CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21-038/S020

Trade Name: Precedex® Injection

Generic Name: dexmedetomidine hydrochloride

Sponsor: Hospira, Inc.

Approval Date: 3/13/2013

Indication: Precedex™ is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-038/S020

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21038/S-020

APPROVAL LETTER

Hospira, Inc.
Attention: Cecilia C. Turoff
Senior Associate, Global Regulatory Affairs
275 N. Field Dr.
Lake Forest, IL 60045

Dear Ms. Turoff:

Please refer to your Supplemental New Drug Application (sNDA) dated and received October 12, 2012, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Precedex® (Dexmedetomidine hydrochloride) Injection.

We acknowledge receipt of your amendments dated, February 1, 2013, March 5, 2013 and March 6, 2013.

This Prior Approval supplemental new drug application provided for an alternate premix formulation of Precedex® Injection. The proposed product will be presented in a 200 mcg/ 50 mL in a 50 mL glass bottle and 400 mcg/ 100 mL in a 100 mL glass bottle. The new formulation will be manufactured at Hospira McPherson, Kansas.

This supplemental new drug application provides for revisions to the labeling for Precedex® (Dexmedetomidine hydrochloride) Injection presentation.

We have completed our review of this supplemental new drug application as amended. This supplement is approved, for use as recommended in the enclosed, agreed-upon labeling text.

Submit final printed container labels that are identical to the enclosed immediate container labels as soon as they are available, but no more than 30 days after they are printed.
Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 21308/S-20**." Approval of this submission by FDA is not required before the labeling is used.

We also remind you of the following postmarketing commitments you made in your March 13, 2013 communication:

2025- 1. Report data regarding the “unrelated substances” (RRT and %) under standard conditions at the 1-year and 2-year stability time point.

If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796-4013.

Sincerely,

{See appended electronic signature page}
Ramesh Raghavachari, Ph.D.
Acting Branch Chief, Branch IX
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

ENCLOSURE(S):
Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAMESH RAGHAVACHARI
03/13/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-038/S020

LABELING

EN3116

Precedex™

(dexmedetomidine hydrochloride) injection

Rx only

For Intravenous Infusion

Hospira, Inc., Lake Forest, IL 60045 USA

Hospira

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

INDICATIONS AND USAGE

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

- Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Administer Precedex by continuous infusion not to exceed 24 hours. (1.1)
- Sedation of non-intubated patients prior to and/or during surgical and other procedures. (1.2)

DOSAGE AND ADMINISTRATION

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

For Intensive Care Unit Sedation: Generally initiate at 1 mcg/kg over 10 minutes, followed by a maintenance infusion of 0.2 to 0.7 mcg/kg/hr. (2.2)

For Procedural Sedation: Generally initiate at 1 mcg/kg over 10 minutes, followed by a maintenance infusion initiated at 0.6 mcg/kg/hr and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 mcg/kg/hr.

Alternative Doses: Recommended for patients over 65 years of age and awake fiberoptic intubation patients. (2.2)

DOSAGE FORMS AND STRENGTHS

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

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

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

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: 09/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Intensive Care Unit Sedation

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

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

1.2 Procedural Sedation

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Guidelines

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

2.2 Dosage Information

Table 1: Dosage Information

INDICATION	DOSAGE AND ADMINISTRATION
Initiation of Intensive Care Unit Sedation	**For adult patients:** a loading infusion of 1 mcg/kg over 10 minutes. **For patients being converted from alternate sedative therapy:** a loading dose may not be required [*see Dosage and Administration: Maintenance of Intensive Care Unit Sedation (2.2)*]. **For patients over 65 years of age:** a dose reduction should be considered [*see Use in Specific Populations (8.5)*]. **For patients with impaired hepatic-function:** a dose reduction should be considered [*see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)*].
Maintenance of Intensive Care Unit Sedation	**For adult patients:** a maintenance infusion of 0.2 to 0.7 mcg/kg/hr. The rate of the maintenance infusion should be adjusted to achieve the desired level of sedation. **For patients over 65 years of age:** a dose reduction should be considered [*see Use in Specific Populations (8.5)*]. **For patients with impaired hepatic function:** a dose reduction should be considered [*see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)*].
Initiation of Procedural Sedation	**For adult patients:** a loading infusion of 1 mcg/kg over 10 minutes. For less invasive procedures such as ophthalmic surgery, a loading infusion of 0.5 mcg/kg given over 10 minutes may be suitable. **For awake fiberoptic intubation patients:** a loading infusion of 1 mcg/kg over 10 minutes. **For patients over 65 years of age:** a loading infusion of 0.5 mcg/kg over 10 minutes [*see Use in Specific Populations (8.5*]. **For patients with impaired hepatic function:** a dose reduction should be considered [*see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)*].
Maintenance of Procedural Sedation	**For adult patients:** the maintenance infusion is generally initiated at 0.6 mcg/kg/hr and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 mcg/kg/hr. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation. **For awake fiberoptic intubation patients:** a maintenance infusion of 0.7 mcg/kg/hr is recommended until the endotracheal tube is secured. **For patients over 65 years of age:** a dose reduction should be considered [*see Use in Specific Populations (8.5)*]. **For patients with impaired hepatic function:** a dose reduction should be considered [*see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)*].

2.3 Dosage Adjustment

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

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

2.4 Preparation of Solution

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

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

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

Precedex must be diluted in 0.9% sodium chloride solution to achieve required concentration (4 mcg/mL) prior to administration. Preparation of solutions is the same, whether for the loading dose or maintenance infusion.

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

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

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

2.5 Administration with Other Fluids

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

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

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

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

2.6 Compatibility with Natural Rubber

Compatibility studies have demonstrated the potential for absorption of Precedex to some types of natural rubber. Although Precedex is dosed to effect, it is advisable to use administration components made with synthetic or coated natural rubber gaskets.

3 DOSAGE FORMS AND STRENGTHS

Precedex Injection, Concentrate

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

Precedex Injection

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

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

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Drug Administration

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

5.2 Hypotension, Bradycardia, and Sinus Arrest

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

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

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

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

5.3 Transient Hypertension

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

5.4 Arousability

Some patients receiving Precedex have been observed to be arousable and alert when stimulated. This alone should not be considered as evidence of lack of efficacy in the absence of other clinical signs and symptoms.

5.5 Withdrawal

Intensive Care Unit Sedation

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

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

Procedural Sedation

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

5.6 Tolerance and Tachyphylaxis

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

5.7 Hepatic Impairment

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

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

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

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

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

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

Intensive Care Unit Sedation

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

Table 2: Adverse Reactions with an Incidence >2%—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 reaction information was also 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 for less than 24 hours. The most frequently observed treatment-emergent adverse events included hypotension, hypertension, nausea, bradycardia, fever, vomiting, hypoxia, tachycardia and anemia (see Table 3).

Table 3: Treatment-Emergent Adverse Events Occurring in >1% Of All Dexmedetomidine-Treated Patients in the Randomized Placebo-Controlled Continuous Infusion <24 Hours 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%

In a controlled clinical trial, Precedex was compared to midazolam for ICU sedation exceeding 24 hours duration. Key treatment emergent adverse events occurring in dexmedetomidine or midazolam treated patients in the randomized active comparator continuous infusion long-term intensive care unit sedation study are provided in Table 4. The number (%) of subjects who had a dose-related increase in treatment-emergent adverse events by maintenance adjusted dose rate range in the Precedex group is provided in Table 5.

Table 4: Key Treatment-Emergent Adverse Events Occurring in Dexmedetomidine- or Midazolam-Treated Patients in the Randomized Active Comparator Continuous Infusion Long-Term Intensive Care Unit Sedation Study

Adverse Event	Dexmedetomidine (N = 244)	Midazolam (N = 122)
Hypotension[1]	56%	56%
Hypotension Requiring Intervention	28%	27%
Bradycardia[2]	42%	19%
Bradycardia Requiring Intervention	5%	1%
Systolic Hypertension[3]	28%	42%
Tachycardia[4]	25%	44%
Tachycardia Requiring Intervention	10%	10%
Diastolic Hypertension[3]	12%	15%
Hypertension[3]	11%	15%
Hypertension Requiring Intervention[†]	19%	30%
Hypokalemia	9%	13%
Pyrexia	7%	2%
Agitation	7%	6%
Hyperglycemia	7%	2%
Constipation	6%	6%
Hypoglycemia	5%	6%
Respiratory Failure	5%	3%
Renal Failure Acute	2%	1%
Acute Respiratory Distress Syndrome	2%	1%
Generalized Edema	2%	6%
Hypomagnesemia	1%	7%

† Includes any type of hypertension.

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

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

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

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

The following adverse events occurred between 2 and 5% for Precedex and Midazolam, respectively: renal failure acute (2.5%, 0.8%), acute respiratory distress syndrome (2.5%, 0.8%), and respiratory failure (4.5%, 3.3%).

Table 5. Number (%) of Subjects Who Had a Dose-Related Increase in Treatment Emergent Adverse Events by Maintenance Adjusted Dose Rate Range in the Precedex Group

	Precedex mcg/kg/hr		
Adverse Event	≤0.7* (N = 95)	>0.7 to ≤1.1* (N = 78)	>1.1* (N = 71)
Constipation	6%	5%	14%
Agitation	5%	8%	14%
Anxiety	5%	5%	9%
Edema Peripheral	3%	5%	7%
Atrial Fibrillation	2%	4%	9%
Respiratory Failure	2%	6%	10%
Acute Respiratory Distress Syndrome	1%	3%	9%

* Average maintenance dose over the entire study drug administration

Procedural Sedation

Adverse reaction information is derived from the two trials for procedural sedation in which 318 patients received Precedex. 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 reactions occurring at an incidence of >2% are provided in Table 6. The most frequent adverse reactions were hypotension, bradycardia, and dry mouth [*see Warnings and Precautions (5.2)*]. 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 6: Adverse Reactions With an Incidence > 2%—Procedural Sedation Population

Adverse Event	Precedex (N = 318) (%)	Placebo (N = 113) (%)
Hypotension[1]	54%	30%
Respiratory Depression[2]	37%	32%
Bradycardia[3]	14%	4%
Hypertension[4]	13%	24%
Tachycardia[5]	5%	17%
Nausea	3%	2%
Dry Mouth	3%	1%
Hypoxia[6]	2%	3%
Bradypnea	2%	4%

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 Respiratory depression was defined in absolute and relative terms as respiratory rate (RR) <8 beats per minute or > 25% decrease from baseline.

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

4 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.

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

6 Hypoxia was defined in absolute and relative terms as SpO_2 <90% or 10% decrease from baseline.

6.2 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 7: Adverse Reactions 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 transpepsidase, hepatic function abnormal, hyperbilirubinemia, alanine transaminase, aspartate aminotransferase
Metabolic and Nutritional Disorders	Acidosis, respiratory acidosis, hyperkalemia, increased alkaline phosphatase, thirst, hypoglycemia
Psychiatric Disorders	Agitation, confusion, delirium, hallucination, illusion
Red Blood Cell Disorders	Anemia
Renal Disorders	Blood urea nitrogen increased, oliguria
Respiratory System Disorders	Apnea, bronchospasm, dyspnea, hypercapnia, hypoventilation, hypoxia, pulmonary congestion
Skin and Appendages Disorders	Increased sweating
Vascular Disorders	Hemorrhage
Vision Disorders	Photopsia, abnormal vision

7 DRUG INTERACTIONS

7.1 Anesthetics, Sedatives, Hypnotics, Opioids

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

7.2 Neuromuscular Blockers

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

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

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

8.2 Labor and Delivery

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

8.3 Nursing Mothers

It is not known whether Precedex is excreted in human milk. Radio-labeled dexmedetomidine administered subcutaneously to lactating female rats was excreted in milk. Because many drugs are excreted in human milk, caution should be exercised when Precedex is administered to a nursing woman.

8.4 Pediatric Use

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

8.5 Geriatric Use

Intensive Care Unit Sedation

A total of 729 patients in the clinical studies were 65 years of age and over. A total of 200 patients were 75 years of age and over. In patients greater than 65 years of age, a higher incidence of bradycardia and hypotension was observed following administration of Precedex [*see Warnings and Precautions (5.2)*]. Therefore a dose reduction may be considered in patients over 65 years of age [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

Procedural Sedation

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

8.6 Hepatic Impairment

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

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Precedex (dexmedetomidine hydrochloride) is not a controlled substance.

9.3 Dependence

The dependence potential of Precedex has not been studied in humans. However, since studies in rodents and primates have demonstrated that Precedex exhibits pharmacologic actions similar to those of clonidine, it is possible that Precedex may produce a clonidine-like withdrawal syndrome upon abrupt discontinuation [*see Warnings and Precautions (5.5)*].

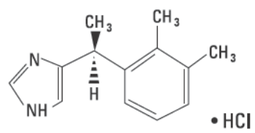
10 OVERDOSAGE

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.

11 DESCRIPTION

Precedex (dexmedetomidine hydrochloride) injection is a sterile, nonpyrogenic solution suitable for intravenous infusion following dilution. Dexmedetomidine hydrochloride is the S-enantiomer of medetomidine and is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride. Precedex has a molecular weight of 236.7 and the empirical formula is $C_{13}H_{16}N_2 \cdot HCl$ and the structural formula is:



Dexmedetomidine hydrochloride is a white or almost white powder that is freely soluble in water and has a pKa of 7.1. Its partition coefficient in-octanol: water at pH 7.4 is 2.89. Precedex is supplied as a clear, colorless, isotonic solution with a pH of 4.5 to 7.0. Each mL of Precedex Injection, Concentrate contains 118 mcg of dexmedetomidine hydrochloride equivalent to 100 mcg of dexmedetomidine and 9 mg of sodium chloride in water. Each mL of Precedex Injection contains 4.72 mcg of dexmedetomidine hydrochloride equivalent to 4 mcg dexmedetomidine and 9 mg of sodium chloride in water. The solution is preservative-free and contains no additives or chemical stabilizers.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

Following intravenous administration, dexmedetomidine exhibits the following pharmacokinetic parameters: a rapid distribution phase with a distribution half-life ($t_{1/2}$) of approximately 6 minutes; a terminal elimination half-life ($t_{1/2}$) of approximately 2 hours; and steady-state volume of distribution (V_{ss}) of approximately 118 liters. Clearance is estimated to be approximately 39 L/h. The mean body weight associated with this clearance estimate was 72 kg.

Dexmedetomidine exhibits linear pharmacokinetics in the dosage range of 0.2 to 0.7 mcg/kg/hr when administered by intravenous infusion for up to 24 hours. Table 8 shows the main pharmacokinetic parameters when Precedex was infused (after appropriate loading doses) at maintenance infusion rates of 0.17 mcg/kg/hr (target plasma concentration of 0.3 ng/mL) for 12 and 24 hours, 0.33 mcg/kg/hr (target plasma concentration of 0.6 ng/mL) for 24 hours, and 0.70 mcg/kg/hr (target plasma concentration of 1.25 ng/mL) for 24 hours.

Table 8: Mean ± SD Pharmacokinetic Parameters

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

* Presented as harmonic mean and pseudo standard deviation.

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

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

Distribution

The steady-state volume of distribution (V_{ss}) of dexmedetomidine was approximately 118 liters. Dexmedetomidine protein binding was assessed in the plasma of normal healthy male and female subjects. The average protein binding was 94% and was constant across the different plasma concentrations tested. Protein binding was similar in males and females. The fraction of Precedex that was bound to plasma proteins was significantly decreased in subjects with hepatic impairment compared to healthy subjects.

The potential for protein binding displacement of dexmedetomidine by fentanyl, ketorolac, theophylline, digoxin and lidocaine was explored *in vitro*, and negligible changes in the plasma protein binding of Precedex were observed. The potential for protein binding displacement of phenytoin, warfarin, ibuprofen, propranolol, theophylline and digoxin by Precedex was explored *in vitro* and none of these compounds appeared to be significantly displaced by Precedex.

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.

Gender

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 Precedex has not been studied in pediatric patients.

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.

Although Precedex is dosed to effect, it may be necessary to consider dose reduction in subjects with hepatic impairment [*see Dosage and Administration (2.2), Warnings and Precautions (5.7)*].

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.

Drug Interactions

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal carcinogenicity studies have not been performed with dexmedetomidine.

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.

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.

13.2 Animal Pharmacology and/or Toxicology

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.

14 CLINICAL STUDIES

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

14.1 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 9.

Table 9: 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 1 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 10).

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 10).

Table 10: 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 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 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 11).

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 11).

Table 11: 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 [*see Adverse Reactions (6.1)*].

14.2 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 12).

Table 12: 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/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 ≤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 13).

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 9). 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/hr. 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 13.

Table 13: 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	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)
	placebo	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)
	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.

16 HOW SUPPLIED/STORAGE AND HANDLING

Precedex Injection, Concentrate

Precedex (dexmedetomidine hydrochloride) injection, Concentrate 200 mcg/2 mL (100 mcg/mL) is available in 2 mL clear glass vial. Vials are intended for single use only.

NDC No.	Container	Size
0409-1638-02	Vial	2 mL

Precedex Injection

Precedex (dexmedetomidine hydrochloride) injection is available as 200 mcg/50 mL (4 mcg/mL) and 400 mcg/100 mL (4 mcg/mL) in 50 mL and 100 mL clear glass bottles, respectively. Containers are intended for single use only.

NDC No.	Container	Size
0409-1660-50	Bottle	50 mL
0409-1660-10	Bottle	100 mL

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

17 PATIENT COUNSELING 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.

Revised: 09/2012

Manufactured and Distributed by:
Hospira, Inc.
Lake Forest, IL 60045 USA

Licensed from:
Orion Corporation
Espoo, Finland

Hospira, Inc., Lake Forest, IL 60045 USA

(b) (4)

20 Units X 50 mL

Rx only

NDC 0409-1660-50

Single-use bottle. Discard unused portion.

Precedex™ Dexmedetomidine HCl in 0.9% Sodium Chloride Injection

200 mcg/50 mL (4 mcg/mL) Dexmedetomidine
Provided as Dexmedetomidine HCl

For Intravenous Infusion
Ready to Use – Do Not Dilute

Hospira

Each mL contains 4 mcg dexmedetomidine provided as 4.72 mcg dexmedetomidine HCl and 9 mg of sodium chloride in water for injection. pH is 4.5 to 7.0.

Usual Dosage: See insert.

This product is not made with natural rubber latex.

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.] Do not freeze.

Preservative-Free.

CA-3234

Hospira, Inc., Lake Forest, IL 60045 USA

(01) 10300409166050 9

20 Units X 50 mL

Rx only

NDC 0409-1660-50

Single-use bottle. Discard unused portion.

Precedex™ Dexmedetomidine HCl in 0.9% Sodium Chloride Injection

200 mcg/50 mL (4 mcg/mL) Dexmedetomidine
Provided as Dexmedetomidine HCl

For Intravenous Infusion
Ready to Use – Do Not Dilute

Hospira

10 Units X 100 mL Rx only NDC 0409-1660-10

Single-use bottle. Discard unused portion.

Precedex™ Dexmedetomidine HCl in 0.9% Sodium Chloride Injection

400 mcg/100 mL (4 mcg/mL) Dexmedetomidine HCl Provided as Dexmedetomidine HCl

For Intravenous Infusion
Ready to Use - Do Not Dilute

Hospira

Each mL contains 4 mcg dexmedetomidine provided as 4.72 mcg dexmedetomidine HCl and 9 mg of sodium chloride in water for injection. pH is 4.5 to 7.0.

Usual Dosage: See insert.

This product is not made with natural rubber latex.

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.] Do not freeze.

Preservative-Free.

CA-3235

Hospira, Inc., Lake Forest, IL 60045 USA

Hospira

(01) 1030409 166010 3

10 Units X 100 mL Rx only NDC 0409-1660-10

Single-use bottle. Discard unused portion.

Precedex™ Dexmedetomidine HCl in 0.9% Sodium Chloride Injection

400 mcg/100 mL (4 mcg/mL) Dexmedetomidine HCl Provided as Dexmedetomidine HCl

For Intravenous Infusion
Ready to Use - Do Not Dilute

Hospira

10 Units X 100 mL Rx only NDC 0409-1660-10

Single-use bottle. Discard unused portion.

Precedex™ Dexmedetomidine HCl in 0.9% Sodium Chloride Injection

400 mcg/100 mL (4 mcg/mL) Dexmedetomidine HCl Provided as Dexmedetomidine HCl

For Intravenous Infusion
Ready to Use - Do Not Dilute

Hospira

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Each mL contains 4 mcg dexmedetomidine provided as 4.72 mcg dexmedetomidine HCl and 9 mg of sodium chloride in water for injection. pH is 4.5 to 7.0.

This product is not made with natural rubber latex.

Usual dosage: See insert. Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

Do not freeze.

Preservative-Free.

Hospira, Inc.
Lake Forest, IL 60045 USA

Hospira

50 mL Rx only NDC 0409-1660-50

Single-use bottle. Discard unused portion.

Precedex™ Dexmedetomidine HCl in 0.9% Sodium Chloride Injection

200 mcg/50 mL (4 mcg/mL) Dexmedetomidine Provided as Dexmedetomidine HCl

For Intravenous Infusion
Ready to Use – Do Not Dilute

200 mcg/50 mL (4 mcg/mL) Dexmedetomidine Provided as Dexmedetomidine HCl

Precedex™ Dexmedetomidine HCl in 0.9% Sodium Chloride Injection

EXP
LOT

RL-4130

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(b) (4)

LIFT
HERE

Each mL contains 4 mcg of dexmedetomidine provided as 4.72 mcg dexmedetomidine HCl and 9 mg of sodium chloride in water for injection.
pH is 4.5 to 7.0.

This product is not made with natural rubber latex.

Usual dosage: See insert.

Store at 20 to 25°C (68 to 77°F).
[See USP Controlled Room Temperature.]

Do not freeze.

Preservative-Free.

Hospira, Inc.
Lake Forest, IL 60045 USA

Hospira

100 mL Rx only **NDC 0409-1660-10**

Single-use bottle. Discard unused portion.

Precedex™

Dexmedetomidine HCl in 0.9% Sodium Chloride Injection

400 mcg/100 mL (4 mcg/mL) Dexmedetomidine Provided as Dexmedetomidine HCl

For Intravenous Infusion
Ready to Use – Do Not Dilute

Precedex™ Dexmedetomidine HCl in 0.9% Sodium Chloride Injection
400 mcg/100 mL (4 mcg/mL) Dexmedetomidine Provided as Dexmedetomidine HCl

RL-4131

(01) 00300409 166010 6

CENTER FOR DRUG EVALUATION AND RESEARCH

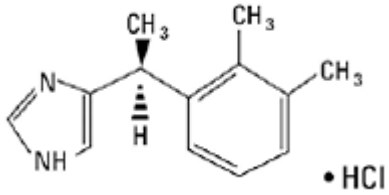
APPLICATION NUMBER:

NDA 21-038/S020

CHEMISTRY REVIEW(S)

Chemistry #1	**1. Division:** HFD-170	**2. NDA Number: 21-038**
3. Name and Address of Applicant: Hospira, Inc. 275 North Field Dr., Dept. 0389, Bldg. H2-2 Lake Forest, IL 60045		**4. Supplement(s):** PAS **Number:** S-020 **Date(s):** 12-OCT-2012
5. Name of Drug: *PRECEDEX*®		**6. Nonproprietary name:** Dexmedetomidine Hydrochloride Injection
7. Supplement Provides for: Addition of an alternate container closure system for 10 ml (2 mg/ml), 20 ml (2 mg/ml) and 20 ml (5 mg/ml) presentations		**8. Amendment(s):**
9. Pharmacological Category: Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting; sedation of non-intubated patients prior to and/or during surgical and other procedures	**10. How Dispensed:** R_x	**11. Related Documents:** Microbiology Consult Review
12. Dosage Form: Injectable Intravenous Solution	**13. Potency:** 100 mcg/mL (2 mLvial), 4 mcg/mL (50,100 mL)	

14. Chemical Name and Structure: (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride, **Molecular Formula:** $C_{13}H_{16}N_2$•HCl; **MW:** 236.7



15. Comments:

- In this PAS, the Applicant is proposing addition of an alternate formulation in two additional packaging configurations. The proposed alternate formulation will be a 4 mcg/mL solution of Precedex™ supplied as 200 mcg/50 mL in a 50 mL bottle and 400 mcg/100 mL in a 100 mL bottle. The new formulation will be manufactured at Hospira's McPherson, Kansas facility. the following changes have been proposed:
  - New product formulation utilizing the same drug substance and excipients as the currently used for the concentrate product;
  - New container closure systems [50 mL and 100 mL glass bottles];
  - A revised sterilization cycle for the new container configurations.
- A microbiology consult was placed and the reviewer recommends Approval (Review by Dr. V. Pawar, 6-DEC-2012).
- Pharm-Tox consult was placed to evaluate the extractables data provided in the supplement to qualify the new rubber stopper with the proposed formulation (Review by Dr. N. Woo, 13-MAR-2013). The consult review recommends approval but needs a Post-Approval commitment to submit data regarding the "unrelated substances" (RRT and %) under standard conditions at the 1- year and 2- year stability time point.
- **From CMC, approval is recommended. Please communicate the comment as stated under Conclusion to the Applicant**

16. Conclusion: The supplement is recommended for APPROVAL. Following comment must be communicated to the Applicant:

Submit a Post-Approval Commitment to report data regarding the "unrelated substances" (RRT and %) under standard conditions at the 1- year and 2- year stability time point.

17. Name: **Deepika Arora Lakhani, Ph.D., Chemist**	**Signature:**	**Date:** **2/6/2013**
18. Concurrence: **Ramesh Raghavachari, Ph.D., Acting Branch Chief, Div., IX, ONDQA**	**Signature:**	**Date:** **2/6/2013**

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/s/

DEEPIKA LAKHANI
03/13/2013
Recommend Approval from CMC perspective.

RAMESH RAGHAVACHARI
03/13/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-038/S020

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHESIA, ANALGESIA AND ADDICTION PRODUCTS

PHARMACOLOGY/TOXICOLOGY MEMO TO FILE

NDA Number:	21-038
Supplement:	Prior Approval Supplement - 20 Manufacturing (CMC)
Supporting Document Number:	420
Submit Date / Received Date:	10-12-2012 / 10-12-2012
Sponsor:	Hospira 275 North Field Dr Bldg H2 Lake Forest, IL 600455046
Product:	Precedex® (dexmedetomidine)
Division Name:	Division of Anesthesia, Analgesia and Addiction Products
HFD #:	170
Reviewer:	Newton H. Woo. PhD
Supervisor:	Adam Wasserman, PhD
Division Director:	Bob A. Rappaport, MD
Project Manager:	Allison Meyer, PhD
Date of Memo:	March 8, 2013

Recommendation: From a nonclinical perspective, the NDA prior approval supplement (NDA 21-038 / S-20), which introduces two additional packaging configurations of a diluted formulation of Precedex (4μg/mL), may be approved. Comments are outlined at the conclusion of this review.

Background/Prior Regulatory History

Precedex® (NDA 21-038) was originally approved for sedation of initially intubated and mechanically ventilated adult patients during treatment in an intensive care setting by the FDA in 1999 and subsequently approved for procedural sedation in 2008 (administration cannot exceed 24 hrs by continuous infusion). In the current

submission, the Sponsor is seeking approval of two additional packaging configurations of a pre-diluted formulation of Precedex (4 µg/mL)[1].

The two new container closure systems (See Sponsor's Table below) consist of:

1) a 50 mL (b) (4) glass bottle, a (b) (4) stopper and a (b) (4) aluminum seal.
2) a 100 mL configuration consists of a 100 mL (b) (4) glass bottle, a (b) (4) stopper and a (b) (4) aluminum seal.

Product Presentation	Stopper	Bottle	Overseal Assembly
50 mL	(b) (4)	Glass bottle, (b) (4) 50 mL, (b) (4) (b) (4) (b) (4)	Aluminum, (b) (4) (b) (4)
100 mL		Glass bottle, (b) (4) 100 mL, (b) (4)	Aluminum, (b) (4) (b) (4)

(b) (4)

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(b) (4)

[redacted]

Internal Recommendations

There are no pharmacology/toxicology concerns for this NDA supplement. Therefore, from the nonclinical Pharmacology/Toxicology perspective, based upon the information reviewed by this reviewer, this prior approval NDA supplement may be approved.

It is recommended that ONDQA request the Sponsor to report data regarding the "unrelated substances" (RRT and %) under standard conditions at the 1- year and 2-year stability time point.

Reviewer Signature: Newton H. Woo, Ph.D.

Supervisor Signature: Concurrence Yes ___ No ____

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/s/

NEWTON H WOO
03/12/2013

ADAM M WASSERMAN
03/13/2013
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-038/S020

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

December 4, 2012

NDA: 21/038/S-020

Drug Product Name
Proprietary: Precedex®
Non-proprietary: dexmedetomidine HCl Injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
October 12, 2012	October 12, 2012	October 22, 2012	October 27, 2012

Submission History (for amendments only) – N/A

Applicant/Sponsor
Name: Hospira, Inc.
Address: 275 North Field Drive
Dept. 389, Bldg. H2-2
Lake Forest, IL 60045

Representative: Cecilia C. Turoff, Sr. Assoc., Global R A
Telephone: 224-212-6310, cecilia.turoff@hospira.com

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: Recommend Approval.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: PAS

2. SUBMISSION PROVIDES FOR:

- New product formulation utilizing the same drug substance and excipients as are currently used for the concentrate product.
- New Container Closure Systems are proposed in 50 mL and 100 mL glass bottles.
- Change in sterilization cycle.

3. MANUFACTURING SITE: Hospira, Inc., 1776 N. Centennial Drive McPherson, KS 67460. Registration No. 1925262

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Precedex® 4 mcg/mL: 200 mcg/50 mL in a 50 mL glass bottle; and 400 mcg/100 mL in a 100 mL glass bottle.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Alpha 2-adrenoreceptor agonist for sedation without respiratory depression

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: The subject Prior Approval Supplement NDA 21-038/S-020 provides for new product formulation, new container closure system and a change in sterilization cycle. This is an electronic submission. This review will focus only on the proposed changes.

filename: **N021038S020R1**

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommend approval

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The sponsor proposes to manufacture the drug product at the approved site with exception of small changes in the process such as change in the formulation to meet the new container/closure systems and a change in the (b) (4) sterilization cycle.

B. Brief Description of Microbiology Deficiencies - None

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____
Vinayak B. Pawar, Ph.D., NDMS, OPS, CDER

B. Endorsement Block _____
John W. Metcalfe, Ph.D., NDMS, OPS, CDER

C. CC Block
N/A

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/s/

VINAYAK B PAWAR
12/06/2012

JOHN W METCALFE
12/06/2012
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-038/S020

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW
Review

Office of New Drug Quality Assessment

Application Number: 21038/ S-020

Name of Drug: Precedex® (dexmedetomidine hydrochloride) Injection

Applicant: Hospira, Inc.

Material Reviewed:

Material	Submit Date	Receipt Date	Compared to
Content of Labeling (SPL)	10/2/2012	10/2/2012	10/13/2010
Carton and Container Labels	3/6/2013	3/6/2013	9/20/2010 (in-use labeling)

Background and Summary

NDA 21038/S-020 was submitted as a Prior Approval supplement on October12, 2012, and provides for a new ready to use formulation containing 4 mcg/mL of dexmedetomidine in 0.9% NaC1. The proposed product will be presented in 2 packaging configurations of 200 mcg/ 50 mL in a 50 mL glass bottle, and 400 mcg/ 100 mL in a 100 mL glass bottle. These packaging configurations were previously proposed in S-016 dated August 31, 2009 along with a new manufacturing site (Rocky Mount, NC). S-016 currently still pending because the overall OC recommendation (Rocky Mount, NC) is still pending. The labels were submitted in S-016 were reviewed on August 2, 2011, by Irene Z. Chan, Division of Medical Error Prevention and Analysis and found unacceptable.

The applicant implemented the DMEPA recommendations for the labels and submitted the revised labels to this supplement, S-020. DMEPA had reviewed these changes and additional recommendations were sent to the applicant. (refer DMEPA review dated March 4, 2013). New labels were submitted on March 6, 2013, incorporating DMEPA's recommendations and found acceptable by Morgan Walker. The CMC Changes were reviewed by Deepika Lakhani on March 13, 2013 and found to be acceptable.

Review

This comparison was done by visually comparing the October 2, 2012 carton and labeling to the last submitted or approved labeling on file.

The following are the assessments for each change identified:

Immediate Container Label:

1. The product strength statement 4mcg/mL is located following the total strength per total volume statement.
2. The route of administration is indicated as "For Intravenous Infusion".
3. The statement "Ready to use- Do Not Dilute" is included into the title case.
4. The storage and preservative-free statement was moved from the side panel (right) to the other (left) side panel.
5. The NDC Numbers; NDC 0409-1660-50, 50 mL bottle; 0409-1660-10, 100 mL bottle were added

Comment: Acceptable. The changes are based on DMEPA August 2, 2011, label and labeling review. The information that was added is consistent with the provision of the supplement.

Carton

1. The product strength statement 4mcg/mL is located following the total strength per total volume statement.
2. The route of administration is indicated as "For Intravenous Infusion".
3. The statement "Ready to use- Do Not Dilute" is included into the title case.

Comment : Acceptable. The changes are based on DMEPA August 2, 2011, label and labeling review. The information that was added is what the supplement provides for.

Content of Package Insert:

1. In the section of Dosage Forms and Strengths the "Precedex Injection Concentrate" and Precedent Injection, 200 mcg/50 mL (4 mcg/mL) in a 50 mL glass bottle" and "Precedex Injection, 400 mcg/ 100 mL (4 mcg/mL) in a 100 mL glass bottle" was added. .
2. In the How Supplied section the statement "Precedex Injection, Concentrate" was added.
3. In the How Supplied section the new 50 mL and 100 mL size bottles are added with their corresponding NDC Numbers. NDC 0409-1660-50, 50 mL bottle; 0409-1660-10, 100 mL bottle were added.

4. In the Description section the statements "of Precedex Injection, Concentrate" and "Each mL of Precedex Injection contains 4.72 mcg of dexmedetomidine hydrochloride in water" was added.

Comment: Acceptable. The changes are based on DMEPA August 2, 2011, label and labeling review. The changes clarified the content and meaning of the statement. The information that was added is what the supplement provides for.

Recommendations

The change to the content of labeling and the container labels are acceptable. All changes are based on DMEPA's recommendations. Changes represent the proposed changes in the supplement. This supplement is recommended for approval.

LCDR Luz E Rivera
Regulatory Project Manager
Office of New Drug Quality Assessment

Michael Folkendt
Chief, Project Management Staff
Office of New Drug Quality Assessment

Enclosure:

Container Labeling
DMEPA's Email

6 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Rivera, Luz E (CDER)

From: Walker, Morgan
Sent: Thursday, March 07, 2013 10:35 AM
To: Rivera, Luz E (CDER)
Cc: Wilkins Parker, Jamie
Subject: RE: 21038/ S-020 Labels

Follow Up Flag: Follow up
Flag Status: Completed

Hi Luz,

I have reviewed the labels and they are acceptable as presented.

Thanks,

Morgan Walker

From: Rivera, Luz E (CDER)
Sent: Wednesday, March 06, 2013 12:04 PM
To: Walker, Morgan
Subject: 21038/ S-020 Labels

Good morning Morgan,

The applicant for sNDA 21038/ S-020, Precedex sent the response to DMEPA's Labeling Review comment.

(For the Carton Labeling and Container Labels: Ensure that there are lot numbers and expiration dates on all carton labeling and container labels. The only draft label that has the lot number and expiration date is the 200 mcg/50 mL container label).

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Do you want me to send another consult for this change?

Thank you,
Luz

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/s/

LUZ E RIVERA
03/13/2013

MICHAEL M FOLKENDT
03/13/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Final Labeling Review

Date:	March 1, 2013
Reviewer:	Morgan Walker, PharmD, MBA Division of Medication Error Prevention and Analysis
Team Leader:	Jamie Wilkins Parker, PharmD Division of Medication Error Prevention and Analysis
Drug Name:	Precedex (Dexmedetomidine Hydrochloride) Injection 200 mcg/50 mL 400 mcg/100 mL
Application Type/Number:	NDA 021038
Submission Number:	S-016 and S-020
Applicant/Sponsor:	Hospira, Inc.
OSE RCM #:	2013-323

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review responds to a request from the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) for a review of the revised container labels, insert and carton labeling for Precedex (Dexmedetomidine Hydrochloride) Injection (NDA 021038) submitted on October 12, 2012 for supplement 16. In addition, the Applicant submitted supplement 20, which provides for a new stopper for the vials proposed in supplement 16. DMEPA previously reviewed and provided comments on the proposed container labels, insert and carton labeling under OSE RCM #2010-683 dated August 2, 2011.

2 MATERIAL REVIEWED

DMEPA reviewed the revised container labels, insert and carton labeling received on October 12, 2012 and the labels received on January 30, 2013, which were the same. We compared the revised container labels, insert and carton labeling (Appendices A and B) against the recommendations contained in OSE review #2010-683 dated August 2, 2011.

3 CONCLUSIONS AND RECOMMENDATIONS

Review of the revised documents show that the Applicant has not implemented all of DMEPA's recommendations in OSE review #2010-683. We provide the following comments to the applicant below.

3.1 COMMENTS TO THE APPLICANT

A. Carton Labeling and Container Labels

- Ensure that there are lot numbers and expiration dates on all carton labeling and container labels. The only draft label that has the lot number and expiration date is the 200 mcg/50 mL container label.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Teena Thomas at 301-796-0549.

3 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MORGAN A WALKER
03/01/2013

JAMIE C WILKINS PARKER
03/04/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-038/S020

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21038/ S-020

INFORMATION REQUEST

Hospira, Inc.
Attention: Cecilia C. Turoff
Senior Associate, Global Regulatory Affairs
275 N. Field Dr.
Lake Forest, IL 60045

Dear Ms. Turoff:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Precedex (Dexmedetomidine hydrochloride) Injection, 100 mcg/ mL, 4 mcg/ mL.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a prompt written response by **Tuesday, March 5, 2013**, in order to continue our evaluation of your supplemental application.

1. Provide information regarding the Unrelated Substances peaks and concentrations at the 6 months stability time point.
2. Provide a list of the other approved products (that you refer to in the submission) that also use the proposed (b) (4) rubber stopper (we are specifically interested if any aqueous based injection formulation is already using this stopper).
3. Clarify if the Hospira Inc., Highway 301 North, Rocky Mount, NC 27801 (CFN: 1021343) is still performing Drug Substance Acceptance Testing (as listed under the Section 3.2.S.2.1, Table 2. Site Establishment Information). If not, remove this site and submit an updated table.

If you have questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796-4013.

Sincerely,

{See appended electronic signature page}

Ramesh Raghavachari, Ph.D.
Acting Branch Chief, Branch IX
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH RAGHAVACHARI
03/01/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21038/ S-020

**REVIEW EXTENSION –
CMC SUPPLEMENT**

Hospira, Inc.
Attention: Cecilia C. Turoff
Senior Associate, Global Regulatory Affairs
275 N. Field Dr.
Lake Forest, IL 60045

Dear Ms. Turoff:

Please refer to your October 12, 2012 Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Precedex (Dexmedetomidine hydrochloride) Injection, 100 mcg/ mL, 4 mcg/ mL.

We received your February 1, 2013, solicited major amendment to this application. Therefore, we are extending the goal date by two months to provide time for a full review of the submission. The extended user fee goal date is April 12, 2013.

If you have any questions, call me, Regulatory Project Manager, at (301) 796- 4013.

Sincerely,

{See appended electronic signature page}

LCDR Luz E Rivera, Psy.D.
Regulatory Project Manager
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

LUZ E RIVERA
02/26/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Mail: OSE (Mark Liberatore)	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Luz E Rivera, ONDQA, Division of Post Marketing Assessment, 301-796-4013

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/30/2013	NA	21038	S-20	10/12/2012

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Precedex	Standard		ASAP

NAME OF FIRM: Hospira

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This PAS proposes two new package configuration

SIGNATURE OF REQUESTOR Luz E Rivera	METHOD OF DELIVERY (Check one) ☐ DFS ☒ EMAIL ☐ MAIL ☒ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

LUZ E RIVERA
01/30/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 21038/S-20

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Hospira, Inc.
Attention: Cecilia C. Turoff
Senior Associate, Global Regulatory Affairs
275 N. Field Dr.
Lake Forest, IL 60045

Dear Ms. Turoff:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 21038

SUPPLEMENT NUMBER: 20

PRODUCT NAME: Precedex™ (dexmedetomidine hydrochloride) Injection, 100 mcg/ mL, 4 mcg/mL

DATE OF SUBMISSION: October 12, 2012

DATE OF RECEIPT: October 12, 2012

This supplemental application proposes the following:

1. Alternate premix formulation of Precedex™ Injection
2. New container closure system in a 50mL and 100 mL glass bottle
3. Change in the sterilization cycle.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 11, 2012, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 12, 2013.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me, at (301) 796- 4013

Sincerely,

LCDR Luz E Rivera, Psy.D.
Regulatory Project Manager
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

LUZ E RIVERA
10/23/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CMC MICRO & STERILITY ASSURANCE REVIEW REQUEST

TO *(Division/Office)*: **New Drug Microbiology Staff**

E-mail to: **CDER OPS IO MICRO**

Paper mail to: **WO Bldg 51, Room 4193**

FROM: Luz E Rivera, PM ONDQA
301 796 4013

PROJECT MANAGER *(if other than sender):*

REQUEST DATE	IND NO.	NDA NO.:	TYPE OF DOCUMENT	DATE OF DOCUMENT
10/22/2012		21038	S-20	10/12/2012

NAMES OF DRUG	PRIORITY CONSIDERATION	PDUFA DATE;	DESIRED COMPLETION DATE
Precedex	Standard	2/12/2013	1/12/2013

NAME OF APPLICANT OR SPONSOR:
Hospira

GENERAL PROVISIONS IN APPLICATION

- ☐ 30-DAY SAFETY REVIEW NEEDED
- ☐ NDA FILING REVIEW NEEDED BY: _____
- ☐ BUNDLED
- ☐ DOCUMENT IN EDR
- ☐ CBE-0 SUPPLEMENT
- ☐ CBE-30 SUPPLEMENT
- ☐ CHANGE IN DOSAGE, STRENGTH / POTENCY

COMMENTS / SPECIAL INSTRUCTIONS:

Applicant proposed an alternate premix formula. Changes in the sterilization cycle are included. Evaluate the microbiology data.

Please let me know who is the signed reviewer.

SIGNATURE OF REQUESTER

Luz E Rivera

REVIEW REQUEST DELIVERED BY (Check one):

X DARRTS ☐ EDR X E-MAIL ☐ MAIL ☐ HAND

DOCUMENTS FOR REVIEW DELIVERED BY (Check one):

☐ EDR ☐ E-MAIL ☐ MAIL ☐ HAND

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/s/

LUZ E RIVERA
10/22/2012