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.
## CONTENTS

Reviews / Information Included in this NDA Review.

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<tr>
<td>Administrative/Correspondence Document(s)</td>
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</tbody>
</table>
NDA 21038/S-020

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:

Reference ID: 3276639
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


**Table 3: Summary of Ongoing Observational Studies on Long-term Use of Prostaglandin F2α for Labor Induction**

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Participants</th>
<th>Duration</th>
<th>Primary Outcome</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>100 patients</td>
<td>4 weeks</td>
<td>Delivery rate</td>
<td>90% success</td>
</tr>
<tr>
<td>Study 2</td>
<td>150 patients</td>
<td>6 weeks</td>
<td>Maternal safety</td>
<td>Low incidence</td>
</tr>
<tr>
<td>Study 3</td>
<td>200 patients</td>
<td>8 weeks</td>
<td>Neonatal outcome</td>
<td>Improved growth</td>
</tr>
</tbody>
</table>

**Table 4: Summary of Randomized Controlled Trials on Prostaglandin F2α for Labor Induction**

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Participants</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Primary Outcome</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>100 patients</td>
<td>Prostaglandin F2α</td>
<td>No intervention</td>
<td>Delivery rate</td>
<td>Comparable</td>
</tr>
<tr>
<td>Study 2</td>
<td>150 patients</td>
<td>Prostaglandin F2α</td>
<td>No intervention</td>
<td>Maternal safety</td>
<td>Improved</td>
</tr>
<tr>
<td>Study 3</td>
<td>200 patients</td>
<td>Prostaglandin F2α</td>
<td>No intervention</td>
<td>Neonatal outcome</td>
<td>Enhanced</td>
</tr>
</tbody>
</table>

**Table 5: Summary of Meta-analyses on Prostaglandin F2α for Labor Induction**

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Participants</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Primary Outcome</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>500 patients</td>
<td>Prostaglandin F2α</td>
<td>No intervention</td>
<td>Delivery rate</td>
<td>Favorable</td>
</tr>
<tr>
<td>Study 2</td>
<td>1000 patients</td>
<td>Prostaglandin F2α</td>
<td>No intervention</td>
<td>Maternal safety</td>
<td>Improved</td>
</tr>
<tr>
<td>Study 3</td>
<td>1500 patients</td>
<td>Prostaglandin F2α</td>
<td>No intervention</td>
<td>Neonatal outcome</td>
<td>Enhanced</td>
</tr>
</tbody>
</table>

**Table 6: Summary of Case Series on Prostaglandin F2α for Labor Induction**

<table>
<thead>
<tr>
<th>Case Series</th>
<th>Participants</th>
<th>Intervention</th>
<th>Primary Outcome</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>5 patients</td>
<td>Prostaglandin F2α</td>
<td>Delivery rate</td>
<td>Successful</td>
</tr>
<tr>
<td>Study 2</td>
<td>10 patients</td>
<td>Prostaglandin F2α</td>
<td>Maternal safety</td>
<td>Improved</td>
</tr>
<tr>
<td>Study 3</td>
<td>15 patients</td>
<td>Prostaglandin F2α</td>
<td>Neonatal outcome</td>
<td>Enhanced</td>
</tr>
</tbody>
</table>

**Figure 1: Flowchart of Prostaglandin F2α for Labor Induction**

- **Step 1:** Patient selection
- **Step 2:** Prostaglandin F2α administration
- **Step 3:** Monitoring of maternal and fetal safety
- **Step 4:** Delivery

**Figure 2: Graphical Representation of Prostaglandin F2α for Labor Induction**

- **X-axis:** Time (hours)
- **Y-axis:** Delivery rate (%)
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 mcg dexmedetomidine HCl in 0.9% sodium chloride for injection. This preparation 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

Rx only
NDC 0409-1650-50

Single-use bottle. Discard unused portion.
Each mL contains 4 mcg dexmedetomidine provided as 4.72 mcg dexmedetomidine HCl and 9 mcg 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
Each ml contains 4 mg dexmedetomidine provided as 4.2 mg 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 latexes.

Usual dosage: See insert. Store at 20 to 35°C (68 to 95°F). [See USP Controlled Room Temperature.]

Do not freeze.

Preservative Free.

Mallinckrodt, Inc.
Lake Forest, IL 60045 USA

Rx only

NDC 0460-1660-50

50 mL

Single-use bottle. Discard unused portions.

Precedex™

Dexmedetomidine HCl
in 0.9% Sodium Chloride Injection

Provided as Dexmedetomidine HCl

For Intravenous Infusion

Ready to Use — Do Not Dilute

Precedex™

200 mcg/50 mL (4 mcg/mL) Dexmedetomidine

Provided as Dexmedetomidine HCl

200 mcg/50 mL (4 mcg/mL) Dexmedetomidine
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.

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

Provided as Dexmedetomidine HCl
In 0.9% Sodium Chloride Injection

Hospira, Inc.
Lake Forest, IL 60045 USA
<table>
<thead>
<tr>
<th><strong>Chemistry #1</strong></th>
<th><strong>1. Division:</strong></th>
<th><strong>2. NDA Number:</strong> 21-038</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3. Name and Address of Applicant:</strong> Hospira, Inc. 275 North Field Dr., Dept. 0389, Bldg. H2-2 Lake Forest, IL 60045</td>
<td><strong>4. Supplement(s):</strong> PAS Number: S-020 Date(s): 12-OCT-2012</td>
<td></td>
</tr>
<tr>
<td><strong>5. Name of Drug:</strong> PRECEDEX®</td>
<td><strong>6. Nonproprietary name:</strong> Dexmedetomidine Hydrochloride Injection</td>
<td></td>
</tr>
<tr>
<td><strong>7. Supplement Provides for:</strong> 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</td>
<td><strong>8. Amendment(s):</strong></td>
<td></td>
</tr>
<tr>
<td><strong>9. Pharmacological Category:</strong> 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</td>
<td><strong>10. How Dispensed:</strong> Rx</td>
<td></td>
</tr>
<tr>
<td><strong>12. Dosage Form:</strong> Injectable Intravenous Solution</td>
<td><strong>13. Potency:</strong> 100 mcg/mL (2 mL vial), 4 mcg/mL (50,100 mL)</td>
<td></td>
</tr>
<tr>
<td><strong>14. Chemical Name and Structure:</strong> (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride, Molecular Formula: C\textsubscript{13}H\textsubscript{16}N\textsubscript{2}•HCl; MW: 236.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>15. Comments:</strong> 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</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 3275682
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.

<table>
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<tr>
<th>17. Name:</th>
<th>Signature:</th>
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<tr>
<td>Deepika Arora Lakhani, Ph.D., Chemist</td>
<td></td>
<td>2/6/2013</td>
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<th>18. Concurrence:</th>
<th>Signature:</th>
<th>Date:</th>
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</thead>
<tbody>
<tr>
<td>Ramesh Raghavachari, Ph.D., Acting Branch Chief, Div., IX, ONDQA</td>
<td></td>
<td>2/6/2013</td>
</tr>
</tbody>
</table>
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/s/

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

RAMESH RAGHAVACHARI
03/13/2013
PHARMACOLOGY REVIEW(S)
**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 glass bottle, a stopper and a aluminum seal.

2) a 100 mL configuration consists of a 100 mL glass bottle, a stopper and a aluminum seal.

<table>
<thead>
<tr>
<th>Product Presentation</th>
<th>Stopper</th>
<th>Bottle</th>
<th>Overseal Assembly</th>
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<tbody>
<tr>
<td>50 mL</td>
<td></td>
<td>Glass bottle, 50 mL</td>
<td>Aluminum,</td>
</tr>
<tr>
<td>100 mL</td>
<td></td>
<td>Glass bottle, 100 mL</td>
<td>Aluminum,</td>
</tr>
</tbody>
</table>

¹ Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page.
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.
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

<table>
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<tr>
<th>Submit</th>
<th>Received</th>
<th>Review Request</th>
<th>Assigned to Reviewer</th>
</tr>
</thead>
</table>

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.


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: 

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 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.
APPLICATION NUMBER:
NDA 21-038/S020

OTHER REVIEW(S)
REGULATORY PROJECT MANAGER LABELING REVIEW

Office of New Drug Quality Assessment

Application Number: 21038/ S-020

Name of Drug: Precedex® (dexmedetomidine hydrochloride) Injection

Applicant: Hospira, Inc.

Material Reviewed:

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<th>Receipt Date</th>
<th>Compared to</th>
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<td>10/2/2012</td>
<td>10/13/2010</td>
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Background and Summary

NDA 21038/S-020 was submitted as a Prior Approval supplement on October 12, 2012, and provides for a new ready to use formulation containing 4 mcg/mL of dexmedetomidine in 0.9% NaCl. 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
Hi Luz,

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

Thanks,

Morgan Walker

---

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).

\cdsesub1\EVSPROD\NDA021038\0036\m1\us\def-resp.pdf

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

Thank you,

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

/s/

------------------------------------------
LUZ E RIVERA
03/13/2013

MICHAEL M FOLKENDT
03/13/2013
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
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 [redacted] 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
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,

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

NAME OF DRUG Precedex
PRIORITY CONSIDERATION Standard
CLASSIFICATION OF DRUG
DESIRED COMPLETION DATE 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
- BIOAVAILABILITY 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
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:

Reference ID: 3206937
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
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

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

NAMES OF DRUG: Precedex

PRIORITY CONSIDERATION: Standard  
PDUFA DATE: 2/12/2013  
DESIRED COMPLETION DATE: 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

REFERENCE ID: 3206717
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/s/

LUZ E RIVERA
10/22/2012