

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206628Orig1s000**

**MEDICAL REVIEW(S)**



**Food and Drug Administration**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**  
 Division of Anesthesia, Analgesia, and Addiction Products  
 10903 New Hampshire Ave.  
 Silver Spring, MD 20993-0002

**Summary Review for Regulatory Action**

<b>Date</b>	March 12, 2015
<b>From</b>	Rigoberto Roca, M.D.
<b>Subject</b>	Deputy Division Director Summary Review
<b>NDA/Supplement No.</b>	206628
<b>Applicant Name</b>	HQ Specialty Pharma Corporation
<b>Date of Submission</b>	May 12, 2014
<b>PDUFA Goal Date</b>	March 12, 2015
<b>Proprietary Name / Established (USAN) Name</b>	Dexmedetomidine hydrochloride injection
<b>Dosage Forms / Strength</b>	400 mcg/4mL 1000 mcg/mL
<b>Proposed Indication</b>	Sedation of non-intubated patients prior to and/or during surgical and other procedures
<b>Action</b>	Complete Response

<b>Material Reviewed/ Consulted</b>	
OND Action Package, including:	
Medical Officer Review	Amelia Luckett, MD
Pharmacology Toxicology Review	Newton Woo, PhD; R. Daniel Mellon, PhD
ONDQA Review	Xiaobin Shen, PhD; Julia Pinto, PhD
ONDQA Biopharmaceutics Review	Tien-Mien Chen, PhD; Tapash Ghosh, PhD
OPS/NDMS Microbiology Review	Jessica Cole, PhD; Stephen Langille, PhD
Clinical Pharmacology Review	Srikanth Nallani, PhD; Yun Xu, PhD
Project Management Staff	Allison Meyer; Parinda Jani
OMP/OPDP	Samuel Skariah
OSE/DMEPA	James Schlick, MBA, RPh Vicky Borders-Hemphill, PharmD

CDTL = Cross-Discipline Team Leader  
 DMEPA = Division of Medication Error Prevention and Analysis  
 NDMS = New Drug Microbiology Staff  
 OMP = Office of Medical Policy  
 OND = Office of New Drugs

ONDQA = Office of New Drug Quality Assessment  
 OPS = Office of Pharmaceutical Sciences  
 OPDP = Office of Professional Drug Promotion  
 OSE = Office of Surveillance and Epidemiology

## 1. Introduction

The Applicant, HQ Specialty Pharma, has submitted a 505(b)(2) application for dexmedetomidine hydrochloride, using Precedex<sup>®</sup> (NDA 21038) as the reference drug. The two formulations are very similar, except for the presence of two preservatives in the Applicant's formulation: methylparaben and propylparaben. Due to the presence of these two preservatives, the Applicant was not able to file this application as a generic drug.

This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling requested by the Applicant.

## 2. Background

Dexmedetomidine is an  $\alpha_2$ -adrenergic agonist, originally approved for marketing in 1999 for the intravenous sedation of mechanically ventilated and intubated patients. A subsequent supplemental application added the additional indication of sedation of non-intubated patients prior to and/or during surgical and other procedures. Due to unexpired patents held by Hospira, the Applicant is only seeking the second indication.

The Applicant was informed prior to submission of this application that the presence of the two preservatives would not require additional clinical studies, provided that adequate information to support the safety of the two excipients was included in the submission. Subsequently, this submission does not contain any data from clinical studies.

## 3. Chemistry, Manufacturing, and Controls (CMC)

### General Product Considerations

The differences between the Applicant's formulation and the reference drug formulation (Precedex, NDA 21038), are summarized in the table below:

Ingredient	Precedex <sup>®</sup> (Concentrate of 100 µg/mL base) 2 mL glass vial	HQ Dexmedetomidine HCl Pharmacy Bulk Solution (Concentrate of 100 µg/mL base) 4 mL and 10 mL glass vial
Dexmedetomidine hydrochloride	118 µg (100 µg base)	118 µg (100 µg base)
Sodium chloride	9 mg	9 mg
Methylparaben	NA	1.6 mg
Propylparaben	NA	0.2 mg
Water for injection	q.s.	q.s.

The following is reproduced from Dr. Shen's review:

The dexmedetomidine hydrochloride drug substance is manufactured by (b) (4) in (b) (4) per DMF (b) (4). The DMF has been last reviewed by this reviewer on 22-Jan-2015 and deemed adequate. The drug substance manufacturer site EES status is acceptable.

Specifications for dexmedetomidine hydrochloride drug substance include both USP and ICH requirements. Collectively they include appearance, identification, assay, impurities, heavy metals, loss on drying, residue on ignition, residual solvents, microbial limits and bacterial endotoxin. The drug substance is packaged in (b) (4). The drug substance stability data was referenced to DMF (b) (4), which is adequate to support its use in the NDA. It has a retest date of (b) (4) months.

The drug product is available as 100 µg/mL injection solution filled as 4 mL (in 5 mL vial) and 10 mL (in 10 mL vial) packaging configurations. The excipients include methylparaben, propylparaben, and sodium chloride. All excipients are of compendial grades. The vials are made of USP Type 1 tubular glass. The vials are stoppered with (b) (4) rubber stopper (non-drug contacting outside) that is secured with aluminum overseas containing a plastic lid. The drug product is manufactured by (b) (4) in (b) (4). The drug product manufacturing site EES status is acceptable.

The drug product specifications include appearance, identification, pH, assay, degradation products, particulate matter, extractable volume, sterility and bacterial endotoxins. The drug product primary stability studies were conducted on 3 batches for each packaging configuration. Up to 24 months of stability data is provided for the product stored under long term (25°C/60% RH) storage conditions and 6 months of stability data is provided for products stored under accelerated conditions (40°C/75% RH). For the tested quality attributes, appearance, assay, API related impurities and degradation products, particulate matter, container closure integrity, sterility and bacterial endotoxins results remained relatively stable and showed no trend during the time periods studied for all product strength/packaging configuration combinations and under all storage conditions. pH stayed relatively unchanged under long term storage conditions, it decreased under accelerated storage conditions although it remained well within specification. The assay of the two preservatives decreased over time but still within specification by 24 months. Consequently, their degradation product (b) (4) (b) (4) increased over time and reached (b) (4)% by month 24 when stored at 25°C/60% RH. This is well within the specification of no more than 1.0% of the total preservatives and deemed acceptable by pharm/tox. Overall, the provided stability data supports the applicant's proposed 36 month product expiry.

The product is intended to be marketed in a multi-dose vial.

#### Product Quality Microbiology

Dr. Cole reviewed the product quality microbiology data submitted to support the application. Several requests for information were sent to the Applicant during the course of the review. With respect to the antimicrobial effectiveness data, Dr. Cole's final assessment of the submitted information was that:

This application does not provide data that demonstrate the preservative system for the multi-dose vials is effective at the minimum proposed preservative content. The data submitted in the 03 March 2014 amendment did not include USP<51> data on Escherichia coli. The applicant's justification is that "E. coli is appropriate when testing oral preparations but not injections." This rationale is unacceptable as the USP<51> compendial test does not allow for alterations to the panel of test organisms. As requested in the 19 December 2014 information request, the proposed minimum preservative content should be supported by complete test results from USP<51> Antimicrobial Effectiveness Testing.

Subsequently, the final risk assessment was that the Applicant had not submitted adequate information to support the position that the multi-dose product is adequately preserved, presenting a potential risk to the patient that was not acceptable.

### Facilities Review/Inspections

The facilities inspection did not find anything that would preclude approval.

### Outstanding or Unresolved Issues

Dr. Shen's review notes that the Applicant has provided adequate information to support the following:

- The drug substance and drug product specifications
- That the drug products excipients are of USP/NF grade
- The drug product container closure systems
- The proposed expiry time period of 36 months for the drug product.

However, he concurs with Dr. Cole's recommendation for a complete response for the application due to the insufficient information submitted regarding the preservative system.

I concur with Drs. Shen, Pinto, Cole and Langille that this deficiency precludes approval at this time.

## **4. Nonclinical Pharmacology/Toxicology**

No new nonclinical pharmacology/toxicology information was submitted in this application. Dr. Woo noted in his review that the excipients in the formulation can be found in equal or higher amounts in approved intravenous products and do not pose any new toxicologic concerns.

The review team did recommend that Applicant be requested to conduct a leachable assessment of their product and its container closure system over the course of stability. This could be performed post-approval because the rubber stopper used by the Applicant is used in several FDA-approved injectable drug products and the extractable data submitted in the application did not raise any significant concerns.

The following request was conveyed to the Applicant during the course of the review:

Conduct an adequate leachable safety assessment for the (b) (4) grey (b) (4) rubber stopper used in your container closure system. This assessment must include leachable data from long-term stability studies (taking into consideration the proposed shelf-life) to determine if the identified extractables leach into the drug product over time. Using this information, conduct a toxicological risk assessment justifying the safety of the leachables, taking into consideration the maximum daily dose of the identified materials for this drug product. For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed (b) (4) mcg/day total daily exposure, or it must be adequately qualified for safety. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceeds (b) (4) mcg/day.

### Outstanding or Unresolved Issues

I concur with the conclusions reached by Drs. Newton and Mellon that there are no pharmacology/toxicology issues that would preclude approval of this supplement. I also concur

with their request to have the Applicant conduct a leachable assessment as a post-marketing requirement.

## 5. Clinical Pharmacology/Biopharmaceutics

There were no clinical pharmacology data submitted in the application. The Applicant requested a waiver from doing an in vivo bioequivalence study. The data and justification were reviewed by the biopharmaceutics team, found to be acceptable, and the Applicant's request was granted.

### Outstanding or Unresolved Issues

I concur with the conclusions reached by Drs. Lee and Xu that there are no outstanding clinical pharmacology issues that preclude approval.

## 6. Clinical Microbiology

Dexmedetomidine is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

## 7. Clinical/Statistical – Efficacy

The Applicant did not submit any new data to address the efficacy of their product. The application relies on previous Agency findings of efficacy for the referenced dexmedetomidine product.

### Outstanding or Unresolved Issues

There are no unresolved efficacy issues that would preclude approval.

## 8. Safety

The Applicant did not submit any new data support the safety of their product. The application relies on previous Agency findings of safety for the referenced dexmedetomidine product. The Applicant did submit a review of the medical literature involving dexmedetomidine dating from December 2007 to November 2014, specifically evaluating for any new risks associated with dexmedetomidine.

Dr. Lockett's review details her findings after her review of the document, as well as her review of the literature citations found in the document. Her conclusions were that there were no new risks identified that would preclude approval of this application.

In addition, the review team consulted the Office of Surveillance and Epidemiology for an assessment of the FDA Adverse Event Reporting System (FAERS) database for all adverse events from 2008 to the present.

Their findings were that, and Dr. Lockett concurs, there are some adverse events reported in the literature that warrant inclusion in “Section 6.2, Postmarketing Experience” of the package insert.

Outstanding or Unresolved Issues

I concur with the review team that there are no outstanding or unresolved safety concerns that would preclude approval.

## 9. Advisory Committee Meeting

An advisory committee meeting was not convened for this NDA, as there was no specific efficacy or new safety concerns noted at the time of filing or during the course of the review of the NDA.

## 10. Pediatrics

This application did not need to address the requirements under PREA, because it did not propose any new active ingredients, new indications, new dosage forms, new dosage regimens, or new routes of administration.

## 11. Labeling

The review team reviewed the proposed package insert and made modifications as appropriate. The package insert will be sent to the Applicant during the next review cycle. The carton and container labels have been reviewed, comments sent to the Applicant, and final agreed-upon carton and container labels has been submitted.

As noted above, representatives from the Office of Surveillance and Epidemiology, the Study Endpoints and Labeling Development team, and the Office of Prescription Drug Promotion, were consulted and their recommendations were incorporated during the discussion of the label during this review cycle.

## 12. Decision/Action/Risk Benefit Assessment

Regulatory Action

Complete response.

Risk:Benefit Assessment

I concur with the review team that the Applicant has not submitted adequate information to support the position that the multi-dose product is adequately preserved. This presents a potential risk to the patient that is not acceptable, and precludes approval of this application at this time.

Recommendation for Postmarketing Risk Management Activities

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As discussed above, during the course of the review, the following post-marketing requirement was conveyed to the Applicant:

Conduct an adequate leachable safety assessment for the (b) (4) grey (b) (4) rubber stopper used in your container closure system. This assessment must include leachable data from long-term stability studies (taking into consideration the proposed shelf-life) to determine if the identified extractables leach into the drug product over time. Using this information, conduct a toxicological risk assessment justifying the safety of the leachables, taking into consideration the maximum daily dose of the identified materials for this drug product. For your toxicological risk assessment, any leachable that contains a structural alert for mutagenicity should not exceed (b) (4) mcg/day total daily exposure, or it must be adequately qualified for safety. A toxicological risk assessment should be provided for any non-genotoxic leachable that exceed (b) (4) mcg/day.

**Recommendation for other Postmarketing Study Commitments**

None.

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/s/  
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RIGOBERTO A ROCA  
03/12/2015

## CLINICAL REVIEW

Application Type 505(b)(2)  
Application Number 206628  
Priority or Standard Standard

Submit Date May 12, 2014  
Received Date May 12, 2014  
PDUFA Goal Date March 12, 2015  
Division / Office Division of Anesthesia, Analgesia and  
Addiction Products/ Office of Drug  
Evaluation II

Reviewer Name Amelia Lockett, MD  
Review Completion Date February 5, 2015

Established Name Precedex® (NDA 021038)  
(Proposed) Trade Name Dexmedetomidine Hydrochloride  
Injection  
Therapeutic Class Sedation Drugs  
Applicant HQ Specialty Pharma Corporation

Formulation Dexmedetomidine Hydrochloride  
Injection  
Dosing Regimen Loading: 0.5 to 1 mcg/kg over 10  
minutes; Maintenance: 0.2 to 1  
mcg/kg/hour, titrated to effect

Indication Sedation of non-intubated patients prior  
to and/or during surgical and other  
procedures  
Intended Population Adults

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

I recommend approval of Dexmedetomidine Hydrochloride Injection NDA 206628 pending completion of the following:

- Consult to the Office of Surveillance and Epidemiology (OSE) for review of FDA Adverse Event Reporting System (FAERS) data associated with dexmedetomidine reveals no concerning new risks associated with dexmedetomidine use.
- A biowaiver is granted by the Office of New Drug Quality Assessment Biopharmaceutics Team.
- Acceptable preservative data have been received from HQ Specialty Pharma.

### 1.2 Risk Benefit Assessment

HQ Specialty Pharma is relying on the previous findings of safety and efficacy of Precedex NDA 021038. Whether this approach is acceptable is dependent on a biowaiver being granted. According to the Clinical Pharmacology Review for this NDA, a biowaiver for Dexmedetomidine Hydrochloride Injection has been agreed to by the Office of New Drug Quality Assessment Biopharmaceutics Team. Dexmedetomidine Hydrochloride Injection has a formulation that is very similar to that of Precedex with the exception of the addition of two preservatives: methylparaben and propylparaben. The methylparaben and propylparaben in the proposed Dexmedetomidine Hydrochloride Injection formulation is likely without significant clinical implications. Further discussion of the addition of these excipients is in Section 2.1 Product Information.

With their NDA submission, HQ Specialty Pharma submitted a document titled “Identification of New Risks in Use of Precedex – Part 2” in which medical literature involving dexmedetomidine was reviewed from December 21, 2007 to present for the purpose of identifying new risks of dexmedetomidine that should be included in Dexmedetomidine Hydrochloride Injection’s package insert.

Of the literature articles captured by this search, eleven contained information HQ Specialty Pharma identified as not currently present in the dexmedetomidine package insert, some of which may be appropriate to add to “6.2 Postmarketing Experience” in the dexmedetomidine package insert. Adverse events found by HQ Specialty Pharma’s search not already present in the package insert include: [REDACTED] (b) (4)

[REDACTED] QTc prolongation, and hypernatremia. A consult was sent to Office of Surveillance and Epidemiology with the purpose of evaluating FDA Adverse Event Reporting System (FAERS) data on dexmedetomidine. The purpose of this consult was

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later focused to search FAERS data for an increased incidence of any of the unlabeled adverse events noted in the literature.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

The safety of dexmedetomidine was established with Precedex NDA 021038. The Reference Drug, Precedex, does not have a REMS and this NDA does not require a REMS either.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

I do not recommend pediatric studies or Postmarket Commitments for this NDA for the following reasons:

1. Pediatric studies are not required for NDA 206628 under the Pediatric Research Equity Act because HQ Specialty Pharma has not proposed new active ingredients, a new indication, new dosage forms, new dosing regimens, or new routes of administration.
2. Confirmatory trials are not required to confirm the clinical benefit of dexmedetomidine because the efficacy of dexmedetomidine was established with Precedex NDA 021038.

Leachables data will be a Postmarket Requirement from the Pharmacology/Toxicology Team. More detail of this requirement can be found in Section 4.3 Preclinical Pharmacology/Toxicology and in the Pharmacology/Toxicology Review.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

Dexmedetomidine is a selective  $\alpha_2$ -agonist. It is indicated (b) (4)

The following is a table comparing the formulation of Dexmedetomidine Hydrochloride Injection with Precedex, the Reference Drug (RD):

**Table 1 Comparison of Active and Inactive Ingredients in Dexmedetomidine Hydrochloride Injection and Precedex**

	Dexmedetomidine Hydrochloride Injection	Precedex
Active Ingredient	Dexmedetomidine HCl	Dexmedetomidine HCl
Inactive Ingredients	sodium chloride WFI methylparaben propylparaben	sodium chloride WFI
Strength	100 micrograms/mL in 4 mL vial 100 micrograms/mL in 10 mL vial	100 micrograms/mL in 2 mL vial

Table derived from NDA 206628 submission module 1.12.12; submitted May 12, 2014

Methylparaben and propylparaben are listed in the FDA Inactive Ingredients Database at maximum levels higher than in the proposed Dexmedetomidine Hydrochloride Injection formulation. The amount of methylparaben and propylparaben in the proposed Dexmedetomidine Hydrochloride Injection formulation appears safe and is likely without significant clinical implications.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Precedex is approved for the following indications in adults:

- 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.

This NDA is only for the procedural sedation indication. There are several products identified by this reviewer that are approved for a similar proposed population and indication. These drugs are listed in Table 2 below.

**Table 2 Drugs Currently Approved for Procedural Sedation Indications Similar to Precedex**

Drug	Indication
Ketamine	Anesthesia for procedures
Midazolam	Sedation for select procedures
Propofol	Monitored Anesthesia Care

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### 2.3 Availability of Proposed Active Ingredient in the United States

Dexmedetomidine was approved in the United States on December 17, 1999.

### 2.4 Important Safety Issues With Consideration to Related Drugs

The labeling for dexmedetomidine contains the following WARNINGS AND PRECAUTIONS:

- **Hypotension, bradycardia and sinus arrest:**

[Redacted text block]

- **Transient hypertension:**

[Redacted text block]

- **Arousability:**

[Redacted text block]

- **Withdrawal:** With administration up to seven days,

[Redacted text block]

Tachycardia and hypertension requiring

- **Tolerance and tachyphylaxis:**

[Redacted text block]

- **Hepatic impairment:** Dose-reduction

[Redacted text block]

- [Redacted text block]

### 2.5 Summary of Presubmission Regulatory Activity Related to Submission

#### Prior to submission of NDA 206628

On June 28, 2013, FDA received a Pre-Investigational New Drug submission from HQ Specialty Pharma. Meeting Preliminary Comments were sent to HQ Specialty Pharma on September 23, 2013. Subsequently, the meeting with FDA and HQ Specialty Pharma was canceled by the Sponsor because the preliminary responses were satisfactory.

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In the Preliminary Comments of this meeting, FDA agreed that the 505(b)(2) pathway is appropriate for the Dexmedetomidine Hydrochloride Injection formulation proposed by HQ Specialty Pharma. FDA agreed that the addition of parabens in the Dexmedetomidine Hydrochloride Injection formulation will not necessitate additional clinical studies if adequate support for the safety of the excipients is provided. FDA did not agree that additional nonclinical for the (b)(4) injection formulation will not be required.

## 2.6 Other Relevant Background Information

Certain regulatory and legal issues pertaining to the Reference Drug, Precedex, also impact this Dexmedetomidine Hydrochloride Injection NDA. Precedex is currently approved for both intensive care unit (ICU) and procedural sedation indications. A dexmedetomidine 505(b)(2) with the ICU indication “carved-out” of the labeling is currently allowable.

On May 12, 2014, HQ Specialty Pharma submitted a 505(b)(2) NDA for Dexmedetomidine Hydrochloride Injection for the procedural sedation indication. (b)(4)

On February 2, 2015, the Applicant (b)(4) to the procedural sedation indication originally applied for in the NDA: “sedation of non-intubated patients prior to and during surgical and other procedures.”

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

Overall, the submission is appropriately organized. The initial submission was incomplete in that it required an adequate summary of worldwide information on dexmedetomidine. This was submitted upon request. The first two summaries of worldwide information submitted by the applicant were inadequate, but the third submitted summary of worldwide information pertaining to dexmedetomidine was adequate and its contents are included in this review.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

The findings discussed in Section 4 are based on preliminary discussions of safety and efficacy.

#### 4.1 Chemistry Manufacturing and Controls

From a CMC perspective, the drug product manufacturing processes appear appropriate and drug product batch analysis results reveal no safety concerns. The stability data that were provided indicate acceptable product stability and support a 36 month product expiry, pending satisfactory overall Establishment Evaluation System (EES).

HQ Specialty Pharma conducted extractable testing, but did not conduct leachable testing for the drug product container closures. HQ Specialty Pharma submitted extractable study results and used that to justify the safety of the product from potential exposure to leachables. They indicated the vial and stopper (b) (4) grey) have been used in multiple approved products. Therefore, there is no significant risk of leachables exposure presented by the vial and stopper. However, the safety of leachables will ultimately be determined by the Pharmacology/Toxicology review team. For further detail on the Chemistry Manufacturing and Controls aspects of this NDA, please see the CMC review.

At present, HQ Specialty Pharma yet has not provided adequate information about the antimicrobial effectiveness of the dexmedetomidine formulation. Antimicrobial effectiveness data should support the minimum preservative content in the specification. The data provided by HQ Specialty Pharma do not support the proposed minimum specification for preservative content. These data have been requested but have not been received by FDA as of January 30, 2015.

Changes proposed to the labeling by the CMC reviewer<sup>1</sup>:

#### 2.4 Preparation of (b) (4)

Dexmedetomidine Hydrochloride Injection must be diluted (b) (4)

#### 11 DESCRIPTION

Dexmedetomidine hydrochloride injection is a sterile, nonpyrogenic solution suitable for intravenous infusion following dilution. Dexmedetomidine hydrochloride is a sedative. Structurally it is the S-enantiomer of medetomidine...

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<sup>1</sup> Additions to the labeling are underlined and deletions are represented by strikethrough

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## 4.2 Clinical Microbiology

Dexmedetomidine Hydrochloride Injection is not a therapeutic antimicrobial. Therefore, clinical microbiology data were not required or submitted in this NDA.

## 4.3 Preclinical Pharmacology/Toxicology

Single dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and local tolerance studies were not required for this NDA and were not conducted.

In regard to the addition of methylparaben and propylparaben, the amount of these excipients in the dexmedetomidine formulation appears to be safe. There are approved products containing methylparaben and propylparaben that are given by the same route of administration as this dexmedetomidine formulation.

In regard to leachables, the Pharmacology/Toxicology reviewer has no significant concerns with this dexmedetomidine formulation. However, leachables data will be required through a Postmarket Requirement.

There will be no changes to the labeling from a Pharmacology/Toxicology standpoint. For further detail on the Pharmacology/Toxicology aspects of this NDA, please see the Pharmacology/Toxicology review.

The following information is derived from the dexmedetomidine package insert:

Animal carcinogenicity studies have not been performed with dexmedetomidine. (b) (4)

[Redacted]

[Redacted] (b) (4)

(b) (4)

## 4.4 Clinical Pharmacology

No new clinical pharmacology studies were conducted for the purpose of this NDA because there is no need for additional clinical pharmacology data for this application. According to the Clinical Pharmacology Review for this NDA, a biowaiver for Dexmedetomidine Hydrochloride Injection has been agreed to by the Office of New Drug Quality Assessment Biopharmaceutics team.

### 4.4.1 Mechanism of Action

Dexmedetomidine is an  $\alpha_2$ -adrenergic agonist.

### 4.4.2 Pharmacodynamics (derived from dexmedetomidine package insert):

(b) (4)

### 4.4.3 Pharmacokinetics (derived from dexmedetomidine package insert)

(b) (4)

## 5 Sources of Clinical Data

This is a 505(b)(2) NDA reliant upon the established safety and efficacy of Precedex NDA 021038.

### 5.1 Tables of Studies/Clinical Trials

No clinical trials have been conducted in support of this application.

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## 5.2 Review Strategy

Numerous sections were deleted from the Clinical Review Template because they were not relevant to the review of this NDA. This is a list of the deleted sections:

Table of Figures

Ethics and Good Clinical Practices Sub-Sections:

- 3.2 Compliance with Good Clinical Practices
- 3.3 Financial Disclosures

Sources of Clinical Data Sub-Sections:

- 5.3 Discussion of Individual Studies/Clinical Trials

The entire Review of Efficacy Sub-Section has been deleted except for the Efficacy Summary and 6.1 Indications.

The entire Review of Safety Sub-Section has been deleted except for the Safety Summary and 7.7 Additional Submissions / Safety Issues.

Appendices Sub-Sections:

- 9.3 Advisory Committee Meeting

## 6 Review of Efficacy

### **Efficacy Summary**

This 505(b)(2) NDA relies on the findings of efficacy in the Precedex Injection Summary Basis of Approval for NDA 021038.

### 6.1 Indications

- sedation of non-intubated patients prior to and/or during surgical and other procedures

## 7 Review of Safety

### **Safety Summary**

This 505(b)(2) NDA relies on the findings of safety in the Precedex Injection Summary Basis of Approval for NDA 021038.

## 7.7 Additional Submissions / Safety Issues

With their NDA submission, HQ Specialty Pharma submitted a document titled “Identification of New Risks in Use of Precedex – Part 2” in which medical literature involving dexmedetomidine was reviewed from December 21, 2007 to November 25, 2014 for the purpose of identifying new risks of dexmedetomidine that should be included in Dexmedetomidine Hydrochloride Injection’s package insert.

Of the literature captured by this search, eleven documents contained information HQ Specialty Pharma identified as not currently present in the dexmedetomidine package insert. Of these eleven articles, seven are case reports, three are clinical trials, and one is a letter published in a medical journal. These articles are described below:

### Case reports:

#### 1. (Marodkar et al., 2014)

This is a case report in which a twenty-five-year-old male was given a Bier block for the surgical removal of a left radial plate. The contents of the Bier block solution were 7.5 ml 2% lidocaine diluted with saline to total volume 40 ml and 25 mcg dexmedetomidine. Ninety seconds after injection of the solution for Bier block, a “wheal and flare” rash was noticed in the limb in which the Bier block was placed. Sensitivity testing for lidocaine in this patient was previously non-reactive.

#### 2. (Ludwig et al., 2009)

This is case report in which a subject received dexmedetomidine and then developed a wheal and flare rash. This case involves a twenty-two-year-old who required sedation for mechanical ventilation. Four hours after beginning a dexmedetomidine infusion, he developed a wheal and flare rash on 60% of his body surface. The infusion was discontinued. The rash receded and was completely resolved within 48 hours of discontinuing dexmedetomidine. This article, combined with the previous citation (Marodkar et al., 2014), reveals a possible new risk associated with dexmedetomidine use. Although causal relationship to dexmedetomidine has not been proven, the two case reports provide sufficient evidence to include [REDACTED] (b) (4) in the “6.2 Postmarketing Experience” section.

To further evaluate this adverse event, the Office of Surveillance and Epidemiology (OSE) is reviewing FAERS data for an association of [REDACTED] (b) (4) with dexmedetomidine.

#### 3. (Kubota et al., 2013)

This is a case report of a neonate born at forty-one weeks gestation. Shortly after birth he was intubated for “severe transient tachypnea of the newborn.” He was given a dexmedetomidine infusion for the purpose of making artificial ventilation more tolerable. After receiving a dexmedetomidine infusion for approximately 80 hours, the patient

began to have “abnormal pedaling-like movements every few hours.” The dexmedetomidine infusion was stopped after 84 hours and the patient was extubated on postnatal day 6. EEG was performed after postnatal day 6 until postnatal day 8, revealing epileptic seizures. The epileptic seizures and abnormal pedaling (non-epileptic) stopped spontaneously twelve hours after stopping the dexmedetomidine infusion. This article reveals a possible new risk associated with dexmedetomidine use.

To further evaluate this adverse event, the Office of Surveillance and Epidemiology (OSE) is reviewing FAERS data for an association of epileptic seizures with dexmedetomidine. I recommend continued monitoring for the adverse event of epileptic seizures associated with dexmedetomidine use and revisiting this issue in one year.

4. (Sichrovsky et al., 2008)

This is a case report of a fifty-year-old man having ablation of paroxysmal atrial fibrillation in the electrophysiology laboratory. He was difficult to sedate with fentanyl and midazolam and a dexmedetomidine infusion was begun. One hour and forty-five minutes after beginning the infusion, the patient developed severe hypotension and bradycardia. This was followed by, among other things, asystole, chest compressions, pericardiocentesis for a pericardial effusion, more hypotension, severe global left ventricular hypokinesia, ventricular fibrillation, advanced cardiac life support, surgical exploration, open cardiac massage, connection to extracorporeal circulation, and slow, partial improvement of left ventricular function. Unfortunately, the patient had suffered severe anoxic injury. This paper does not necessarily reveal any new risks of dexmedetomidine. Hypotension, bradycardia, and sinus arrest are in the “WARNINGS AND PRECAUTIONS” section of the dexmedetomidine package insert. However, a search of the FAERS data is being conducted to determine if a trend of hypotension and bradycardia related to dexmedetomidine that eventually precipitates severe anoxic brain injury is emerging.

5. (Burns and Greene, 2014)

This is a case report in which a twenty-two-month-old with pneumonia required intubation and was given a dexmedetomidine infusion. Four hours after starting dexmedetomidine, the patient developed bradycardia and later, giant T waves, for which an ECG was performed, revealing QTc prolongation of 700 milliseconds. The dexmedetomidine infusion was stopped. Five hours later, the QTc had decreased to 473 milliseconds. The authors hypothesize that this patient may have congenital long QT syndrome that was revealed by dexmedetomidine. QTc prolongation may be a newly identified risk associated with dexmedetomidine.

6. (Shields, 2008)

This is a case report in which a forty-one-year-old woman underwent a short-limb Roux-en-Y gastroenterostomy. General anesthesia maintenance was with desflurane and a dexmedetomidine infusion. As the procedure finished, the patient received 0.625 mg droperidol, 0.6 mg glycopyrrolate, and 4 mg neostigmine. Five minutes after

glycopyrrolate and neostigmine were given, the patient became bradycardic and hypotensive. Atropine was given and heart rate and blood pressure improved. A post-operative ECG revealed QTc interval of .441 seconds compared with ECG four hours after dexmedetomidine was discontinued in which QTc was 0.414 seconds. This paper, combined with the previous citation (Burns and Greene, 2014), reveals a possible new risk associated with dexmedetomidine use.

To further evaluate this adverse event, the Office of Surveillance and Epidemiology (OSE) is reviewing FAERS data for an association of prolonged QTc with dexmedetomidine. I recommend continued monitoring for the adverse event of prolonged QTc associated with dexmedetomidine use and revisiting this issue in one year.

7. (Ji and Liu, 2013)

This is a case report of a seventy-one-year-old woman having surgery of the lumbar spine. General anesthesia maintenance was with sevoflurane, remifentanil infusion, and dexmedetomidine infusion. The procedure was seven hours long. During the surgery, she developed hypernatremia with a decrease in urine gravity, and high plasma osmolality that was consistent with polyuric syndrome. The case report authors hypothesize that this may have been caused by the dexmedetomidine infusion. This paper reveals a possible new risk associated with dexmedetomidine use.

To further evaluate this adverse event, the Office of Surveillance and Epidemiology (OSE) is reviewing FAERS data for an association of hypernatremia with dexmedetomidine. I recommend continued monitoring for the adverse event of hypernatremia associated with dexmedetomidine use and revisiting this issue in one year.

Clinical Trials:

1. (Jakob et al., 2012)

This article describes two phase 3 multicenter trials. One of these multicenter trials compared propofol with dexmedetomidine in adult intensive care unit patients on mechanical ventilation. In this trial, 214 patients received propofol and 223 patients received dexmedetomidine. As a result of this trial, the authors conclude that critical illness polyneuropathy was less common in patients who received dexmedetomidine versus propofol during prolonged mechanical ventilation. This article does not reveal new risks of dexmedetomidine and no modification to the labeling is suggested as a result of these findings.

2. (Hayama et al., 2012)

This is a trial of forty-eight volunteers who received dexmedetomidine or placebo and were given neuroimaging while viewing pictures. This study concluded that “dexmedetomidine impaired long-term picture memory, but did not disproportionately

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block memory for emotionally arousing items.” This article does not reveal any new risks of dexmedetomidine.

3. (Pryor et al., 2010)

In this trial, sixty-one volunteers were given propofol, thiopental, midazolam, dexmedetomidine, or placebo and tests of memory. The authors conclude that dexmedetomidine will impair memory, but memories that are formed will be normal. This article does not reveal any new risks of dexmedetomidine.

Letter:

(Weber et al., 2008)

This is a letter in the journal Pediatric Anesthesia. In it, the authors describe a two-year-old patient who received a dexmedetomidine infusion for what is described as approximately eight days. After discontinuation of the dexmedetomidine infusion, the patient developed tachycardia, hypertension, and emesis. Dexmedetomidine withdrawal was suspected and the infusion was restarted and then titrated off.

Of note, “withdrawal” is in the WARNINGS AND PRECAUTIONS section of the dexmedetomidine package insert. The symptoms include (b) (4)  
This paper does not reveal any new risks of dexmedetomidine.

Conclusion from Additional Safety Information:

Overall, the document submitted by HQ Specialty Pharma, “Identification of New Risks in Use of Precedex – Part 2,” does not reveal any definitive new risks associated with use of dexmedetomidine. However, some case reports suggest that additions to the “6.2 Postmarketing Experience” section are appropriate. Section “6.2 Postmarketing Experience” in the dexmedetomidine package insert states that “ (b) (4)

With this disclaimer, adverse events discussed in case reports can be added to the package insert despite lack of a causal relationship between dexmedetomidine and the adverse event. With this rationale, I recommend addition of the (b) (4) to section “6.2 Postmarketing Experience.”

Pending the recommendations of the Office of Surveillance and Epidemiology (OSE), I recommend continued monitoring of the adverse events of epileptic seizure, prolonged QTc, and hyponatremia. The occurrence of these adverse events in association with dexmedetomidine will be revisited in one year

## 8 Postmarket Experience

A consult was sent to Office of Surveillance and Epidemiology (OSE) on October 2, 2014 requesting a review of FAERS for all adverse events with dexmedetomidine from 2008 to present. At the request of OSE, more specific questions were formulated based on the findings of the literature search conducted by HQ Specialty Pharma for unlabeled adverse events:

1. Have there been “wheal and flare” type rashes associated with dexmedetomidine?
2. Have there been reports of epileptic seizures related to dexmedetomidine?
3. Have there been reports of severe hypotension, bradycardia, or myocardial dysfunction related to dexmedetomidine that may have precipitated anoxic brain injury and death?
4. Have there been reports of dexmedetomidine causing Q-Tc prolongation?
5. Have there been any reports of dexmedetomidine causing hypernatremia?

## 9 Appendices

### 9.1 Literature Review/References

Burns,K.M., and Greene,E.A. (2014). Long QT syndrome unmasked by dexmedetomidine: a case report. *Congenit. Heart Dis* 9, E11-E15.

Hayama,H.R., Drumheller,K.M., Mastro Monaco,M., Reist,C., Cahill,L.F., and Alkire,M.T. (2012). Event-related functional magnetic resonance imaging of a low dose of dexmedetomidine that impairs long-term memory. *Anesthesiology* 117, 981-995.

Jakob,S.M., Ruokonen,E., Grounds,R.M., Sarapohja,T., Garratt,C., Pocock,S.J., Bratty,J.R., and Takala,J. (2012). Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA* 307, 1151-1160.

Ji,F., and Liu,H. (2013). Intraoperative hypernatremia and polyuric syndrome induced by dexmedetomidine. *J Anesth.* 27, 599-603.

Kubota,T., Fukasawa,T., Kitamura,E., Magota,M., Kato,Y., Natsume,J., and Okumura,A. (2013). Epileptic seizures induced by dexmedetomidine in a neonate. *Brain Dev* 35, 360-362.

Ludwig,K., Sorrell,M., and Liu,P. (2009). Severe rash associated with dexmedetomidine use during mechanical ventilation. *Pharmacotherapy* 29, 479-481.

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Marodkar,K., Bhargava,S., Chopde,N., and Bhure,A. (2014). Dermatological allergic reaction caused by dexmedetomidine in a patient administered intravenous regional anesthesia with dexmedetomidine-lignocaine combination. *Egyptian Journal of Anaesthesia* 30, 319-321.

Pryor,K.O., Reinsel,R.A., Mehta,M., Li,Y., Wixted,J.T., and Veselis,R.A. (2010). Visual P2-N2 complex and arousal at the time of encoding predict the time domain characteristics of amnesia for multiple intravenous anesthetic drugs in humans. *Anesthesiology* 113, 313-326.

Shields,J.A. (2008). Heart block and prolonged Q-Tc interval following muscle relaxant reversal: a case report. *AANA. J* 76, 41-45.

Sichrovsky,T.C., Mittal,S., and Steinberg,J.S. (2008). Dexmedetomidine sedation leading to refractory cardiogenic shock. *Anesth. Analg.* 106, 1784-1786.

Weber,M.D., Thammasitboon,S., and Rosen,D.A. (2008). Acute discontinuation syndrome from dexmedetomidine after protracted use in a pediatric patient. *Paediatr. Anaesth* 18, 87-88.

## 9.2 Labeling Recommendations

I recommend the addition of [REDACTED] (b) (4) to section “6.2 Postmarketing Experience.”

A label and labeling review has been performed by the Division of Medication Error Prevention and Analysis (DMEPA). This review, dated January 12, 2015, proposes general revisions to Section 3 and Section 16 in the package insert proposed by HQ Specialty Pharma. DMEPA also proposes: (verbatim from DMEPA review 01/12/2015)

- Addition of background colors to further differentiate between strengths on the container labels and carton labeling
- The inclusion of a [REDACTED] (b) (4) statement on the container label
- Increasing the prominence of the “[REDACTED] (b) (4)” statement on the container label

Additional details of the changes to the labeling proposed by DMEPA can be found in the DMEPA Label and Labeling Review dated January 12, 2015.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY A LUCKETT  
02/05/2015

RIGOBERTO A ROCA  
02/05/2015





## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	been exposed at the dose (or dose range) believed to be efficacious?				Agency's prior finding of safety and efficacy for Precedex.
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	This application is referencing the Agency's prior finding of safety and efficacy for Precedex.
26.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?			X	This application is referencing the Agency's prior finding of safety and efficacy for Precedex.
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	This application is referencing the Agency's prior finding of safety and efficacy for Precedex.
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	This application is referencing the Agency's prior finding of safety and efficacy for Precedex.
<b>OTHER STUDIES</b>					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Applicant requests a waiver on the basis that: "The product would be ineffective or unsafe in one or more of the pediatric age group(s) for which a waiver is being requested."  Additionally, the applicant feels "the requirement for pediatric assessment is met under section 505B(a)(4)(B)(ii) of the Act"
<b>ABUSE LIABILITY</b>					

<sup>2</sup> The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	This application is referencing the Agency's prior finding of safety and efficacy for Precedex.
<b>FOREIGN STUDIES</b>					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	This application is referencing the Agency's prior finding of safety and efficacy for Precedex.
<b>DATASETS</b>					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	This application is referencing the Agency's prior finding of safety and efficacy for Precedex.
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	This application is referencing the Agency's prior finding of safety and efficacy for Precedex.
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	This application is referencing the Agency's prior finding of safety and efficacy for Precedex.
37.	Are all datasets to support the critical safety analyses available and complete?			X	This application is referencing the Agency's prior finding of safety and efficacy for Precedex.
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	This application is referencing the Agency's prior finding of safety and efficacy for Precedex.
<b>CASE REPORT FORMS</b>					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	This application is referencing the Agency's prior finding of safety and efficacy for Precedex.
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	This application is referencing the Agency's prior finding of safety and efficacy for Precedex.
<b>FINANCIAL DISCLOSURE</b>					
41.	Has the applicant submitted the required Financial Disclosure information?			X	This application is referencing the Agency's prior finding of safety and efficacy for Precedex.

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## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
<b>GOOD CLINICAL PRACTICE</b>					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			<b>X</b>	This application is referencing the Agency's prior finding of safety and efficacy for Precedex.

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?       YES**

Potential Review Issues

1. You provided a preliminary summary of worldwide literature of safety and efficacy for Precedex in humans from 2008 to present. However, you did not provide adequate detail to determine if labeling changes are needed. This will be addressed in an information request.

2. You sent us a pediatric plan consisting of waiver requests for (b) (4) the procedural (b) (4) indications. However, you have not provided sufficient evidence that “the product would be ineffective or unsafe in one or more of the pediatric age group(s) for which a waiver is being requested.” Therefore, we disagree with your request for a waiver.

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Reviewing Medical Officer Date

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Clinical Team Leader Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY A LUCKETT  
07/10/2014

CHRISTOPHER D BREDER  
07/10/2014