PRECEDEX™ (dexmedetomidine hydrochloride) in 0.9% Sodium Chloride Injection 4 mcg/mL

1. NAME OF THE MEDICINAL PRODUCT

PRECEDEX™

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PRECEDEX (dexmedetomidine hydrochloride) in 0.9% Sodium Chloride Injection (4 mcg/mL) is a sterile, nonpyrogenic ready to use solution suitable for intravenous infusion.

Each mL contains 4.72 mcg of dexmedetomidine hydrochloride (equivalent to 4 mcg or 0.004 mg of dexmedetomidine) and 9 mg sodium chloride in water for injection. The solution is preservative-free and contains no additives or chemical stabilizers.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion (ready to use).

It is supplied as a clear, colorless, isotonic solution with a pH between 4.5 to 8.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Intensive Care Unit (ICU) Sedation

PRECEDEX is indicated for sedation of initially intubated and mechanically ventilated adult patients during treatment in an intensive care setting.

Procedural Sedation

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

4.2 Posology and method of administration

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

Intensive Care Unit Sedation

PRECEDEX should be administered by continuous infusion not to exceed 24 hours.

PRECEDEX has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post-extubation. It is not necessary to discontinue PRECEDEX prior to extubation.

Loading dose

For adult patients, it is recommended that administration of dexmedetomidine hydrochloride starts with a 1.0 mcg/kg loading dose administered over 10 minutes followed by a maintenance dose.

For adult patients already intubated and sedated who are being converted from alternate sedative therapy, a loading dose may not be required.

Maintenance dose

For adult patients, a maintenance infusion of 0.2 to 0.7 mcg/kg/hour is recommended. The rate of the maintenance infusion should be adjusted to achieve the desired level of sedation for optimal clinical effect.

Elderly patients

A dose reduction for both the loading and maintenance doses should be considered for patients over 65 years of age (see sections 4.4 and 5.1).

Patients with renal impairment

No dose adjustment is required for patients with renal impairment (see section 5.2).

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 sections 4.4 and 5.2).

Procedural Sedation

Loading dose

For adult patients, it is recommended that administration of dexmedetomidine hydrochloride starts with a 1.0 mcg/kg loading dose administered over 10 minutes followed by a maintenance dose.

For awake fiberoptic intubation in adult patients: a loading infusion of 1.0 mcg/kg over 10 minutes may be suitable.

For less invasive procedures such as ophthalmic surgery, a loading infusion of 0.5 mcg/kg given over 10 minutes may be suitable.

Elderly patients: For patients over 65 years of age, a dose reduction in the loading dose to 0.5 mcg/kg over 10 minutes should be considered (see sections 4.4, 5.1 and 5.2).

Maintenance dose

The maintenance infusion is generally initiated at 0.6 mcg/kg/hour and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1.0 mcg/kg/hour. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation.

For awake fiberoptic intubation in adult patients: a maintenance infusion of 0.7 mcg/kg/hour is recommended until the endotracheal tube is secured.

Elderly patients: A maintenance dose reduction should be considered in patients over 65 years of age (see sections 4.4, 5.1 and 5.2).

Patients with renal impairment

No dose adjustment is required for patients with renal impairment (see section 5.2).

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 sections 4.4 and 5.2).

Pediatric Use

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 (see sections 4.8 and 5.1).

4.3 Contraindications

Hypersensitivity to dexmedetomidine hydrochloride or to any of the excipients.

4.4 Special warnings and precautions for use

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 or operating room 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, apnea, dyspnea 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 reported with dexmedetomidine hydrochloride administration in young, healthy adult 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 intravenous 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., glycopyrrolate, atropine) should be considered to modify vagal tone. In clinical trials, glycopyrrolate or atropine 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 PRECEDEX 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 patients with hypovolemia, diabetes mellitus, or chronic hypertension and in elderly patients.

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

Transient Hypertension

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.

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 PRECEDEX supportive therapy is indicated.

Procedural Sedation

In adult subjects, withdrawal symptoms were not seen after discontinuation of short-term infusions of dexmedetomidine hydrochloride (<6 hours).

Tolerance and Tachyphylaxis

Use of dexmedetomidine hydrochloride beyond 24 hours has been associated with tolerance and tachyphylaxis and a dose-related increase in adverse reactions.

Hyperthermia or Pyrexia

Dexmedetomidine hydrochloride may induce hyperthermia or pyrexia, which may be resistant to traditional cooling methods, such as administration of cooled intravenous fluids and antipyretic medications. Discontinue PRECEDEX if drug-related hyperthermia or pyrexia is suspected and monitor patients until body temperature normalizes. 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 section 4.2).

Risk of Mortality

Use of dexmedetomidine greater than 24 hours has been associated with an increased mortality in critically ill adult ICU patients 63.7 years of age and younger compared to usual care (see section 5.1).

Seizures

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

4.5 Interaction with other medicinal products and other forms of interaction

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 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 adult 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.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy

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.

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

pregnant rats at 8 and 32 mcg/kg (representing a dose less than the maximum recommended human intravenous dose based on a body surface area comparison) from gestation day 16 through weaning, lower offspring weights were observed. Additionally, when offspring of the 32 mcg/kg group were allowed to mate, elevated fetal and embryocidal toxicity and delayed motor development was observed in second generation offspring.

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

Use in Lactation

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 breastfed child from dexmedetomidine.

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

4.7 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.

4.8 Undesirable effects

The following tables list adverse drug reactions (ADRs) by patient population. ADRs within each standard System Organ Class (SOC) are listed by decreasing order of medical seriousness.

Adverse drug reactions in the adult ICU sedation population are presented in Table 1.

Table 1: Adverse Drug Reactions (Adult ICU Sedation Population; Integrated Data)

System Organ Class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100
Blood and lymphatic system disorders	--	Anemia	--
Metabolism and nutrition disorders	--	Hypokalemia Hyperglycemia Hypovolemia	Hypocalcemia Acidosis
Psychiatric disorders	--	Agitation	--
Cardiac disorders	Bradycardia Tachycardia	Atrial fibrillation	Sinus tachycardia Ventricular tachycardia
Vascular disorders	Hypotension Hypertension	--	--

System Organ Class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100
Respiratory, thoracic and mediastinal disorders	--	Pleural effusion Atelectasis Hypoxia	Pulmonary edema Wheezing
Gastrointestinal disorders	--	Nausea Vomiting	Dry mouth
General disorders and administration site conditions	--	Edema peripheral Pyrexia Hyperthermia Chills	--
Injury, poisoning and procedural complications	--	Post-procedural hemorrhage	--
Investigations	--	Urine output decreased	--

Adverse drug reactions in the adult procedural sedation population are presented in Table 2.

Table 2: Adverse Drug Reactions (Adult Procedural Sedation Population; Integrated Data)

System Organ Class	Very common ≥1/10	Common ≥1/100 to <1/10
Cardiac disorders	Bradycardia	Tachycardia
Vascular disorders	Hypotension Hypertension	--
Respiratory, thoracic and mediastinal disorders	Respiratory depression	Hypoxia Bradypnea
Gastrointestinal disorders	--	Nausea Dry mouth

Post-marketing Reports

In addition to the events reported during clinical studies, the following adverse drug reactions have been identified during post-approval use of dexmedetomidine hydrochloride.

Table 3: Adverse Drug Reactions

System Organ Class	Adverse Drug Reactions
Metabolism and nutrition disorders	Acidosis, hypoglycemia, hypernatremia
Psychiatric disorders	Delirium, hallucination
Cardiac disorders	Cardiac arrest, atrioventricular block, myocardial infarction, arrhythmia
Vascular disorders	Hypertension
Respiratory, thoracic and mediastinal disorders	Apnea, hypoxia
Gastrointestinal disorders	Vomiting
Renal and urinary disorders	Polyuria
General disorders and administration site conditions	Thirst

Pediatric Population

The safety profile of dexmedetomidine hydrochloride is generally similar to that of adults, although increased frequencies of adverse events of bradycardia, hypotension and respiratory depression were seen in a Japan ICU sedation study (see sections 4.2 and 5.1).

4.9 Overdose

The tolerability of dexmedetomidine hydrochloride was studied in one study in which healthy adult subjects were administered doses at and above the recommended dose of 0.2 to 0.7 mcg/kg/h. 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 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/h. 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.

4.10 Abuse and dependence

Dependence

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 section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, other hypnotics and sedatives.

Mechanism of Action

Dexmedetomidine is a relatively selective alpha$_2$-adrenergic agonist with sedative properties. Alpha$_2$ selectivity is observed in animals following slow intravenous infusion of low and medium doses (10 - 300 mcg/kg). Both alpha$_1$ and alpha$_2$ activity is observed following slow intravenous infusion of high doses (≥1,000 mcg/kg) or with rapid intravenous administration.

Pharmacodynamics

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

The safety and efficacy of PRECEDEX has been evaluated in four randomized, double-blind, placebo-controlled multicenter clinical trials in 1,185 adult patients.

Intensive Care Unit Sedation

Two randomized, double-blind, parallel-group, placebo-controlled multicenter clinical trials included 754 adult 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 4.

Table 4: 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 adult patients were randomized to receive placebo and 178 to receive PRECEDEX by intravenous infusion at a dose of 0.4 mcg/kg/h (with allowed adjustment between 0.2 and 0.7 mcg/kg/h) 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 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 5).

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 5).

Table 5: 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	
	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.
* 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/h (with allowed adjustment between 0.2 and 0.7 mcg/kg/h) 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. 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 6).

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 6).

Table 6: 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	
Categorized 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%). In addition, administration of PRECEDEX for longer than 24 hours was associated with tolerance, tachyphylaxis, and a dose-related increase in adverse events.

In study 3005012, patients were sedated with propofol prior to randomization to either propofol (3005012) or dexmedetomidine.

In study 3005013, patients were sedated with midazolam prior to randomization to either midazolam (3005013) or dexmedetomidine.

In both study 3005012 and 3005013, the loading dose was omitted in order to reduce the risk of occurrence of cardiovascular events at the start of treatment.

3005012

The adjusted mean (95% CI) percentage of the time at target sedation level without use of rescue treatment was 64.6 (60.0 to 69.1)% for subjects on dexmedetomidine and 64.7 (59.9 to 69.4)% for subjects on propofol. As the lower limit of the 2-sided 95% CI for the estimated ratio of dexmedetomidine vs. propofol (0.92) was above the predefined non-inferiority margin (>0.85), dexmedetomidine was proven to be non-inferior to propofol in maintaining a target depth of sedation. The median duration of mechanical ventilation was 21 hours shorter in the dexmedetomidine group (96.5 hours) than in the propofol group (117.5 hours).

The length of stay in the ICU from randomization to medically fit for discharge or transfer did not differ (p = 0.535) between groups.

72.5% of subjects in the dexmedetomidine group and 64.4% of subjects in the propofol group needed the first-line (i.e. midazolam boli) rescue treatment for inadequate sedation during the

treatment period (p = 0.054). The total number of doses of the rescue treatment was 2495 and 1986 in the dexmedetomidine and propofol groups, respectively. The mean average dose (0.74 vs. 0.31 mg/h, p <0.001) and the mean total dose (32.9 vs. 22.8 mg, p = 0.024) of the first-line rescue treatment were higher in the dexmedetomidine group than in the propofol group. The first-line rescue treatment also started earlier in the dexmedetomidine group (median of 1.4 vs. 4.3 hours, p = 0.018). No differences between groups were observed in the use of second-line rescue treatment (mostly fentanyl) during the study treatment period or in the total use of fentanyl during the study.

3005013

The adjusted mean (95% CI) percentage of the time at target sedation level without use of rescue treatment was 60.7 (55.4 to 66.1)% for subjects on dexmedetomidine and 56.6 (51.2 to 61.9)% for subjects on midazolam. As the lower limit of the 2-sided 95% CI for the estimated ratio of dexmedetomidine vs. midazolam (0.97) was above the predefined non-inferiority margin (>0.85), dexmedetomidine was proven to be non-inferior to midazolam in maintaining a target depth of sedation. The median duration of mechanical ventilation was 41 hours shorter in the dexmedetomidine group (123.0 hours) than in the midazolam group (164.0 hours).

The length of stay in the ICU from randomization to medically fit for discharge or transfer did not differ (p = 0.269) between groups.

A similar percentage of subjects in the dexmedetomidine group (43.8%) and midazolam group (45.4%) received the first-line (i.e. propofol boli) rescue treatment for inadequate sedation during the treatment period (p = 0.720). The total number of doses (1100 vs. 1008), the mean average total dose (5.00 vs. 3.59 mg/h, p = 0.173) and the mean total dose (360 vs. 299 mg, p = 0.317) of the first-line rescue treatment were similar in both groups. The median time to the first use (19.3 vs. 20.0 hours) was also similar (p = 0.741). No differences between groups were observed in the use of second-line rescue treatment (mostly fentanyl) during the study treatment period or in the total use of fentanyl during the study.

Sedation Practice in Intensive Care Evaluation (SPICE) III Study

In a published randomized controlled trial (Sedation Practice in Intensive Care Evaluation (SPICE) III trial) of 3,904 critically ill adult ICU patients, dexmedetomidine was used as primary sedative and compared with usual care. In the study, exposure to dexmedetomidine was greater than 24 hours with a median duration of treatment of 2.56 days (interquartile range, 1.10 to 5.23). The administration of dexmedetomidine was continued as clinically required for up to 28 days after randomization.

There was no overall significant difference in the primary outcome of 90-day mortality between the dexmedetomidine and usual care group (mortality 29.1% in both groups). In exploratory subgroup analyses, dexmedetomidine was associated with a decreased mortality in patients with age greater than the median age of 63.7 years (risk difference -4.4; 95% confidence interval -8.7 to -0.1) compared to usual care. Conversely, dexmedetomidine was associated with an increased mortality in patients with age less than or equal to the median age of 63.7 years (risk difference 4.4; 95% confidence interval 0.8 to 7.9) compared to usual care.

The significance of these findings is unknown, but they should be weighed against the expected clinical benefit of dexmedetomidine compared to alternative sedatives in patients less than or equal to 63.7 years old. Dexmedetomidine is not indicated for use longer than 24 hours and therefore its administration should not exceed 24 hours (see section 4.2).

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 section 4.4). Therefore, a dose reduction may be considered in patients over 65 years of age (see sections 4.2 and 5.2).

Procedural 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 (see Table 7).

Table 7: Observer's Assessment of Alertness/Sedation

Assessment Categories				
Responsiveness	**Speech**	**Facial Expression**	**Eyes**	**Composite Score**
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, PRECEDEX 0.5 mcg/kg, or placebo (normal saline) given over 10 minutes and followed by a maintenance infusion started at 0.6 mcg/kg/h. The maintenance infusion of study drug could

be titrated from 0.2 mcg/kg/h to 1 mcg/kg/h to achieve the targeted sedation score (Observer's Assessment of Alertness/Sedation Scale ≤4). Patients were allowed to receive rescue midazolam as needed to achieve and/or maintain an Observer's Assessment of Alertness/Sedation Scale ≤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 8).

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 ≥2 (see Table 4). Patients were randomized to receive a loading infusion of PRECEDEX 1 mcg/kg or placebo (normal saline) given over 10 minutes and followed by a fixed maintenance infusion of 0.7 mcg/kg/h. After achieving the desired level of sedation, topicalization of the airway occurred. Patients were allowed to receive rescue midazolam as needed to achieve and/or maintain a Ramsay Sedation Scale ≥2. Demographic characteristics were similar between the PRECEDEX and comparator groups. For efficacy results see Table 8.

Table 8: Key Efficacy Results of Procedural Sedation Studies

Study	Loading Infusion Treatment Arm	Number 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	Dexmedetomidine 0.5 mcg/kg	134	40	37 (27, 48)	1.4 (1.7)	-2.7 (-3.4, -2.0)
	Dexmedetomidine 1 mcg/kg	129	54	51 (40, 62)	0.9 (1.5)	-3.1 (-3.8, -2.5)
	Placebo	63	3	–	4.1 (3.0)	–
Study 2	Dexmedetomidine 1 mcg/kg	55	53	39 (20, 57)	1.1 (1.5)	-1.8 (-2.7, -0.9)
	Placebo	50	14	–	2.9 (3.0)	–

[a] Based on ITT population defined as all randomized and treated patients.
[b] Normal approximation to the binomial with continuity correction.

Procedural Sedation – Elderly

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

Pediatric Population

One assessor-blinded trial in pediatric patients and two open-label studies in neonates were conducted to assess efficacy for ICU sedation. These studies did not meet their primary

efficacy endpoints and the safety data submitted were insufficient to fully characterize the safety profile of PRECEDEX for this patient population (see sections 4.2 and 4.8). One open-label study conducted in pediatric patients for procedural sedation also did not meet its efficacy endpoint (see sections 4.2 and 4.8).

5.2 Pharmacokinetic properties

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/h when administered by intravenous infusion for up to 24 hours. Table 9 shows the main pharmacokinetic parameters when PRECEDEX was infused (after appropriate loading doses) at maintenance infusion rates of 0.17 mcg/kg/h (target plasma concentration of 0.3 ng/mL) for 12 and 24 hours, 0.33 mcg/kg/h (target plasma concentration of 0.6 ng/mL) for 24 hours, and 0.70 mcg/kg/h (target plasma concentration of 1.25 ng/mL) for 24 hours.

Table 9: Mean ± SD Pharmacokinetic Parameters

	Loading Infusion (min)/Total Infusion Duration (h)			
	10 min/12 h	**10 min/24 h**	**10 min/24 h**	**35 min/24 h**
	Dexmedetomidine Target Plasma Concentration (ng/mL) and Dose (mcg/kg/h)			
Parameter	**0.3/0.17**	**0.3/0.17**	**0.6/0.33**	**1.25/0.70**
$t_{1/2}$*, hour	1.78 ± 0.30	2.22 ± 0.59	2.23 ± 0.21	2.50 ± 0.61
CL, liter/hour	46.3 ± 8.3	43.1 ± 6.5	35.3 ± 6.8	36.5 ± 7.5
V_{ss}, liter	88.7 ± 22.9	102.4 ± 20.3	93.6 ± 17.0	99.6 ± 17.8
Avg C_{ss}#, ng/mL	0.27 ± 0.05	0.27 ± 0.05	0.67 ± 0.10	1.37 ± 0.20

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 hours samples for 12 hour infusion and post-dose sampling from 2.5 to 18 hours for 24 hour infusions.

The loading doses for each of the above indicated groups were 0.5, 0.5, 1 and 2.2 mcg/kg, respectively.

Dexmedetomidine pharmacokinetic parameters after PRECEDEX maintenance doses of 0.2 to 1.4 mcg/kg/h for >24 hours were similar to the pharmacokinetic (PK) parameters after PRECEDEX maintenance dosing for <24 hours in other studies. The values for clearance (CL), volume of distribution (V), and $t_{1/2}$ were 39.4 L/h, 152 L, and 2.67 hours, respectively.

Distribution

The steady-state volume of distribution (V_{ss}) of dexmedetomidine was approximately 118 liters. Dexmedetomidine protein binding was assessed in the plasma of normal healthy

male and female subjects. The average protein binding was 94% and was constant across the different plasma concentrations tested. Protein binding was similar in males and females. The fraction of 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 dexmedetomidine-N-methyl O-glucuronide.

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 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.

Specific Populations

Male and Female Patients

There was no observed difference in dexmedetomidine pharmacokinetics due to gender.

Elderly

The pharmacokinetic profile of dexmedetomidine was not altered by age. There were no differences in the pharmacokinetics of dexmedetomidine in young (18–40 years), middle age (41–65 years), and elderly (>65 years) subjects.

Patients with 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.

Patients with 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 sections 4.2 and 4.4).

Drug Interaction

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

5.3 Preclinical safety data

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 clastogenic in an *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 of dexmedetomidine at 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/h and 10 mcg/kg/h 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections

6.2 Incompatibilities

Administration with Other Fluids

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

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

PRECEDEX has been shown to be compatible when administered with the following intravenous fluids:

- 0.9% sodium chloride in water
- 5% dextrose in water
- 20% mannitol
- Lactated Ringer’s solution
- 100 mg/mL magnesium sulfate solution
- 0.3% potassium chloride solution

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.

6.3 Shelf life

Refer to outer carton.

6.4 Special precautions for storage

Store below 30°C. Do not freeze.

6.5 Nature and contents of container

PRECEDEX 200 mcg/50 mL (4 mcg/mL) is available as a single-dose, 50 mL clear glass bottle.

6.6 Special precautions for disposal and other handling

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

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if product is discolored or if precipitate matter is present.

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

Discard unused portion.

7. PRODUCT OWNER

Pfizer Inc.
New York,
United States

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