics

Dexmedetomidine administered subcutaneously (SC) in mice using the rotarod and traction tests indicated that it was a poor muscle-relaxant, and that it impaired motor coordination only at the clearly sedative doses of 0.01 and 0.1 mg/kg.

Secondary Pharmacodynamics

Dexmedetomidine administered subcutaneously in doses up to 0.3 mg/kg in fed rats demonstrated a significant, dose-dependent elevation of blood glucose levels, with negative correlation to plasma immunoreactive insulin levels. Insulin secretion was almost totally inhibited beginning at the 0.1 mg/kg dose. Dexmedetomidine did not show any effect on the level of free fatty acids.

Dexmedetomidine given intravenously is devoid of clear CNS activity up to 0.001 mg/kg in mice and rats; at higher doses (≥ 0.003 mg/kg), dexmedetomidine induced clear CNS depressant effects.

Pharmacokinetics

In beagle dogs, dexmedetomidine was rapidly eliminated following a 50 mcg/kg IV dose with a mean apparent $t_{1/2}$ of 0.68 hour; plasma elimination $t_{1/2}$ was slightly longer following intramuscular (IM) dosing.

Rats administered an intravenous 20 mcg/kg dose of [³H]dexmedetomidine showed drug-related radioactivity widely distributed throughout the body, with the highest mean concentrations in blood, plasma, and selected tissues occurring from 0.25 to 12 hours postdose.

[³H]dexmedetomidine was extensively metabolized by rats. Less than 1% of the dose was excreted in the urine as the parent drug. Major urinary metabolites included the COOH, OH, G-OH, SO₃OH, M-2, and M-5 metabolites. Levels of the SO₃OH metabolite were greater in female urine than in male urine. Fecal patterns generally resembled those found in urine.

The metabolism of [³H]dexmedetomidine in beagle dogs was similar to that observed in rats. Biliary excretion of [³H]dexmedetomidine following IV and SC administration was studied in rats with an implanted bile-duct cannula; an average of 51.6% and 45.4% of the radioactive dose was recovered in rat bile 24 hours after IV and SC administration, respectively. Major biliary metabolites were the glucuronide of a hydroxylated metabolite (G-OH) and an unidentified conjugate, M-2. Unidentified metabolites represented 12% to 18% of the dose.

Lacteal excretion, tissue distribution, and placental transfer of radioactivity were studied in rats following administration of a 0.015 mg/kg SC dose of [³H]dexmedetomidine. Radioactivity was distributed in maternal tissues and crossed the placenta to distribute in fetal tissues. Drug-related radioactivity was detected in the milk of dams at 0.5 hours and reached a maximum mean concentration at 4 hours. Thereafter, levels of radioactivity in milk decreased to non-detectable levels at 72 hours. The milk:plasma concentration ratio was less than 1 at all collection time points, indicating that radioactivity did not accumulate in the milk.

TOXICOLOGY

Acute Toxicity

The highest non-lethal dose by intravenous injects were 1000 mcg/kg in mice, rats and dogs in both sexes.

Long-Term Toxicology

A two-week IV infusion study in adult dogs was performed to investigate the potential effect of dexmedetomidine on toxicologic, pathologic, and hormone secretion parameters.

Dexmedetomidine at 50 or 100 mcg/kg/day was well-tolerated, with treatment-related effects (sedation, hypothermia (↓ 3-4°C)) reversed by the end of the recovery period.

Dexmedetomidine increased cortisol secretion, decreased LH secretion in males, decreased TSH secretion, and at the 100 mcg/kg/day dose level, decreased ACTH-stimulated cortisol secretion.

Rats receiving dexmedetomidine by IV administration for four weeks at doses up to 160 mcg/kg/day showed sedation and piloerection occurring at all doses, with exophthalmos observed only at the highest dose. No deaths occurred. Based on the drug-related small decreases in thymus and body weights at 160 mcg/kg/day, the no-toxic-effect-dose (NTED) of dexmedetomidine was determined to be 40 mcg/kg/day.

Carcinogenicity

Animal carcinogenicity studies have not been performed with dexmedetomidine.

Genotoxicity

Dexmedetomidine was not found to be mutagenic in the Ames *Salmonella* and *E. coli* assays, L5178/*tk*^{+/−} mouse lymphoma assay, in vitro human lymphocyte cytogenetics assays, and in vivo mouse micronucleus assays. No structural or numerical chromosome aberrations were noted in the presence or absence of metabolic activation. Dexmedetomidine did not demonstrate clastogenic activity.

Reproductive Toxicology

Reproductive and developmental toxicity studies were performed with dexmedetomidine in rats and rabbits.

A fertility study (Segment I) in rats at doses up to 54 mcg/kg/day administered subcutaneously showed that the No-Observed-Adverse-Effect Level (NOAEL) for F0 males and females was 54 mcg/kg/day for fertility indices and 6 mcg/kg/day for systemic toxicity. The NOAEL for F1 development was considered to be at 6 mcg/kg/day

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/m² 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 post-implantation losses and reduced live pups, was observed in rats at 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/m² 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 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/m² 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/m² basis). No such effects were observed at a dose of 2 mcg/kg (less than the maximum recommended intravenous dose on a mcg/m² basis). Placental transfer of dexmedetomidine was observed when radiolabeled dexmedetomidine was administered subcutaneously to pregnant rats.

In rabbits, the influence of dexmedetomidine on teratogenicity (Segment II) after IV administration in doses up to 96 mcg/kg/day was investigated. The NOAEL was 96 mcg/kg/day for maternal toxicity and 96 mcg/kg/day for F1 development. No higher dose was feasible. No teratogenicity was observed in any dose level tested.

Prenatal and postnatal development (Segment III study) was examined in rats at doses up to 32 mcg/kg/day administered subcutaneously. The NOAEL was 8 mcg/kg/day for maternal toxicity and 2 mcg/kg/day for F1 development.

Local Tolerance Studies

A solution of dexmedetomidine was shown to be mildly irritating in rats when injected intramuscularly.

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PART III: CONSUMER INFORMATION

 **Precedex™**

Dexmedetomidine Hydrochloride for Injection

This leaflet is part III of a three-part "Product Monograph" published when Precedex™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Precedex™. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Precedex™ is used

- for continuous sedation (to keep you calm) after you arrive at the intensive care unit after your surgery under a general anesthesia
- for sedation when you receive certain surgical procedures under a local anesthesia or nerve block or when you receiving a breathing tube while awake

What it does:

Precedex™ acts by activating a part of the brain which helps keep you calm.

When it should not be used:

You should tell your doctor if you are pregnant or nursing.

What the medicinal ingredient is:

The active ingredient in Precedex™ is dexmedetomidine hydrochloride.

What the important nonmedicinal ingredients are:

The only nonmedicinal ingredients in Precedex™ are sodium chloride and water. Precedex™ is preservative-free and contains no additives or other chemicals.

What dosage forms it comes in:

Precedex™ is available as a solution containing 100 micrograms/mL of dexmedetomidine that will be further diluted into saline and given to you by intravenous infusion. The Precedex™ solution is available in a 2mL glass vial.

WARNINGS AND PRECAUTIONS

BEFORE you use Precedex™ talk to your doctor or pharmacist if:

- you have heart problems, including chronic high blood pressure
- you have diabetes mellitus
- you have liver problems
- you are taking any other medicines
- you are pregnant or think you might be pregnant
- you are nursing
- you have any allergies to this drug or its ingredients or components of the container

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with Precedex™ include: sevoflurane, isoflurane, propofol, alfentanil, and midazolam. Administration of Precedex™ with such anesthetic, sedative, hypnotic or opioid drugs are likely to lead to an increase in effect.

PROPER USE OF THIS MEDICATION

Usual dose:

Dosage will be individualized and titrated to the desired clinical effect. You will be given a loading dose followed by a maintenance dose, specific for your body weight and the procedure you are undergoing. Your doctor will decide what the appropriate dose is for your specific case.

Your doctor and/or nurse will monitor blood pressure, heart rate and oxygen levels, both continuously during the infusion of Precedex™ and as clinically appropriate after discontinuation.

It is important that following the return of consciousness, you do not attempt to change position or rise from bed without assistance.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects of Precedex™

administration are: low or high blood pressure, slowing of the heartbeat, and dry mouth.

If Precedex™ is given to you in an infusion for more than 6 hours, it is important that you report to your doctor any nervousness, agitation, and headaches that may occur for up to 48 hours.

Additionally, you should report symptoms that may occur within 48 hours after you are given Precedex™ such as: weakness, confusion, excessive sweating, weight loss, abdominal pain, salt cravings, diarrhea, constipation, dizziness or light-headedness.

Report immediately any pounding or unusual heartbeat, or respiratory difficulty.

Excessive sweating	Talk with your doctor.
Weight loss	Talk with your doctor.
Abdominal pain	Talk with your doctor.
Salt cravings	Talk with your doctor.
Diarrhea	Talk with your doctor.
Constipation	Talk with your doctor.
Dizziness/ Lightheadedness	Talk with your doctor.
Respiratory difficulty	Call your doctor immediately or 911.

This is not a complete list of side effects. For any unexpected effects while taking Precedex™, contact your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

After exposure to Precedex™, you should contact your physician or anesthesia professional if you have any of the following reactions:

Symptom / effect

Common

Hypotension (low blood pressure)	Call your doctor immediately or 911.
Hypertension (high blood pressure)	Call your doctor immediately or 911.
Bradycardia (slow heart beat)	Call your doctor immediately or 911.
Tachycardia (fast heart beat)	Call your doctor immediately or 911.
Dry mouth	Talk with your doctor.

Uncommon

Nervousness	Talk with your doctor.
Headaches	Talk with your doctor.
Agitation	Talk with your doctor.
Weakness	Talk with your doctor.
Confusion	Talk with your doctor.

HOW TO STORE IT

Precedex™ is stored between 15 to 30°C.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways.

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available in the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Hospira Healthcare Corporation at:
1-800-488-6088

This leaflet was prepared by Hospira Healthcare Corporation

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