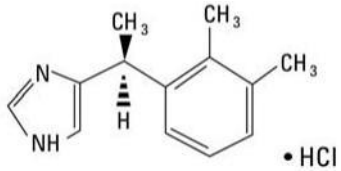
PT PFIZER INDONESIA
Local Product Document

Generic Name: Dexmedetomidine Hydrochloride
Trade Name: Precedex®
CDS Effective Date: Dec 23, 2025
Supersedes: N/A

Precedex® 100 µg/mL
Dexmedetomidine
Hydrochloride
Injection R_x only

DESCRIPTION

Precedex® (dexmedetomidine hydrochloride injection) is a sterile, nonpyrogenic solution suitable for intravenous infusion following dilution. Dexmedetomidine hydrochloride is the S-enantiomer of medetomidine and is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride. Dexmedetomidine has a molecular weight of 236.7 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 1 mL of Precedex® contains 118 mcg of dexmedetomidine HCl (equivalent to 100 mcg dexmedetomidine base) and 9 mg of sodium chloride in water. The solution is preservative-free and contains no additives or chemical stabilizers.

CLINICAL PHARMACOLOGY

General:

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

In a study in healthy volunteers (N=10), respiratory rate and oxygen saturation remained within normal limits and there was no evidence of respiratory depression when dexmedetomidine was administered by intravenous infusion at doses within the recommended dose range (0.2 - 0.7 mcg/kg/hr).

The safety and efficacy of Precedex® has been evaluated in four randomized, double-blind, placebo-controlled multicenter clinical trials in 1185 adult patients.

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

Table 1. Mean ± SD Pharmacokinetic Parameters

Parameter	Loading Infusion (min)/Total Infusion Duration (hrs)			
	10 min/12 hrs	10 min/24 hrs	10 min/24 hrs	35 min/24 hrs
	Dexmedetomidine Target Plasma 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
A_{vg} C_{ss}#, ng/mL	0.27 ± 0.05	0.27 ± 0.05	0.67 ± 0.10	1.37 ± 0.20

Abbreviations: $t_{1/2}$ = half-life, CL = clearance, V_{ss} = steady state volume of distribution.
* Presented as harmonic mean and pseudo standard deviation.
# Mean C_{ss} = Average steady-state concentration of dexmedetomidine. The mean C_{ss} was calculated based on post-dose sampling from 2.5 to 9 hour samples for 12 hour infusion and post-dose sampling from 2.5 to 18 hour samples 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.

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 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 Precedex® was explored *in vitro* and none of these compounds appeared to be significantly displaced by Precedex®.

Elimination

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 with a minor role of CYP1A2, CYP2E1, CYP2D6 and CYP2C19) of dexmedetomidine to generate 3-hydroxy dexmedetomidine, the glucuronide of 3-hydroxy dexmedetomidine, and 3-carboxy dexmedetomidine; and N-methylation of dexmedetomidine to generate 3-hydroxy N-methyl dexmedetomidine, 3-carboxy N-methyl dexmedetomidine, and N-methyl O-glucuronide dexmedetomidine.

Excretion

The terminal elimination half-life ($t_{1/2}$) of dexmedetomidine is approximately 2 hours and clearance is estimated to be approximately 39 L/h. A mass balance study demonstrated that after nine days an average of 95% of the radioactivity, following IV administration of radiolabeled dexmedetomidine, was recovered in the urine and 4% in the feces. No unchanged dexmedetomidine was detected in the urine. Approximately 85% of the radioactivity recovered in the urine was excreted within 24 hours after the infusion. Fractionation of the radioactivity excreted in urine demonstrated that products of N-glucuronidation accounted for approximately 34% of the cumulative urinary excretion. In addition, aliphatic hydroxylation of parent drug to form 3-hydroxy dexmedetomidine, the glucuronide of 3-hydroxy dexmedetomidine, and 3-carboxylic acid dexmedetomidine together represented approximately 14% of the dose in urine. N-methylation of dexmedetomidine to form 3-hydroxy N-methyl dexmedetomidine, 3-carboxy N-methyl dexmedetomidine, and N-methyl O-glucuronide dexmedetomidine accounted for approximately 18% of the dose in urine. The N-Methyl metabolite itself was a minor circulating component and was undetected in urine. Approximately 28% of the urinary metabolites have not been identified.

Specific Populations

Male and Female Patients:

There was no observed difference in Precedex® pharmacokinetics due to gender.

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.

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

Renal Impairment:
Dexmedetomidine pharmacokinetics (C_{max}, T_{max}, AUC, $t_{1/2,}$ CL, and $V_{SS)}$ were not significantly different in patients with severe renal impairment (creatinine clearance: <30 mL/min) compared to healthy subjects. However, the pharmacokinetics of the metabolites of dexmedetomidine have not been evaluated in patients with impaired renal function. Since the majority of metabolites are excreted in the urine, it is possible that the metabolites may accumulate upon long-term infusions in patients with impaired renal function. (See ***WARNINGS AND PRECAUTIONS***, ***DOSAGE AND ADMINISTRATION***).

Hepatic Impairment:
In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values for dexmedetomidine were lower than in healthy subjects. The mean clearance values for 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.

Although Precedex® is dosed to effect, it may be necessary to consider dose reduction in subjects with hepatic impairment (see ***WARNINGS AND PRECAUTIONS***, **Hepatic Impairment** and ***DOSAGE AND ADMINISTRATION***).

Clinical Trials:
The safety and efficacy of Precedex® has been evaluated in two randomized, double-blind, parallel-group, placebo-controlled multicenter clinical trials included 754 adult patients being treated in a surgical intensive care unit (ICU). All patients were initially intubated and received mechanical ventilation. These trials evaluated the sedative properties of 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 2.

Table 2: Ramsay Level of Sedation Scale	
Clinical Score	**Level of Sedation Achieved**
6	Asleep, no response
5	Asleep, sluggish response to light glabellar tap or loud auditory stimulus
4	Asleep, but with brisk response to light glabellar tap or loud auditory stimulus
3	Patient responds to commands
2	Patient cooperative, oriented, and tranquil
1	Patient anxious, agitated, or restless

In the first study, 175 patients were randomized to receive placebo and 178 to receive 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 IV 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 primary outcome measure for this study was the total amount of rescue medication (midazolam) needed to maintain sedation as specified while intubated. Patients randomized to placebo received significantly more midazolam than patients randomized to Precedex® (see Table 3).

A second 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 3).

Table 3: Midazolam Use as Rescue Medication During Intubation (ITT) Study One			
	Placebo (N=175)	**Precedex® (N=178)**	**p-value**
Mean Total Dose (mg) of Midazolam	19 mg	5 mg	0.0011*
Standard deviation	53 mg	19 mg	
Categorised 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.
*ANOVA model with treatment center.
**Chi-square

A prospective secondary analysis assessed the dose of morphine sulfate administered to patients in the Precedex® and placebo groups. On average, Precedex®-treated patients received less morphine sulfate for pain than placebo-treated patients (0.47 versus 0.83 mg/h). In addition, 44% (79 of 178 patients) of Precedex® patients received no morphine sulfate for pain versus 19% (33 of 175 patients) in the placebo group.

In a second study, 198 adult 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 1 (one) mcg/kg IV over 10 minutes. The study drug infusion was adjusted to maintain a Ramsay sedation score of ≥ 3. Patients were allowed to receive "rescue" propofol as needed to augment the study drug infusion. In addition, morphine sulfate was administered as needed for pain. The primary outcome measure for this study was the total amount of rescue medication (propofol) needed to maintain sedation as specified while intubated.

Patients randomized to placebo received significantly more propofol than patients randomized to Precedex® (see Table 4).

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 4).

Table 4: Propofol Use as Rescue Medication During Intubation (ITT) Study Two

	Placebo (N=198)	**Precedex® (N=203)**	**p-value**
Mean Total Dose (mg) of Propofol	513 mg	72 mg	<0.0001*
Standard deviation	782 mg	249 mg	
Categorised Propofol Use			
0 mg	47 (24%)	122 (60%)	<0.001**
0-50 mg	30 (15%)	43 (21%)	
>50 mg	121 (61%)	38 (19%)	

*ANOVA model with treatment center.
**Chi-square

A prospective secondary analysis assessed the dose of morphine sulfate administered to patients in the Precedex® and placebo groups. On average, Precedex®-treated patients received less morphine sulfate for pain than placebo-treated patients (0.43 versus 0.89 mg/h). In addition, 41% (83 of 203 patients) of Precedex® patients received no morphine sulfate for pain versus 15% (30 of 198 patients) in the placebo group.

In a controlled clinical trial, Precedex® was compared to midazolam for ICU sedation exceeding 24 hours duration. Precedex® was not shown to be superior to midazolam for the primary efficacy endpoint, the percent of time patients were adequately sedated (81% versus 81%).

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

WARNINGS AND PRECAUTIONS

Drug Administration:

Dexmedetomidine hydrochloride is for hospital use only. Dexmedetomidine hydrochloride should be administered only by persons skilled in the management of patients in the intensive care setting. Due to the known pharmacological effects of dexmedetomidine hydrochloride, patients should be continuously monitored (MAC: Monitored Anesthesia Care) for early signs of hypotension, hypertension, bradycardia, respiratory depression, airway obstruction, apnoea, dyspnoea and/or oxygen desaturation while receiving dexmedetomidine hydrochloride. Supplemental oxygen should be immediately available and provided when indicated.

Hypotension, Bradycardia, and Sinus Arrest

Clinically significant episodes of bradycardia and sinus arrest have been associated with dexmedetomidine hydrochloride 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 dexmedetomidine hydrochloride infusion. Some of these cases have resulted in fatalities. If medical intervention is required, treatment may include decreasing or stopping the infusion of dexmedetomidine hydrochloride, increasing the rate of IV fluid administration, elevation of the lower extremities, and use of pressor agents. Because dexmedetomidine hydrochloride has the potential to augment bradycardia induced by vagal stimuli, clinicians should be prepared to intervene. The intravenous administration of anticholinergic agents (e.g., atropine) should be considered to modify vagal tone. In clinical trials, atropine or glycopyrrolate were effective in the treatment of most episodes of dexmedetomidine hydrochloride-induced bradycardia. However, in some patients with significant cardiovascular dysfunction, more advanced resuscitative measures were required.

Caution should be exercised when administering dexmedetomidine hydrochloride to patients with advanced heart block and/or severe ventricular dysfunction. Because dexmedetomidine hydrochloride decreases sympathetic nervous system activity, hypotension and/or bradycardia may be expected to be more pronounced in hypovolemic patients and in those with diabetes mellitus or chronic hypertension and in the elderly.

General

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

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

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

Arousability
Some patients receiving dexmedetomidine hydrochloride 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 Sedation
With administration up to 7 days, regardless of dose, 12 (5%) dexmedetomidine hydrochloride adult subjects experienced at least 1 event related to withdrawal within the first 24 hours after discontinuing study drug and 7 (3%) dexmedetomidine hydrochloride adult subjects experienced at least 1 event 24 to 48 hours after end of study drug. The most common events were nausea, vomiting, and agitation.

In adult subjects, 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 dexmedetomidine hydrochloride, supportive therapy is indicated.

Hyperthermia

Dexmedetomidine hydrochloride may induce hyperthermia that may be resistant to traditional cooling methods. Precedex® should be discontinued and hyperthermia should be managed with conventional medical measures.

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

Seizures
Dexmedetomidine lacks the anticonvulsant action of some other sedatives and so will not suppress underlying seizure activity.

Drug Interactions
General
In vitro studies did not demonstrate evidence for clinically relevant cytochrome P450-mediated drug interactions.

Anesthetics/Sedatives/Hypnotics/Opioids
Co-administration of dexmedetomidine hydrochloride with anesthetics, sedatives, hypnotics, and opioids is likely to lead to an enhancement of effects. Specific studies have confirmed these effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam. No pharmacokinetic interactions between dexmedetomidine hydrochloride and isoflurane, propofol, alfentanil and midazolam have been demonstrated. However, due to possible pharmacodynamic interactions, when co-administered with dexmedetomidine hydrochloride, a reduction in dosage of dexmedetomidine hydrochloride or the concomitant anesthetic, sedative, hypnotic or opioid may be required.

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

Drugs with Cardiovascular Activities
The possibility of enhanced hypotensive and bradycardic effects should be considered in patients receiving other medicinal products causing these effects, for example beta blockers, although additional effects in an interaction study with esmolol were modest.

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

Mutagenesis

Dexmedetomidine was not mutagenic *in vitro*, in either the bacterial reverse mutation assay *(E. coli* and *Salmonella typhimurium)* or the mammalian cell forward mutation assay (mouse lymphoma). Dexmedetomidine was clastogenic in the *in vitro* human lymphocyte chromosome aberration test with, but not without, rat S9 metabolic activation. In contrast, dexmedetomidine was not clastogenic in the *in vitro* human lymphocyte chromosome aberration test with or without human S9 metabolic activation. Although dexmedetomidine was also clastogenic in the *in vivo* mouse micronucleus test in NMRI mice, there was no evidence of clastogenicity in CD-1 mice.

Impairment of Fertility

Fertility in male or female rats was not affected after daily subcutaneous injections at of dexmedetomidine doses up to 54 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m^2 basis) administered from 10 weeks prior to mating in males, and 3 weeks prior to mating and during mating in females.

Animal Toxicology and/or Pharmacology

There were no differences in the adrenocorticotropic hormone (ACTH)-stimulated cortisol response in dogs following a single dose of dexmedetomidine compared to saline control. However, after continuous subcutaneous infusions of dexmedetomidine at 3 mcg/kg/hr and 10 mcg/kg/hr for one week in dogs (exposures estimated to be within the clinical range), the ACTH-stimulated cortisol response was diminished by approximately 27% and 40%, respectively, compared to saline-treated control animals indicating a dose-dependent adrenal suppression.

Pregnancy: Teratogenic Effects. *Pregnancy Category C*

Teratogenic effects were not observed following administration of dexmedetomidine at subcutaneous doses up to 200 mcg/kg in rats from day 5 to day 16 of gestation and intravenous doses up to 96 mcg/kg in rabbits from day 6 to day 18 of gestation. The dose in rats is approximately 2 times the maximum recommended human intravenous dose on a mcg/m^2 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/m^2 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/m^2 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/m^2 basis). No such effects were

observed at a dose of 2 mcg/kg (less than the maximum recommended intravenous dose on a mcg/m^2 basis).

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

There are no adequate and well-controlled studies of dexmedetomidine hydrochloride use in pregnant women. Dexmedetomidine has been shown to cross the placental barrier in both animal and human published studies.

The limited available information on dexmedetomidine hydrochloride use during pregnancy is not sufficient to inform a drug-associated risk of birth defects or miscarriage. Precedex® should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

It has been reported that prenatal exposure to dexmedetomidine may be associated with some degree of functional impairment at birth in some neonates.

Perioperative administration of dexmedetomidine in pregnant women receiving general anesthesia for elective caesarean section was associated with a longer time to clinical recovery and extubation compared with other anesthetic agents.

In a study in the pregnant rat, placental transfer of dexmedetomidine was observed when radiolabeled dexmedetomidine was administered subcutaneously.

Nursing Mothers:
Dexmedetomidine is excreted in human milk, but no studies assessing the effects of dexmedetomidine in breastfed children and on milk production have been performed.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for dexmedetomidine and any potential adverse effects on the breast fed child from dexmedetomidine.

A lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk for 24 hours after receiving dexmedetomidine in order to minimize potential drug exposure to a breastfed neonate.

Pediatrics:
The efficacy and safety of Precedex® in pediatric patients less than 18 years of age have not been established for procedural or ICU sedation. Therefore, Precedex® is not recommended in this population.

Three pivotal studies in ICU sedation did not meet their primary efficacy endpoint, and the safety data were insufficient to fully characterize the safety profile of Precedex®.

One open-label ICU sedation study conducted in Japanese patients did meet its primary efficacy endpoint.

One open-label study conducted in pediatric patients for procedural sedation also did not meet its efficacy endpoint.

The safety profile of Precedex® in these studies was generally similar to that of adults, although increased frequencies of adverse events of bradycardia, hypotension, and respiratory depression were seen in the Japan ICU sedation study.

Geriatrics:
Intensive Care Unit Sedation – Elderly
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***, **Hypotension, Bradycardia, and Sinus Arrest**). Therefore, a dose reduction may be considered in patients over 65 years of age (see ***CLINICAL PHARMACOLOGY,*** **Geriatrics** and ***DOSAGE AND ADMINISTRATION,*** **Dosage Adjustment**).

Dexmedetomidine is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in elderly patients, and it may be useful to monitor renal function.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, may be impaired for some time after sedation.

ADVERSE REACTIONS
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***)
- 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 procedural sedation studies include hypotension, bradycardia and dry mouth.

Adverse reaction information is derived from the continuous infusion trials of Precedex® for sedation in the Intensive Care Unit setting in which 1007 adult 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% ≥65 years of age, 77% male and 93% Caucasian. Treatment-emergent adverse reactions occurring at an incidence of >2% are provided in Table 5. The most frequent adverse reactions were hypotension, bradycardia and dry mouth (see ***WARNINGS AND PRECAUTIONS***).

Table 5: Adverse Reactions with an Incidence >2%-Adult Intensive Care Unit Sedation Population <24 hours*

Adverse Event	All Precedex® (N = 1007) (%)	Randomized Precedex® (N = 798) (%)	Placebo (N = 400) (%)	Propofol (N = 188) (%)
Hypotension	25%	24%	12%	13%
Hypertension	12%	13%	19%	4%
Nausea	9%	9%	9%	11%
Bradycardia	5%	5%	3%	0
Atrial Fibrillation	4%	5%	3%	7%
Pyrexia	4%	4%	4%	4%
Dry Mouth	4%	3%	1%	1%
Vomiting	3%	3%	5%	3%
Hypovolemia	3%	3%	2%	5%
Atelectasis	3%	3%	3%	6%
Pleural Effusion	2%	2%	1%	6%
Agitation	2%	2%	3%	1%
Tachycardia	2%	2%	4%	1%
Anemia	2%	2%	2%	2%
Hyperthermia	2%	2%	3%	0
Chills	2%	2%	3%	2%
Hyperglycemia	2%	2%	2%	3%
Hypoxia	2%	2%	2%	3%
Post-procedural Hemorrhage	2%	2%	3%	4%
Pulmonary Edema	1%	1%	1%	3%
Hypocalcemia	1%	1%	0	2%
Acidosis	1%	1%	1%	2%
Urine Output Decreased	1%	1%	0	2%
Sinus Tachycardia	1%	1%	1%	2%
Ventricular Tachycardia	<1%	1%	1%	5%
Wheezing	<1%	1%	0	2%
Edema Peripheral	<1%	0	1%	2%

* 26 subjects in the all Precedex® group and 10 subjects in the randomized Precedex® group had exposure for greater than 24 hours.

Adverse event information is derived from the placebo-controlled, continuous infusion trials of dexmedetomidine for sedation in the ICU setting in which 387 patients received Precedex®. Overall, the most frequently observed treatment-emergent adverse events included hypotension, hypertension, nausea, bradycardia, fever, vomiting, hypoxia, tachycardia and anemia (see Table 6).

Table 6: Treatment-Emergent Adverse Events Occurring in >1% of All Dexmedetomidine-Treated Patients in the Randomized Placebo-controlled Continuous Infusion ICU Sedation Studies

Adverse Event	Randomized Dexmedetomidine (N=387)	Placebo (N=379)
Hypotension	28%	13%
Hypertension	16%	18%
Nausea	11%	9%
Bradycardia	7%	3%
Fever	5%	4%
Vomiting	4%	6%
Atrial Fibrillation	4%	3%
Hypoxia	4%	4%
Tachycardia	3%	5%
Hemorrhage	3%	4%
Anemia	3%	2%
Dry Mouth	3%	1%
Rigors	2%	3%
Agitation	2%	3%
Hyperpyrexia	2%	3%
Pain	2%	2%
Hyperglycemia	2%	2%
Acidosis	2%	2%
Pleural Effusion	2%	1%
Oliguria	2%	<1%
Thirst	2%	<1%

The treatment-emergent adverse events in Table 7 were reported in ≤1% of all dexmedetomidine-treated patients that are potentially clinically relevant.

Table 7: Potentially Clinically Relevant Treatment-Emergent Adverse Events to Dexmedetomidine Reported in ≤1% of Patients in the Continuous Infusion ICU Sedation Trials

Body System	Preferred Term
Body as a Whole	Fever, Hyperpyrexia, Hypovolemia, Light Anesthesia, Pain, Rigors

Cardiovascular Disorders, General	Blood pressure fluctuation, Heart disorder, Aggravated hypertension
Central and Peripheral Nervous System Disorders	Dizziness, Headache, Neuralgia, Neuritis, Speech disorder
Gastrointestinal System Disorders	Abdominal pain, Diarrhea, Vomiting
Heart Rate and Rhythm Disorders	Arrhythmia, Ventricular arrhythmia, AV block, Cardiac arrest, Extrasystoles, Atrial fibrillation, Heart block, T wave inversion, Tachycardia, Supraventricular tachycardia, Ventricular tachycardia
Liver and Biliary System Disorders	Increased GGT, Increased SGOT, Increased SGPT
Metabolic and Nutritional Disorders	Acidosis, Respiratory acidosis, Hyperkalemia, Increased alkaline phosphatase, Thirst
Psychiatric Disorders	Agitation, Confusion, Delirium, Hallucination, Illusion
Red Blood Cell Disorders	Anemia
Respiratory System Disorders	Apnoea, Bronchospasm, Dyspnea, Hypercapnia, Hypoventilation, Hypoxia, Pulmonary congestion
Skin and Appendages Disorders	Increased sweating
Vision Disorders	Photopsia, Abnormal vision

Postmarketing Experience

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 8: Adverse Reactions Experienced During Post-approval Use of Precedex®

System Organ Class	Preferred Term
Blood and Lymphatic System Disorders	Anemia
Cardiac Disorders	Arrhythmia, atrial fibrillation, atrioventricular block, bradycardia, cardiac arrest, cardiac disorder, extrasystoles, myocardial infarction, supraventricular

	tachycardia, tachycardia, ventricular arrhythmia, ventricular tachycardia
Eye Disorders	Photopsia, visual impairment
Gastrointestinal Disorders	Abdominal pain, diarrhea, nausea, vomiting
General Disorders and Administration Site Conditions	Chills, hyperpyrexia, pain, pyrexia, thirst
Hepatobiliary Disorders	Hepatic function abnormal, hyperbilirubinemia
Investigations	Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood urea increased, electrocardiogram T wave inversion, gamma glutamyl transferase increased, electrocardiogram QT prolonged
Metabolism and Nutrition Disorders	Acidosis, hyperkalemia, hypoglycaemia, hypovolemia, hypernatremia, hypokalaemia
Nervous System Disorders	Convulsion, dizziness, headache, neuralgia, neuritis, speech disorder
Psychiatric Disorders	Agitation, confusional state, delirium, hallucination, illusion
Renal and Urinary Disorders	Oliguria, polyuria
Respiratory, Thoracic and Mediastinal Disorders	Apnoea, bronchospasm, dyspnea, hypercapnia, hypoventilation, hypoxia, pulmonary congestion, respiratory acidosis
Skin and Subcutaneous Tissue Disorders	Hyperhidrosis, pruritus, rash, urticaria
Surgical and Medical Procedures	Light anesthesia
Vascular Disorders	Blood pressure fluctuation, hemorrhage, hypertension, hypotension

Description of selected adverse reactions

Urinary/electrolytes abnormalities

Polyuria in association with electrolyte abnormalities (i.e.: hypernatremia), resembling diabetes insipidus, have been co-reported in patients receiving dexmedetomidine. These have resolved upon dexmedetomidine discontinuation.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor lmpor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
JI. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext .1079
Website: https://e-meso.pom.go.id/ADR

PT Pfizer Indonesia
Email: IDN.AEReporting@pfizer.com
Website: www.pfizersafetyreporting.com

DRUG ABUSE AND DEPENDENCE
Precedex® (dexmedetomidine hydrochloride) is not a controlled substance.

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

OVERDOSAGE
The tolerability of dexmedetomidine hydrochloride 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 AV block and second degree heart block. No hemodynamic compromise was noted with the AV block and the heart block resolved spontaneously within one minute.

Five adult patients received an overdose of dexmedetomidine hydrochloride 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 dexmedetomidine hydrochloride (19.4 mcg/kg), had cardiac arrest from which he was successfully resuscitated.

DOSAGE AND ADMINISTRATION

Precedex® should be administered using a controlled infusion device.

Precedex® dosing should be individualized and titrated to the desired clinical effect. For adult patients, Precedex® is generally initiated with a loading infusion of 1 (one) mcg/kg over 10 minutes, followed by a maintenance infusion of 0.2 to 0.7 mcg/kg/hr. The rate of the maintenance infusion should be adjusted to achieve the desired level of sedation.

Dexmedetomidine is not indicated for infusions lasting longer than 24 hours.

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

Dosage Adjustment

Elderly patients

A dose reduction for both the loading and maintenance doses should be considered for patients over 65 years of age (see ***WARNINGS AND PRECAUTIONS*, General and Geriatrics**).

Patients with renal impairment

No dose adjustment is required for patients with renal impairment (see ***CLINICAL PHARMACOLOGY***, **Pharmacokinetics**).

Patients with hepatic impairment

Dexmedetomidine hydrochloride should be used with caution in adult patients with hepatic impairment. A dose reduction should be considered for both the loading and maintenance doses (see ***WARNINGS AND PRECAUTIONS*, Hepatic Impairment** and ***CLINICAL PHARMACOLOGY***, **Pharmacokinetics**).

Dilution Prior to Administration

Precedex® must be diluted in 0.9% sodium chloride injection to achieve required concentration (4 mcg/mL) prior to administration.

Preparation of solutions is the same, whether for the loading dose or maintenance infusion (see ***DOSAGE AND ADMINISTRATION***).

To prepare the infusion, withdraw 2 mL of Precedex® and add to 48 mL of 0.9% sodium chloride injection to a total of 50 mL. Shake gently to mix well.

Administration with Other Fluids
Precedex® 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 and drugs:
Lactated Ringer's solution, 5% dextrose in water, 0.9% sodium chloride in water, 20% mannitol, 100mg/mL magnesium sulfate solution, 0.3% potassium chloride solution, thiopental sodium, etomidate, vecuronium bromide, pancuronium bromide, succinylcholine, atracurium besylate, mivacurium chloride, glycopyrrolate bromide, phenylephrine HCl, atropine sulfate, midazolam, morphine sulfate, fentanyl citrate and a plasma-substitute.

Handling Procedures
Parenteral products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Strict aseptic technique must always be maintained during handling of dexmedetomidine. Vials are intended for single use only.

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.

PHARMACEUTICAL PARTICULARS

Appearance:
Clear and colorless sterile solution.

List of excipients:
Sodium chloride, nitrogen and water for injection.

HOW SUPPLIED

Precedex® (dexmedetomidine hydrochloride injection), 100 mcg/mL as the base is available in
2 mL clear glass vial.

List No.	Container	Size
1638	Vial	2 mL

Store below 25°C.

HARUS DENGAN RESEP DOKTER

Manufactured by:
Hospira, Inc. Rocky Mount,
NC 27801, USA

Packed by:
Avara Liscate Pharmaceutical Services S.p.A., Liscate (MI), Italy

Licensed from:
Orion Corporation
Espoo, Finland

Imported by:
PT Pfizer Indonesia,
Jakarta-Indonesia

REG No: DKI1811901443A1