Summary Basis of Decision (SBD)
Pr'PRECEDEX™
Dexmedetomidine Hydrochloride, 100 µg/mL, solution
Hospira Healthcare Corporation
Submission Control Number: 126931

Date Issued 2010/09/23

Health Products and Food Branch

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- promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.  
*Health Products and Food Branch*

Également disponible en français sous le titre : Sommaire des motifs de décision (SMD), PPRECEDEX\textsuperscript{MC}, chlorhydrate de dexmédétomidine, 100 µg/mL, Hospira Healthcare Corporation, Numéro de contrôle de la présentation : 126931
FOREWORD

Health Canada’s Summary Basis of Decision (SBD) documents outline the scientific and regulatory considerations that factor into Health Canada regulatory decisions related to drugs and medical devices. SBDs are written in technical language for stakeholders interested in product-specific Health Canada decisions, and are a direct reflection of observations detailed within the evaluation reports. As such, SBDs are intended to complement and not duplicate information provided within the Product Monograph.

Readers are encouraged to consult the ‘Reader’s Guide to the Summary Basis of Decision - Drugs’ to assist with interpretation of terms and acronyms referred to herein. In addition, a brief overview of the drug submission review process is provided in the Fact Sheet entitled ‘How Drugs are Reviewed in Canada’. This Fact Sheet describes the factors considered by Health Canada during the review and authorization process of a drug submission. Readers should also consult the ‘Summary Basis of Decision Initiative - Frequently Asked Questions’ document. These documents are all available on the Health Canada website.

The SBD reflects the information available to Health Canada regulators at the time a decision has been rendered. Subsequent submissions reviewed for additional uses will not be captured under Phase I of the SBD implementation strategy. For up-to-date information on a particular product, readers should refer to the most recent Product Monograph for a product. For information related to post-market warnings or advisories as a result of adverse events (AE), interested parties are advised to access the Health Canada website.

For further information on a particular product, readers may also access websites of other regulatory jurisdictions, available under ‘Related Links’ on the Health Canada website. The information received in support of a Canadian drug submission may not be identical to that received by other jurisdictions.

Other Drug Policies and Guidance:

Readers should consult the Health Canada website for other drug policies and guidance documents. In particular, readers may wish to refer to the ‘Management of Drug Submissions Guidance’.
Table of Contents

1 PRODUCT AND SUBMISSION INFORMATION ............................................................... 1

2 NOTICE OF DECISION ................................................................................................... 2

3 SCIENTIFIC AND REGULATORY BASIS FOR DECISION .............................................. 3

   3.1 Quality Basis for Decision ......................................................................................... 3

   3.1.1 Drug Substance (Medicinal Ingredient)............................................................... 3

   3.1.2 Drug Product........................................................................................................ 4

   3.1.3 Facilities and Equipment ..................................................................................... 6

   3.1.4 Adventitious Agents Safety Evaluation................................................................. 6

   3.1.5 Conclusion............................................................................................................ 6

   3.2 Non-clinical Basis for Decision .................................................................................. 6

   3.2.1 Pharmacodynamics .............................................................................................. 6

   3.2.2 Pharmacokinetics ............................................................................................... 7

   3.2.3 Toxicology ............................................................................................................ 7

   3.2.4 Conclusion ............................................................................................................ 9

   3.3 Clinical Basis for Decision ......................................................................................... 10

   3.3.1 Pharmacodynamics ............................................................................................ 10

   3.3.2 Pharmacokinetics ............................................................................................... 10

   3.3.3 Clinical Efficacy................................................................................................. 11

   3.3.4 Clinical Safety .................................................................................................... 13

   3.4 Benefit/Risk Assessment and Recommendation .......................................................... 15

   3.4.1 Benefit/Risk Assessment ..................................................................................... 15

   3.4.2 Recommendation ............................................................................................... 15

4 SUBMISSION MILESTONES ........................................................................................... 16
## 1 PRODUCT AND SUBMISSION INFORMATION

| Brand Name: | PrPRECEDEX™ |
| Manufacturer/Sponsor: | Hospira Healthcare Corporation |
| Medicinal Ingredient: | Dexmedetomidine Hydrochloride |
| International Non-proprietary Name: | Dexmedetomidine Hydrochloride |
| Strength: | 100 µg/mL |
| Dosage form: | Solution |
| Route of Administration: | Intravenous |
| Drug Identification Number (DIN): | 02339366 |
| Therapeutic Classification: | Alpha-2-adrenergic agonist |
| Non-medicinal Ingredients: | Sodium Chloride and Water for Injection |
| Submission Type and Control Number: | New Drug Submission, Control Number: 126931 |
| Date of Submission: | 2008/12/19 |
| Date of Authorization: | 2009/12/09 |
2 NOTICE OF DECISION

On December 9, 2009, Health Canada issued a Notice of Compliance to Hospira Healthcare Corporation for the drug product Precedex™.

Precedex™ contains the medicinal ingredient dexmedetomidine hydrochloride, an alpha2-adrenergic agonist with sedative properties.

Precedex™ is indicated for:

- **Intensive Care Unit (ICU) Sedation**
  Precedex™ is indicated for sedation of initially intubated and mechanically ventilated postsurgical patients during treatment in an intensive care setting by continuous intravenous infusion. The Precedex™ infusion must not exceed 24 hours.

  Precedex™ has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post-extubation. It is not necessary to discontinue Precedex™ prior to extubation. After extubation, the dose of Precedex™ should be reduced by half. The mean time of continued infusion is approximately 6.6 hours.

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

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

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

The market authorization was based on quality, non-clinical, and clinical information submitted. The efficacy and safety of Precedex™ were primarily evaluated in four randomized, double-blind, placebo-controlled multicentre clinical studies in 1185 patients. In the two ICU sedation studies, a significantly greater percentage of patients in the Precedex™ group maintained a Ramsay sedation score of ≥3 without receiving any rescue medication compared to the placebo group. In the other two studies, the efficacy results showed that Precedex™ was more effective than placebo with patients requiring MAC and patients in elective AFI. The patients that were treated with Precedex™ required less frequent rescue medication than the placebo group. Reports of hypotension and bradycardia have been associated with Precedex™ infusion. When used as
directed, mild to moderate hypotension and/or bradycardia are manageable as per standard clinical practice.

Precedex™ (100 µg/mL, dexmedetomidine hydrochloride) is presented as a solution suitable for intravenous infusion following dilution. Dosing considerations, instructions, and guidelines are available in the Product Monograph.

Precedex™ is contraindicated for patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. Precedex™ should be administered under the conditions stated in the Product Monograph taking into consideration the potential risks associated with the administration of this drug product. Detailed conditions for the use of Precedex™ are described in the Product Monograph.

Based on the Health Canada review of data on quality, safety, and efficacy, Health Canada considers that the benefit/risk profile of Precedex™ is favourable for the indications stated above.

3 SCIENTIFIC AND REGULATORY BASIS FOR DECISION

On May 12, 2000, Abbott Laboratories submitted to Health Canada a New Drug Submission (NDS) for Precedex™ (then named Primadex, control number 061297). On September 1, 2000, a Notice of Deficiency (NOD) was issued because of numerous deficiencies in the non-clinical and clinical data. The sponsor responded, however the response was still considered incomplete, and the sponsor withdrew the submission without prejudice to re-filing. Subsequently, Abbott Laboratories divested Precedex™ to Hospira Healthcare Corporation. On December 19, 2008, Hospira Healthcare Corporation re-filed the submission (control number 126931) and submitted additional non-clinical and clinical data addressing the questions raised in the NOD. The indication proposed by the sponsor was revised to reflect the efficacy and safety data. The non-clinical and clinical data supported the revised indication and outstanding issues were adequately addressed. A Notice of Compliance (NOC) was issued for Precedex™ on December 9, 2009. A timeline of these events are reported in section 4 Submission Milestones.

3.1 Quality Basis for Decision

3.1.1 Drug Substance (Medicinal Ingredient)

General Information

Dexmedetomidine hydrochloride, the medicinal ingredient of Precedex™, is an alpha-2-adrenergic agonist. Evidence indicates that dexmedetomidine induces sedation and sympatholysis. The sedative effect is believed to result from the activation of the alpha-2-
adrenoceptors and the consequent inhibition of norepinephrine release in the locus ceruleus of the brain stem. Dexmedetomidine enhances the anxiolytic and analgesic effects of other concomitant sedatives and opioids. The sympatholytic effect of dexmedetomidine reduces blood pressure and heart rate without a significant inhibitory effect on respiration.

**Manufacturing Process and Process Controls**

The drug substance is synthetically derived. Each step of the manufacturing process is considered to be controlled within acceptable limits.

**Characterization**

The structure of dexmedetomidine hydrochloride has been adequately elucidated. Physical and chemical properties have been described and are satisfactory.

Appropriate tests are adequately controlling the levels of product- and process-related impurities. The impurities that were reported and characterized were found to be within International Conference on Harmonisation (ICH) established limits.

**Control of Drug Substance**

Copies of the analytical methods and, where appropriate, validation reports were provided and are considered satisfactory for all analytical procedures used for release and stability testing of dexmedetomidine hydrochloride.

The drug substance packaging is considered acceptable.

**Stability**

Based on the long-term, real-time, accelerated, and stress stability data submitted, the proposed retest period and storage conditions for the drug substance were supported and are considered to be satisfactory.

**3.1.2 Drug Product**

**Description and Composition**

Precedex™ (dexmedetomidine hydrochloride) is a sterile, nonpyrogenic solution suitable for intravenous (IV) infusion following dilution.
Each 1 mL of Precedex™ contains 118 µg of dexmedetomidine hydrochloride equivalent to 100 µg dexmedetomidine, as well as 9 mg of sodium chloride in water (Water for Injection). The solution is preservative-free and contains no additives or chemical stabilizers.

Precedex™ is available in 2-mL clear glass vials (200 µg/2 mL). Vials are intended for single-use only.

All non-medicinal ingredients (excipients) found in the drug product are acceptable for use in drugs according to the Food and Drug Regulations. The compatibility of dexmedetomidine hydrochloride with the excipients is demonstrated by the stability data presented on the proposed commercial formulation.

**Pharmaceutical Development**

No pharmaceutical development studies were submitted. The absence of this information is acceptable as Precedex™ is a simple solution and is prepared by standard processes routinely used in parenteral drug product manufacturing.

**Manufacturing Process and Process Controls**

The method of manufacturing is considered acceptable and the process is considered adequately controlled within justified limits.

**Control of Drug Product**

Precedex™ is tested to verify that its identity, appearance, assay, clarity, colour, pH, optical purity, particulate matter, fill volume, sterility, drug-related impurities, bacterial endotoxins, sodium chloride (titration), and parametric-release parameters are within acceptance criteria. The test specifications and analytical methods are considered acceptable.

Copies of the analytical methods and, where appropriate, validation reports were provided and are considered satisfactory for all analytical procedures used for release and stability testing of Precedex™.

Data from final batch analyses were reviewed and are considered to be acceptable according to the specifications of the drug product.


**Stability**

Long-term stability studies were performed under ICH intermediate/long term storage conditions and the expiry period was assessed based on the results from these storage conditions. Stability data support the proposed 24-month expiration date, with storage at room temperature (15-30°C).

### 3.1.3 Facilities and Equipment

The design, operations, and controls of the facility and equipment that are involved in the production of Precedex™ are considered suitable for the activities and products manufactured.

All of the proposed manufacturing sites comply with the requirements of Division 2 of the *Food and Drug Regulations*.

### 3.1.4 Adventitious Agents Safety Evaluation

Not applicable. The excipients used in the drug product formulation are not from animal or human origin.

### 3.1.5 Conclusion

The Chemistry and Manufacturing information submitted for Precedex™ has demonstrated that the drug substance and drug product can be consistently manufactured to meet the approved specifications. Proper development and validation studies were conducted, and adequate controls are in place for the commercial processes.

### 3.2 Non-clinical Basis for Decision

#### 3.2.1 Pharmacodynamics

In rodents, dexmedetomidine induced sedation with an effect similar to but not identical to opioid analgesia. Dexmedetomidine induced hypotension and bradycardia, caused moderate increases in blood glucose independent of insulin decrease, reduced insulin release, reduced intestinal motility, and caused diuretic effects with natriuresis and kaliuresis. Dexmedetomidine exhibited reinforcing effects in monkeys but its cross-dependence with morphine was weak in rodents.
3.2.2 Pharmacokinetics

Distribution

Following IV administration in rats, dexmedetomidine had a wide distribution throughout the body with higher levels in the liver and kidneys. Dexmedetomidine crossed the placental barrier and was secreted in milk.

Metabolism

Dexmedetomidine was extensively metabolized in the liver through both oxidation and conjugation. The metabolism is species specific. In rodents, the main metabolites were hydroxyl (OH), carboxyl (COOH), glucuronide hydroxylated (G-OH), sulphate (SO3-OH), and mercapturic acid conjugate (M-OH) products. In dogs, the metabolites were similar with the exception of M-OH. Approximately 30% to 50% of the urinary metabolites from the species studied have not been identified. In human liver tissue, dexmedetomidine had no clinically relevant interaction with the cytochrome P450 (CYP) coenzymes.

Excretion

Dexmedetomidine has a half-life ranging from 0.5 to 1 hour because of its fast metabolism in the liver. The metabolites of dexmedetomidine were eliminated via the bile and urine. Due to the extensive metabolism of dexmedetomidine in dogs, only 1% of the dose was eliminated in the urine as the parent drug.

3.2.3 Toxicology

Single-Dose Toxicity

In mice, rats, and dogs, the highest acute IV non-lethal dose was 1 mg/kg.

Repeat-Dose Toxicity

Chronic toxicity studies with IV and subcutaneous (SC) injections of dexmedetomidine were conducted in rats of both sexes. In a 28-day IV toxicity study, the No-Toxic-Effect Dosage Level was 40 μg/kg/day in rats. The target organ of toxicity was the adrenal zona glomerulosa in female rats only. In a 28-day toxicity study with SC injection, the target organ was the adrenal zona glomerulosa in both sexes; and the prostate, and seminal vesicles in males.
In dogs, a 14-day IV study found that supra-therapeutic blood levels of dexmedetomidine induced hypothermia and bradycardia when the dogs were sedated. In a 28-day IV dog study, there were increases in cortisol secretion, reduction in Thyroid Stimulating Hormone (TSH) secretion, reduction in adrenocorticotropic hormone (ACTH)-stimulated cortisol secretion, and reduction of Luteinizing Hormone (LH). Concomitant IV injection of dexmedetomidine with midazolam and propofol significantly increased the exposures and peak concentrations of midazolam and propofol, with little effect on dexmedetomidine.

The chronic toxicity of three human-specific glucuronide-conjugated metabolites, designated as G-Dex-1 G-Dex-2, and H-1, were studied in rats. No clinically relevant adverse effects were found.

**Mutagenicity and Genotoxicity**

*In vitro* and *in vivo* genotoxicity studies found no mutagenesis in the Ames bacterial reverse mutation assay or in the mouse lymphoma assay. No clastogenesis was found in human lymphocytes *ex vivo*. A repeat mouse micronucleus study indicated that dexmedetomidine was not clastogenic.

**Carcinogenicity**

Carcinogenicity studies were not conducted with dexmedetomidine in animals. Pharmaceuticals administered for a short duration of time do not require carcinogenicity studies unless there is cause for concern.

**Reproductive and Developmental Toxicity**

In a rat fertility study in which rats were administered dexmedetomidine by SC injection, the No-Observed-Adverse-Effect Level (NOAEL) for the initial parent (F0) generation (males and females) was 54 µg/kg/day for the fertility indices and 6 µg/kg/day for systemic toxicity. The NOAEL for first filial (F1) generation development was 6 µg/kg/day.

In a teratogenicity study in which rats and rabbits were administered dexmedetomidine by SC injection, the NOAEL for rats was 2 µg/kg/day for maternal toxicity and 20 µg/kg/day for F1 development. The NOAEL for rabbits was 96 µg/kg/day for maternal toxicity and 96 µg/kg/day for F1 development. In both rats and rabbits, no teratogenicity was observed at any dose tested. The dose used in rats, when normalized with the body surface area, was approximately two-times the maximum recommended
therapeutic dose. The exposure in rabbits was approximately equal to that in humans at the maximum recommended IV dose based on plasma area-under-the-curve (AUC) values.

In a peri-and post-natal reproductive study in which rats were administered dexmedetomidine by SC injection, the NOAEL was 8 µg/kg/day for maternal toxicity and 2 µg/kg/day for F1 development. Dexmedetomidine was shown to delay foetal development even though it was found to be not teratogenic.

**Local Tolerance**

In guinea pigs, dexmedetomidine was negative for the passive cutaneous anaphylaxis test and the delayed contact hypersensitivity test. An intramuscular injection of dexmedetomidine resulted in reversible tissue irritation. An intraarterial injection resulted in little arterial irritation beyond the point of injection.

**3.2.4 Conclusion**

The non-clinical studies for this drug submission are considered suitable. There are no pharmacological/toxicological issues within the submission which preclude the intended clinical usage of dexmedetomidine.

Dexmedetomidine has a profile of acute and chronic toxicities consistent with other sedatives. When used as an anaesthetic with proper specialized support, it has a relatively wide safety margin. In rats and dogs, chronic exposure to dexmedetomidine may interfere with the function of the thyroid gland, adrenal gland, and/or the sex glands. In humans, these adverse effects (AEs) seem inconsequential as long as the use of dexmedetomidine is restricted to a relatively short period of time. Dexmedetomidine has not been found to be mutagenic or clastogenic. It crosses the placental barrier and is secreted in milk. It delays foetal development although no teratogenicity has been found.

Overall, the non-clinical pharmacology and toxicology data submitted support the use of Precedex™ (dexmedetomidine hydrochloride) for the currently approved indication. Clinical monitoring will clarify the safety profile of Precedex™ in the clinical setting.
3.3 **Clinical Basis for Decision**

### 3.3.1 Pharmacodynamics

Precedex™ is a relatively selective alpha-2-adrenergic agonist with sedative properties. Dexmedetomidine causes dose-dependent decreases in blood pressure and heart rate as part of its mechanism of action. In a study with ten healthy volunteers, the respiratory rate and oxygen saturation remained within normal limits and there was no evidence of respiratory depression when Precedex™ was administered by IV infusion at doses within the recommended dose range (0.2 to 0.7 µg/kg/hr).

Dexmedetomidine was shown to decrease the cardiac output in a dose-dependent manner. At the plasma concentration of 0.3 to 0.6 ng/mL, its inhibitory effect on cardiac output ranged from 3 to 8%. At 1.2 ng/mL, this effect increased to 19%, which in turn may reduce its own clearance. Its inhibitory effects on the cardiovascular system are expected to be more pronounced in patients with an existing higher sympathetic tension. Dexmedetomidine is unsuitable for clinical conditions that are associated with fast changes in blood drug concentration, such as bypass and brain surgeries.

### 3.3.2 Pharmacokinetics

#### Distribution

Following IV administration, dexmedetomidine showed a rapid distribution phase with a distribution half-life of approximately 6 minutes, and a steady-state volume of distribution of approximately 118 L. Dexmedetomidine was highly bound to plasma proteins. The average protein binding was 94%.

#### Metabolism

Dexmedetomidine undergoes quick and extensive metabolism in the liver. Its metabolism involves both direct glucuronidation as well as CYP mediated oxidation. Dexmedetomidine is metabolized to two main classes of metabolites: the N-glucuronides (G-Dex-1 and G-Dex-2), and N-methylation products (G-N-Me-OH and N-Me-COOH, N-Me), in addition to other minor metabolites found in rodents. Approximately 30% to 50% of the urinary metabolites were not identified.

Dexmedetomidine’s oxidation is mediated mainly by CYP2A6 although other CYP coenzymes are involved, including CYP1A2, CYP2E1, CYP2D6, and CYP2C19.
Dexmedetomidine is also a broad spectrum inhibitor of the CYP isoenzymes including CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4; however its inhibitory effect on the CYP coenzymes is negligible at sedation blood concentrations up to 10 ng/mL.

**Excretion**

Due to the extensive metabolism of dexmedetomidine, very little of the unchanged drug was excreted in the urine and faeces. Most of the metabolites were excreted in the urine. The elimination half-life of dexmedetomidine was approximately 2 hours.

**Drug Interaction Studies**

Dexmedetomidine enhances not only the anaesthetic effects of isoflurane but also its inhibitory effect on respiration. The pharmacodynamic interactions of dexmedetomidine with midazolam and propofol seem to be additive without clinically significant pharmacokinetic interactions. Both dexmedetomidine and propofol have more inhibitory effects on the cardiovascular functions and these effects may become additive. Dexmedetomidine potentiates the analgesic effect of alfentanil as well as its inhibitory effect on respiration.

**Special Populations**

In patients with renal and hepatic impairment, dexmedetomidine clearance is reduced proportionately with the severity of the impairment. The metabolism of dexmedetomidine is not affected by age, but caution is recommended with administration to the elderly as they are generally more sensitive to inhibitory agents, and they have lower renal clearance and a higher prevalence of cardiovascular conditions.

**3.3.3 Clinical Efficacy**

The clinical efficacy of Precedex™ was evaluated in randomized, double-blind placebo-controlled multicentre studies for its use in post-surgical Intensive Care Unit (ICU) sedation and in conscious sedation.

**Post-surgical ICU Sedation**

Two pivotal studies (Study W97-245 and Study W97-246) demonstrated the efficacy of Precedex™ in post-surgical ICU sedation. Precedex™ was initiated by infusion as soon as possible but no later than 1 hour after admission to the ICU. Precedex™ could continue for 6 hours after extubation but no longer than 24 hours.
In Study W97-245, 175 patients were randomized to receive placebo and 178 patients were randomized to receive Precedex™ as a loading dose of 1 µg/kg over 10 minutes followed by a maintenance dose ranging from 0.2 to 0.7 µg/kg/hr. Patients were supplemented with midazolam as needed for both groups. In addition, morphine was given for pain as needed. The primary efficacy endpoint was the percentage of patients who used no midazolam to achieve adequate sedation based on the Ramsay sedation scale. The total dose of midazolam needed in addition to Precedex™ during indwelling intubation to achieve adequate sedation was considered a secondary efficacy endpoint. Other secondary efficacy endpoints were the total dose of midazolam during the study period, total dose of morphine during the study period, the integrated Ramsay sedation score, time to extubation and weaning duration, and nurse assessment. The prospective primary analysis showed that a significantly greater percentage of patients on Precedex™ (61%) maintained a Ramsay sedation score of \( \geq 3 \) without receiving any midazolam rescue medication compared with those in the placebo group (25%). The results from the secondary efficacy endpoints were consistent with those from the primary efficacy endpoint.

In Study W97-246, 198 patients were randomized to receive placebo and 203 patients were randomized to receive Precedex™ as a loading dose of 1 µg/kg over 10 minutes followed by maintenance dose ranging from 0.2 to 0.7 µg/kg/hr. Patients were supplemented with propofol as needed for both groups. In addition, morphine was given for pain as needed. The efficacy endpoints were the same as used in the study above except that propofol was the rescue medication instead of midazolam. The prospective primary analysis showed that a significantly greater percentage of patients on Precedex™ (60%) maintained a Ramsay sedation score of \( \geq 3 \) without receiving any propofol rescue medication compared with those in the placebo group (24%). The secondary efficacy endpoints were consistent with the findings of the primary endpoint.

In both studies, approximately 25% of the patients in the placebo group did not require any rescue medication (midazolam or propofol). This was probably due to the carry-over effects of anaesthetics used during the surgical anaesthesia. In the Precedex™ groups of both studies, approximately 40% of the patients still required the use of rescue medication indicating that Precedex™ alone is not sufficient to sedate a significant portion of the patients.

**Conscious Sedation**

Two pivotal studies (Study 2005-005 and Study 2005-006) were conducted to demonstrate the efficacy of Precedex™ in conscious sedation.
Study 2005-005 included 326 patients who underwent a variety of elective surgeries/procedures performed under monitored anaesthesia care. Sixty-three patients were randomized to receive placebo, 134 received a loading dose of Precedex™ 0.5 µg/kg, and 129 received a loading dose of Precedex™ 1.0 µg/kg. Both loading doses were given over 10 minutes followed by a maintenance dose ranging from 0.2 to 1.0 µg/kg/hr. After achieving the desired level of sedation, a local or regional anaesthetic block was performed. Patients were supplemented with midazolam as needed for all three groups. In addition, fentanyl was given for pain as needed. 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. The prospective primary analysis showed that a significantly greater percentage of patients on Precedex™ maintained an Observer’s Assessment of Alertness/Sedation Scale <4 without receiving any midazolam compared with patients in the placebo group. The percentage of patients that did not require midazolam rescue was 40% and 54% in the Precedex™ 0.5 µg/kg group and the Precedex™ 1.0 µg/kg group, respectively, compared with 3% in the placebo group.

Study 2005-006 included 105 patients who underwent awake fiberoptic intubation prior to a surgical or diagnostic procedure. Fifty patients were randomized to receive placebo and 55 were randomized to receive Precedex™ as a loading dose of 1 µg/kg over 10 minutes followed by a maintenance dose at 0.7 µg/kg/hr. After achieving the desired level of sedation, topicalization of the airway was carried out with lidocaine formulations. Patients were supplemented with midazolam as needed for both groups. 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. The prospective primary analysis showed that a significantly greater percentage of patients in the Precedex™ group (53%) maintained a Ramsay Sedation Scale ≥2 without receiving any midazolam compared with those in the placebo group (14%).

In both studies, the secondary efficacy endpoint outcomes were generally consistent with the primary outcome results.

3.3.4 Clinical Safety

The clinical safety of Precedex™ was evaluated in randomized, double-blind placebo-controlled multicentre studies for its use in post-surgical ICU sedation and in conscious sedation. See section 3.3.3 Clinical Efficacy. The inhibitory effects of Precedex™ on the cardiovascular system were reflected in the data from the pivotal studies on post-surgical ICU sedation and conscious sedation.
**Post-surgical ICU Sedation**

The safety data from Study W97-245 and Study W97-246 included 766 patients. Of this total, 387 patients received Precedex™ with supplemental midazolam or propofol, and 379 patients received placebo with supplemental midazolam or propofol. Approximately twice as many patients in the Precedex™ group reported hypotension and bradycardia compared to the placebo group. The most frequently observed treatment-emergent AEs included hypotension, hypertension, nausea, bradycardia, fever, vomiting, hypoxia, tachycardia and anemia. Precedex™ at therapeutic doses caused decreases in both blood pressure (systolic and diastolic) and heart rate. A notable number of cases with transient QTc prolongation were reported in the clinical studies. Although there was no clear indication to link these reports to dexmedetomidine, patients must be monitored closely because of the therapeutic complexities in post-surgical ICU care and during anaesthesia.

Study 2001-001 evaluated the sedative properties of Precedex™ compared to midazolam in patients requiring sedation beyond 24 hours up to 30 days in the ICU. Precedex™ was given with maintenance infusions ranging from 0.2 to 1.4 µg/kg/hr while midazolam was given with infusions ranging from 0.02 to 0.1 mg/kg/hr. The safety data showed that a higher percentage of patients on Precedex™ experienced clinically significant AEs than patients on midazolam (46% vs. 40%). The overall AE profile was similar to that observed in the studies less than 24 hours, but more frequent. Consistent with the pharmacological action of Precedex™, AEs of the cardiovascular system dominated. More patients on Precedex™ experienced bradycardia [45% versus (vs.) 23%] and more patients experienced a treatment-related AE on Precedex™, (40.6% vs. 28.7%). More cases of bradycardia associated with Precedex™ required medical intervention (4.9% vs. 0.8%). In view of the safety results of this study, the use of Precedex™ is restricted to up to 24 hours.

**Conscious Sedation**

The safety data from the two conscious sedation studies (Study 2005-005 and Study 2005-006) included a total of 431 patients, of which 318 patients received Precedex™. The safety results were consistent with those observed in the post-surgical ICU sedation studies. Similar to the other studies, bradycardia and hypotension were more frequent in the Precedex™ group. The most frequent AEs were hypotension, bradycardia, and dry mouth. The safety data did not reveal any additional safety issues. Post-market safety data were consistent with the safety profile observed in the pre-market database.
3.4 Benefit/Risk Assessment and Recommendation

3.4.1 Benefit/Risk Assessment

Precedex™ has been shown to be efficacious and safe for post-surgical ICU sedation, as well as conscious sedation for monitored anaesthetic care and awake fiberoptic intubation supplemented with adequate local techniques. Its use should not exceed 24 hours in the ICU setting as there is uncertainty as to its efficacy and safety for unrestricted ICU sedation beyond 24 hours.

Precedex™ reduces blood pressure and heart rate as part of its mechanism of action. These dose-dependent AEs are reflected in both the data for ICU sedation and for conscious sedation. In patients with severe renal and hepatic impairment, a dose reduction, commensurate with the degree of impairment is recommended. Similar dose reductions should also be used in the elderly.

Reports of hypotension and bradycardia have been associated with Precedex™ infusion. When Precedex™ is used as directed, mild to moderate hypotension and/or bradycardia are manageable as per standard clinical practice. The approved labelling provides all the appropriate warnings and precautions to ensure the safe use of Precedex™ and clearly identifies hypotension and bradycardia as the major adverse reactions. Overall, the benefit/risk profile is favourable and supports the use of Precedex™ for the revised indications.

3.4.2 Recommendation

Based on the Health Canada review of data on quality, safety and efficacy, Health Canada considers that the benefit/risk profile of Precedex™ is favourable for the indications previously stated in section 2 Notice of Decision. The NDS complies with the requirements of sections C.08.002 and C.08.005.1 and therefore Health Canada has granted the NOC pursuant to section C.08.004 of the Food and Drug Regulations.
4 SUBMISSION MILESTONES

<table>
<thead>
<tr>
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