

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206628Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 206628	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: dexmedetomidine hydrochloride Dosage Form: Injection Strengths: 400 mcg/4mL and 1000mcg/10mL		
Applicant: HQ Specialty Pharma Corporation		
Date of Receipt: April 21, 2015		
PDUFA Goal Date: October 21, 2015		Action Goal Date (if different):
<ul style="list-style-type: none">Proposed Indication(s): sedation of non-intubated patients prior to and/or during surgical and other procedures		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 021038	Pharmacology/Toxicology data, labeling
Published literature	Safety justification for drug product degradant

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

A waiver of in vivo BA/BE studies was requested for the proposed product based on the following relationships with the referenced literature products: (1) Products are administered intravenously; (2) Products include the same active moiety; (3) Products have the same intended use. The biowaiver was granted.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO,” proceed to question #5.

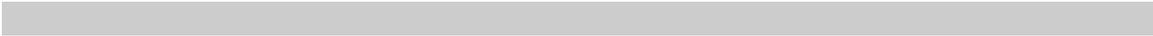
If “YES”, list the listed drug(s) identified by name and answer question #4(c).

Precedex

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

N/A NO YES

NDA 021038 Precedex (dexmedetomidine hydrochloride)



APPEARS THIS WAY ON ORIGINAL

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Precedex	021038	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process: NDA 000654

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The change from the listed drug is in the formulation, specifically inactive ingredients methylparaben and propylparaben.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including*

potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "**NO**" to (a) proceed to question #11.
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 6716867, exp 3/31/19, U-1472
6716867*PED, exp 10/1/19
8242158, exp 1/4/32
8242158*PED, exp 7/4/32
8338470, exp 1/4/32
8338470*PED, exp 7/4/32
8455527, exp 1/4/32
8455527*PED, exp 7/4/32
8648106, exp 1/4/32
8648106*PED, exp 7/4/32

No patents listed proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If “**NO**”, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

- 15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 8242158, 8338470, 8455527, 8648106

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): 8/5/14, 8/19/14, 2/5/15, 2/6/15

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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

/s/

ALLISON MEYER
10/21/2015

PARINDA JANI
10/21/2015

PMR/PMC Development Template

NDA 206628

PMR/PMC Description: 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 testing at least three batches (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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	10/31/2015 (complete)
	Study/Trial Completion:	1/31/2016
	Final Report Submission:	4/30 2016

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Potential leachables from the container closure system have not been quantified to date and prior clinical experience does not fully address their safety. There is a concern that due to the nature of the materials in the container closure, some of the impurities may result in the potential for adverse effects. Given the clinical experience with this (b) (4) rubber stopper, and based on preliminary extractables data suggesting no significant concerns, this study was deemed acceptable as a post-marketing requirement.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Although the rubber stopper that is part of the container closure system has been used in several FDA-approved drug products, the leachable profile of the dexmedetomidine HCl injection product has not been fully characterized. This study will be completed to assess the safety of the container closure based on current practices.

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)?
If the study or trial will be performed in a subpopulation, list here.

The study is a leachable study to more fully characterize the container closure system.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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

/s/

ALLISON MEYER
10/21/2015

JUDITH A RACOOSIN
10/21/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: August 21, 2015

To: Allison Meyer, Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Sharon Hertz, MD, Director - DAAAP

From: Kounq Lee, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Jessica Fox, Regulatory Review Officer - OPDP
Sam Skariah, Team Leader – OPDP

CC: Olga Salis, Senior Regulatory Project Manager - OPDP

Subject: NDA 206628
Dexmedetomidine HCl Injection
Professional Labeling Review

As requested in DAAAP's consult dated December 22, 2014, OPDP has reviewed the substantially complete prescribing information for Dexmedetomidine HCl Injection. The substantially complete prescribing information was provided to OPDP on August 12, 2015, via email by Allison Meyer with the file name "clean working copy FDA.doc".

OPDP has reviewed the substantially complete prescribing information and have no comments.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact me at (240) 402-8686 or by email, Kounq.Lee@fda.hhs.gov.

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

/s/

KOUNG U LEE
08/21/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: June 11, 2015

Requesting Office or Division: Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)

Application Type and Number: NDA 206628

Product Name and Strength: Dexmedetomidine Hydrochloride Injection
400 mcg/4 mL and 1,000 mcg/10 mL (100 mcg/mL)

Submission Date: April 21, 2015

Applicant/Sponsor Name: HQ Specialty Pharma

OSE RCM #: 2015-950

DMEPA Primary Reviewer: James Schlick, MBA, RPh

DMEPA Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

HQ Pharma submitted a Class 2 resubmission on April 21, 2015 with additional data for the preservative used in the vial. The Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) requested that we review the revised container labels and carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^{1,2}

¹ Schlick J. Label and Labeling Review for Dexmedetomidine (NDA 206628). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 JAN 12. 18 p. OSE RCM No.: 2014-1140

² Schlick J. Label and Labeling Review for Dexmedetomidine (NDA 206628). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 FEB 04. 3 p. OSE RCM No.: 2014-1140-1

2 OVERVIEW AND CONCLUSION

HQ Pharma submitted revisions to their container labels and carton labeling on February 2, 2015 based on DMEPA comments in OSE Review No. 2014-1140. In this submission HQ Pharma made all of the recommended changes and we had no further comments (see OSE Review No. 2014-1140-1). We reviewed the current Prescribing Information (PI) working document on June 4, 2015 and all of our recommended changes in OSE Review No. 2014-1140 are incorporated in the document.

Thus, the revised container labels, carton labeling, and Prescribing Information are acceptable from a medication error perspective.

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

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

/s/

JAMES H SCHLICK
06/11/2015

BRENDA V BORDERS-HEMPHILL
06/11/2015

**Department of Health and Human Services
Public Health Service Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology**

Pharmacovigilance Review

Date: 5/4/2015

Reviewer: Martin Pollock PharmD, Safety Evaluator,
Division of Pharmacovigilance II (DPV II)

Team Leader: Sara Camilli, PharmD, Safety Evaluator Team Leader,
DPV II

Division Director: Scott Proestel, MD, Director,
DPV II

Product Name: Dexmedetomidine

Subject: Selected events

Application Type/Number: NDA/206628

Applicant/Sponsor: HQ Specialty Pharma

OSE RCM #: 2014-2063

TABLE OF CONTENTS

EXECUTIVE SUMMARY

1.1	Background	3
1.2	Regulatory History	3
1.3	Product Labeling	4
2	METHODS	4
2.1	FAERS Search Strategy	4
3	RESULTS	4
3.1	FAERS Case Selection	4
3.2	Fatal Brain Injury, Bradycardia, and/or Hypotension (N=6)	5
3.3	QT Prolongation (N=5)	7
3.4	Epileptic Seizures (N=1)	8
3.5	Hypernatremia (N=2)	8
3.6	Skin Rash (N=6)	9
4	DISCUSSION	10
5	CONCLUSION	11
6	RECOMMENDATIONS	12
7	APPENDICES	13
7.1	Sponsor’s Proposed Dexmedetomidine Labeling (Selected Sections)	13
7.2	FDA Adverse Event Reporting System (FAERS)	16
7.3	FAERS Case series (n=20) for Dexmedetomidine: Line Listing	17
7.4	FAERS Dexmedetomidine Cases Of Rash-Related Events (N=6)	19
7.5	MedDRA Terminology Status For ‘Wheals’ And ‘Wheal And Flare’ ⁺	20

EXECUTIVE SUMMARY

The Division of Addiction, Anesthesia, and Analgesia Products (DAAAP) is reviewing HQ Specialty Pharma's NDA (206628) for a new formulation of the intravenous (i.v.) anesthetic dexmedetomidine (DEX). As the application references an approved formulation of the product (Precedex), HQ Specialty Pharma provided a review of published literature for postmarket safety data. Based on a review of these literature reports, DAAAP consulted the Division of Pharmacovigilance II (DPV II) to review FAERS for five event groups of interest: 1) fatalities reporting brain injury, bradycardia or hypotension, 2) QT prolongation (included torsade de pointes), 3) hypernatremia, 4) epileptic seizures, and 5) rash.

The FAERS review for DEX found 20 cases received from 2008 to 2014 encompassing all of DAAAP's event groups of interest, and included DEX use in both non-intubated and intubated patients. DEX appeared to be a contributor to the events in all 20 cases. Based on the assessment of FAERS data, DPV II recommends adding to the WARNINGS AND PRECAUTIONS section that bradycardia and hypotension can have a fatal outcome, and that QT prolongation, hypernatremia,¹ and rash¹ should be added to ADVERSE EVENTS/Postmarketing Experience section.

1 INTRODUCTION

1.1 BACKGROUND

DAAAP is reviewing HQ Specialty Pharma's NDA (206628) as a 505(b)(2) application for a new formulation² of the i.v. anesthetic DEX. Based upon HQ Specialty's submission of DEX clinical safety data from the published literature, DAAAP consulted DPV II to review FAERS data to address the following questions:³

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?

1.2 REGULATORY HISTORY

Precedex (dexmedetomidine, NDA 21038, Hospira), was approved on 12/17/99 for an indication of intubated intensive care unit sedation. On 10/17/08, Precedex received approval for an additional indication, sedation of non-intubated patients prior to and/or during surgical and other procedures.⁴ The NDA under review (NDA 206628) is only seeking approval for the indication of sedation of non-intubated patients prior to and/or during surgical and other procedures.

¹DPV II recommends additional terms related to hypernatremia and rash; see Section 6.

²HQ Specialty's DEX contains preservatives; Precedex does not. Therefore this application was not filed as an ANDA.

³Hereafter, the events mentioned in each question are collectively called 'event groups of interest.'

⁴DAAAP asked that the FAERS search start in 2008 because this was the year when Precedex received the 'non-intubated' approval.

1.3 PRODUCT LABELING

The sponsor's proposed labeling for DAAAP's events of interest are listed in Table 1.

Event of interest	Label section where mentioned	DPV II Comments
Hypotension/Bradycardia	5.2 Warnings and Precautions	Does not mention <i>fatal</i> ; See Appendix 7.1 for complete wording
Anoxic brain injury/death	Not labeled	
QT prolongation	Not labeled	
Seizures	6.2 Adverse Reactions, Postmarketing experience	Mentioned as 'convulsion'; no mention of epileptic seizures
Hypernatremia	Not labeled	
'Wheal and flare' rash	Not labeled	

Additional information from the sponsor's proposed labeling is in Appendix 7.1

2 METHODS

2.1 FAERS SEARCH STRATEGY

The FAERS database was searched with the strategy described in Table 2.

Search date	2/3/15
Search time period	1/1/2008– 2/3/15
Search type	Standard: Quick query
Product Terms	Dexmedetomidine; Dexmedetomidine hydrochloride
Outcome	Serious
*See Appendix 7.2 for a description of the FAERS database.	

The subset of reports that had PTs from any of the event groups of interest was reviewed. As agreed by DAAAP, we did not limit our review to only the proposed indication (i.e., non-intubated patients for procedural sedation). This is because Precedex is labeled for the wider indication of patients that are intubated *and* non-intubated (Section 1.2). As it is reasonable to believe that HQ Specialty's dexmedetomidine product may be used off label, we assessed the FAERS safety data without restriction to indication.

3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS search retrieved 352 reports. Among these 352 reports, we identified 27 unique MedDRA preferred terms (PTs) related to the event groups of interest (Appendix 7.3).

One or more of the 27 PTs (Appendix 7.3) were mentioned in 61 reports. Removal of 17 duplicates yielded 44 unique cases. After 24 exclusions, our case series was 20 cases (received between 2008 and 2014), including 10 literature reports (Table 4). The line listing of the 20 cases is in Appendix 7.4

Event of interest group	N	Exclusions [#]	Included	Literature ⁺
Bradycardia and or hypotension [†]	10	6	4	0
Bradycardia and or hypotension and brain injury [†]	2	0	2	1
Brain injury [†]	1	1	0	0
QT prolongation	9	4	5	3
Hypernatremia	2	0	2	2
Skin rash	11	5 [▲]	6	3
Seizure	9	8 [◊]	1	1
Total	44	24	20	10

[†]From included cases.

[#]Cases were excluded for lack of information for assessment, alternative etiology, or miscoding. For seizures, cases were excluded if there was no mention of *epileptic seizures*. Of the eight seizure cases excluded, one involved a pediatric (8-yr-old) patient; the rest were adult patients.

⁺Initial selection restricted to reports with a fatal outcome.

[▲]One of the exclusions was a literature report: Toshitaka Koinuma, et al. Case report: hemophagocytic syndrome developed after drug eruption: report of two cases. *Journal of the Japanese Society of Internal Medicine*. 2014;103:1931-1934.

[◊]One of the exclusions was a literature report: Belgrade M, Hall S. Dexmedetomidine infusion for the management of opioid-induced. *Pain Medicine*. 2010;11:1819-1826.

3.2 FATAL CASES OF BRAIN INJURY, BRADYCARDIA, OR HYPOTENSION (N=6)

We identified two cases of brain injury.⁵

The first case was a literature report⁶ (6699195; U.S.)⁷ of a 50-year-old male who received a 2-hour infusion of fentanyl and midazolam for sedation for ablation of paroxysmal atrial fibrillation. Later, the patient was switched to dexmedetomidine (DEX), 2.2 mcg/kg/hr for 45 minutes and then 0.6 mcg/kg/hr for 1 hour. He then experienced severe hypotension (42/22 mmHg) and bradycardia (30 bpm); DEX was discontinued. He then had asystole which was treated with chest compression and sympathomimetics. Imaging revealed cardiac tamponade and pericardiocentesis was performed (100 mL fluid removed), restoring the vital signs to normal. The patient again became hypotensive; no pericardial fluid (via imaging) was seen, but the patient did have ‘severe global left ventricular hypokinesia.’ The patient experienced ventricular fibrillation and ST elevation. He was given continuous cardiopulmonary resuscitation and a small amount of residual pericardial fluid was removed (via pericardial window technique). Cardiac massage and extracorporeal circulation was given. There was a slight improvement in left ventricular function but the patient ‘sustained severe anoxic injury leading to brain death’ (autopsy showed ‘anoxic encephalopathy with transtentorial herniation’). This case was coded for the MedDRA PTs *brain death* and *hypoxic-ischaemic encephalopathy*.

There are several factors that could have contributed to the patient’s deterioration following the initial bradycardia/hypotension that occurred after DEX. The patient had cardiac disease

⁵These two cases also had hypotension.

⁶Sichrovsky TC, Mittal S, Steinberg JS. Dexmedetomidine sedation leading to refractory cardiogenic shock. *Anesth & Analgesia* 2008;106:1784-1786.

⁷Case ID followed by reporter country.

(myocardial hypertrophy and necrosis and 50% left anterior descending artery stenosis). He received concomitant drugs that can depress cardiac function: metoprol and diltiazem as maintenance therapy and fentanyl and midazolam given in the beginning of the procedure. The authors also mentioned that it is possible that the patient could have had an alpha₂-adrenergic receptor polymorphism.⁸ This could have made the patient more sensitive to the cardiac depressant effects of an alpha agonist like DEX.

The second case was a 75-year-old male (9928922; foreign) who received an unknown DEX dose at an unknown time on Day 1 as a subject in a clinical trial.⁹ He experienced severe hypotension at 1800 on Day 2. He also experienced 'cognitive impairment,' coma, and renal failure at unknown times on Day 2. DEX was discontinued on Day 2. He experienced septic shock on Day 3 and a fatal cardiac arrest at a subsequent unknown day. Medical history and concomitant medications were unknown. This case was coded for the MedDRA PT *coma*.

The four remaining cases described hypotension and/or bradycardia.

A 10-year-old female (7418166; foreign) with history of Rett's¹⁰ syndrome and scoliosis surgery received a DEX infusion (unknown dose) on Day 1 for an unknown indication. Within 20-30 minutes after the start of the infusion, she experienced severe hypotension and bradycardia. DEX was discontinued on Day 1. The patient was given cardiac resuscitation, but died on Day 4.

An adult (8694324; U.S.) female in her late 50's with history of psychiatric illness was admitted to the ICU agitated and confused. She was placed on a ventilator and sedated with midazolam and fentanyl. She was put on DEX (unknown dose) because of her high breathing rate. Her breathing rate was controlled, and on the same day, she experienced bradycardia ('low 40's'). She was found to have anemia; there were no symptoms of GI bleeding or other hemorrhages, and she had no history of renal failure. DEX was discontinued, and she received blood transfusions. The patient died at an unknown later time as her husband 'withdrew care.' Concomitant medications were unknown.

A 70-year-old female (8717925; foreign) with American Society of Anesthesiologists Physical Status Classification System (ASA) score of 3¹¹ status and history of cardiac disease, diabetes, and rheumatic fever received DEX (unknown dose) for sedation for a laparoscopic total abdominal hysterectomy. Forty minutes later, propofol was added. At a later (unknown) time during the procedure, the patient experienced bradycardia which led to cardiorespiratory arrest. The patient was transferred to the ICU and died 6 days later. The pharmacist reporter considered the events to be a drug interaction between DEX and propofol.

A 50-year-old male (7677739; U.S.) with history of arrhythmias received DEX (0.7 mcg/kg/hr) propofol, fentanyl and midazolam for sedation for atrial fibrillation ablation. He became

⁸Flordellis, C, Manolis AS, Scheinin M, Paris H. Clinical and pharmacological significance of α_2 -adrenoceptor polymorphisms in cardiovascular diseases. *Int. J. Card.* 2004;97:367-372.

⁹*Prospective open randomized multicenter phase IIIb study of effects of dexmedetomidine and propofol on patient/ventilator interaction in difficult-to-wean mechanically ventilated patients.* This was an Italian study (phase IIIb) executed by the foreign sponsor Orion Pharmaceuticals (marketer of DEX).

¹⁰Rett's syndrome is a genetic (X chromosome-linked) neurological disorder principally manifested by mental retardation. There can be autonomic abnormalities which can result in cardiac abnormalities such as prolonged QT interval. Weng SM, Bailey ES, Cobb SR. Rett syndrome: from bed to bench. *Peds and Neonatol.* 2011;52:309-316.

¹¹The American Society of Anesthesiologists (ASA) Physical Status Classification System classifies patients into 6 different levels based upon morbidity; '1' is a normal healthy patient and '6' is brain dead. ASA '3' is a patient with 'severe systemic disease,' with functional limitations, e.g., poorly controlled cardiac or respiratory disease.

<http://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system>; accessed 3/9/15

hypotensive after 1 hour of the multi-drug infusion. He then had sinus arrest. DEX and propofol were discontinued; blood pressure was 38/28 mmHg. After multiple subsequent sinus arrests, cardiopulmonary resuscitation was given; 80 mL of pericardial fluid was withdrawn. The patient died 8 hours after anesthetic induction and 1 hour after sedation drugs were discontinued.

3.3 QT PROLONGATION (N=5)

There were five cases of QT prolongation. All were non-fatal, and three were reported in the literature.

The first literature case¹² (6596731; U.S.) was a 41-year-old female who received DEX (highest dose, 0.7 mcg/kg/hr) and other anesthetic-related drugs and underwent gastroenterostomy for morbid obesity. Toward the end of the operation, neostigmine was given to reverse neuromuscular blockade. Five minutes later, she experienced a 2nd-degree heart block (ventricular rate 31 beats per minute) which responded to atropine; DEX was discontinued. After surgical wound closure, she experienced another 2nd-degree heart block which responded to atropine. She then experienced a QTc prolongation 0.441 sec (pre-op QTc: 0.386 sec) while in the post-anesthesia care unit. The prolongation resolved 4 hours after DEX was discontinued. The patient also received the following medications which are all labeled for QT prolongation: dolasetron, droperidol and fentanyl.

The second literature case¹³ (7998254; foreign) was an 8-month-old (born premature with ileal stenosis) who received DEX for sedation post a gastrointestinal operation. DEX was given for 4 days (highest dose, 0.66 mcg/kg/hr).¹⁴ QTc was normal prior to surgery. QTc was 591 msec one day after the infusion ended; the elevation resolved after 5 days. Haloperidol, which is labeled for QT prolongation, was a concomitant medication.

The third literature case¹⁵ (9254944; U.S.) was a 22-month-old male who was initially given ICU-sedation post-thoracostomy (and still intubated) with morphine and midazolam for 66 hours. Fentanyl (labeled for QT prolongation) was also given exact timing unknown. Midazolam was discontinued and DEX (highest dose, 0.7 mcg/kg/hr) was added. The patient experienced bradycardia 4 hours after the DEX infusion start; after about 4 more hours, the QTc was 700 msec; there were also 'giant T waves'. DEX was discontinued and the QTc resolved over the next 3 days. The most recent (15 months prior) ECG showed a normal QTc. Genetic testing covering for long QT syndrome mutations was negative. The authors speculated that the patient might have a genetic QT long propensity because the genetic testing performed on the patient (results negative) covered only 75% of the known mutations.

There were two other adult cases from non-literature sources. The first case (10028447; U.S.) was a 26-year-old male with unknown medical history. QT prolongation with T wave inversion occurred 5 minutes after the DEX infusion (duration was 30-45 minutes; highest dose, 0.8 mcg/kg/hr). The prolongation resolved between 5 and 20 minutes after DEX was discontinued. The second case (9416267; foreign) was a 54-year-old male with medical history of hepatitis C, deep vein thrombosis, splenectomy and 'liver disorder' NOS. After one hour or more of a DEX infusion (unknown dose), he experienced bradycardia and QT prolongation. DEX was discontinued on the same day. He was discharged to his home on an unknown date. Concomitant contributing medications were quetiapine (first case) and fentanyl (second

¹²Shields JA. Heart block and prolonged Q-Tc interval following muscle relaxant reversal: a case report. *Am Assoc Nurse Anesthet J*. 2008;76:41-45.

¹³Matras ME, Lavole A, Closos A, Bussieres JF. QT interval prolongation and polypharmacy in pediatrics. *Quebec Pharmacie*. 2011;58:45-49.

¹⁴DEX use in pediatrics is off label. The dose given to the patient is within the adult labeled recommendation.

¹⁵Burns KM, Greene EA. Long QT Syndrome Unmasked by Dexmedetomidine: A case report. *Congenit Heart Dis*. 2014;9(1):E11-E15.

case) as both drugs are labeled for QT prolongation. The DEX indication was not reported for either case nor was the specific interval (msec) of the QT prolongation.

3.4 EPILEPTIC SEIZURES (N=1)

The single literature report¹⁶ (8718282; foreign) was a neonatal male with an Apgar score of 9 at 1 and 5 minutes after birth. However, the next day, he ‘displayed signs of respiratory distress’ and was transferred to the NICU where he was given surfactant and put on artificial respiration. He had difficulty adapting to artificial respiration and was sedated with DEX infusion (highest dose, 0.625 mcg/kg/hr).¹⁴ On postnatal day 5, he experienced epileptic¹⁷ seizures after 80 hours of the DEX infusion. The only concomitant medication was a single midazolam dose (timing during the DEX infusion was not specified). The neonate did not have a family history of seizures. The seizures resolved after DEX discontinuation, and at 8 months of age, the patient was developing normally and showed no signs of any neurologic abnormalities. This case was coded for the MedDRA PT epilepsy.

3.5 HYPERNATREMIA (N=2)

There were two cases of hypernatremia; both were literature reports.^{18,19}

A 71-year-old female (9289002; U.S.) had anesthesia induction with intubation and then received DEX (0.42 mcg/kg/hour); procedure was an elective spinal fusion surgery.^{18,19} During surgery, she had hypernatremia (151 mEq/L; preop: 138 mEq/L; normal: 135-145 mEq/L²⁰). The procedure lasted 7 hours after which DEX was discontinued; the hypernatremia resolved within the first 4 hours of the post-operative period. The hypernatremia was also accompanied by polyuria,²¹ low urine specific gravity, low urine osmolality, and high serum osmolality. Concomitant drugs administered were fentanyl, propofol, rocuronium, sevoflurane and remifentanyl. The patient did not experience any ‘sodium or urine output complications’ during her prior surgeries (abdominal and eye), for which DEX was not used.

A 40-year-old achondroplastic male (8440861; U.S.) had anesthesia induction with intubation and then received DEX (0.5 mcg/kg/hr) for a laminectomy/spinal fusion.¹⁹ His serum sodium was 136 mEq/L and increased to 145 mEq/L during the procedure. The procedure lasted 6 hours, after which DEX was discontinued. Serum sodium peaked at 148 mEq/L shortly after transfer to the ICU. The hypernatremia resolved over the next 24 hours. The hypernatremia was also accompanied by polyuria,²² low urine specific gravity, and low urine osmolality. Concomitant drugs were gabapentin (pre-medication), midazolam, propofol, vecuronium, ketamine, and sufentanil.

Of all the anesthetic drugs given to these two patients, both authors thought DEX was the likely suspect for the hypernatremia. The authors mention published preclinical data showing that DEX can suppress

¹⁶Kubota T, Fukasawa T, Kitamura E, Magota M, et al. Epileptic seizures induced by dexmedetomidine in a neonate. *Brain development*. 2013;35:360-362.

¹⁷The patient experienced epileptic and non-epileptic seizures. Epileptic seizures were determined by a combination of EEG with video monitoring. The patient was not given an epilepsy diagnoses.

¹⁸Ji F, Hong L. Intraoperative hypernatremia and polyuric syndrome induced by dexmedetomidine. *Journal of Anesthes*. 2013;27:599-603

¹⁹Greening A, Mathews L, Blair J. Apparent dexmedetomidine-induced polyuric syndrome in an acnodroplastic patient undergoing spinal fusion. *Anesth Analges*. 2011;113:1381-1383.

²⁰<http://www.nlm.nih.gov/medlineplus/ency/article/003481.htm>; accessed 2/27/15.

²¹During surgery, her urine output increased to 300, 970, 600 and 705 mL/hr during the 1st, 3rd, 4th and 5th surgical hour, respectively.

²²During surgery, urine output began to increase and reached 950 ml/hr by the fourth hour.

vasopressin²³ and clinical data showing DEX-dosed patients had high urine output.²⁴ The authors also commented that these patients had characteristics of diabetes insipidus.

3.6 SKIN RASH (N=6)

There were three reports from the literature reporting ‘wheal-and-flare’ rash,^{25,26} and a ‘drug-induced hypersensitivity syndrome.’²⁷

The first case²⁵ (6973672; U.S.) was a 22-year-old male who came to the ICU to be stabilized after a motor vehicle accident injury. Propofol and fentanyl infusions were started. At least 24 hours later, a DEX infusion (0.2 mcg/kg/hr) was added, and propofol was discontinued. After 4 hours of the DEX infusion, the patient experienced a wheal-and-flare rash with pruritus over 60% of his body, without head or mucous involvement and without systemic symptoms. There was a positive dechallenge to DEX.

The second case²⁶ 26 (10591443; foreign) was a 25-year-old male who underwent surgery for his fractured left hand. DEX (0.4 mcg/kg/hr) and lidocaine (2.4 mg/kg/hr for Bier block) was infused into the operative-hand through the same line over 1 minute.²⁸ The patient experienced a wheal and flare type of rash in the operative-hand about 90 seconds after the combination injection. A rash was not seen in any other place. Ceftriaxone was given about a half-hour before the DEX. There was no bronchospasm, hypotension, bradycardia or arrhythmias. Surgery lasted 75 min after which the rash resolved 4 hours after appearance. The patient had a negative lidocaine skin sensitivity test prior to the procedure; no testing was done for DEX.

The third case²⁷ (7635498; foreign) was an 11-year-old male with history of a lesion in the medulla oblongata who received a two-day DEX infusion (unknown dose, unknown indication). The next day (after DEX infusion completed), a ‘drug-induced hypersensitivity syndrome’ that spread to the whole body occurred. This event was further described as ‘skin eruption...erythema, vermeil to dark purple in color, with pigmentation, and purpura...multiple exanthemas, with healthy skin remaining, and itching.’ There was a positive dechallenge. The patient had numerous concomitant drugs. Of the nine drugs (DEX not included) tested for drug hypersensitivity (DLST²⁹), four were positive. All four drugs were started between 4 and 17 days before DEX. Rocuronium was given before and during DEX which suggests that this patient was intubated while being sedated.

The remaining 3 non-fatal adult FAERS cases (7850739;10477341;9916479; all foreign) reported wheals, urticaria, and a pruritic rash, respectively. The first two cases had a positive dechallenge (unknown in

²³Villela NR, Nascimento P, Carvalho LR, Teixeira AB. Effects of dexmedetomidine on renal system and on vasopressin plasma levels. Experimental study in dogs. *Rev Bras Anesthesiol.* 2005;55:429–440.

²⁴Herr DL, Sum-Ping J, England M. ICU sedation after coronary artery bypass graft surgery: dexmedetomidine-based versus propofol-based sedation regimens. *J Cardiothorac Vasc Anesthes.* 2003;17:576-584.

²⁵Ludwig K, Sorrell M, Lui S. Severe rash associated with dexmedetomidine use during mechanical ventilation. *Pharmacotherapy.* 2009;29:479-481.

²⁶Marodkar K, Bhargava S, Chopde N, Bhure A. Dermatological allergic reaction caused by dexmedetomidine in a patient administered intravenous regional anesthesia with dexmedetomidine-lidocaine combination. *Egyptian Journal of Anaesthesia.* 2014; Jan 01;30:31

²⁷Yukiko Shigematsu. A case of child DIHS due to phenobarbital presenting multiple drug sensitization. *Japan J Derm.* 2011;121(3):574.

²⁸DEX and lidocaine were prepared in 40 mL of ‘saline.’ The drug concentrations were 0.4 mcg/mL (DEX) and 3.75 mg/mL (lidocaine). The infusion was administered over 1 minute. ‘Y site injection compatibility’ data show these two drugs physically compatible for 4 hours @23°C (Dexmedetomidine monograph in Handbook on Injectable Drugs. 18th Ed. (2015); American Society of Health-System Pharmacists; Bethesda, MD).

²⁹DLST=drug lymphocyte stimulation test.

third). DEX infusion duration was 30 min, unknown and 4 days respectively; event onset was same day, unknown and third infusion day respectively. DEX dosage was 6 mcg/kg/hr (loading or maintenance not specified), 6 mcg/kg/hr loading dose then 0.4 mcg/kg/hr maintenance dose, and unknown respectively.³⁰ Event onset was same day, unknown and on the third day of infusion. The first case had a history of drug allergy and asthma; medical history was unknown in the other two cases. The first and third cases received concomitant medication(s) that may have contributed; status unknown in the second case. The reasons for sedation were ‘stability of intubation,’ unknown, and agitation (appeared to be non-intubated), respectively.

Appendix 7.5 includes a line listing of the six FAERS cases, including the verbatim description of the rash-related events and the FAERS MedDRA PT coding. Appendix 7.6 shows the MedDRA terminology status of ‘wheal and flare’ which was mentioned in two of the above cases.

4 DISCUSSION

We identified 20 postmarket reports in FAERS for the five events of interest. Indications reported included the proposed indication (i.e., non-intubated procedural intubation) for the HQ Specialty NDA and the other approved indication (i.e., ICU intubated sedation) for Precedex.

Bradycardia and hypotension are well known events for DEX. Our review identified six cases that show the known cardiovascular events of hypotension and bradycardia can progress to a fatal outcome (e.g., cardiac arrest). An excessive DEX dose is expected to increase the risk of these cardiovascular events. At least three of the FAERS (non-literature) cases had DEX dosages within the recommended range.

For hypernatremia, we identified two literature cases.^{19,19} These two cases suggest that DEX, which was dosed within the recommended range, had a role in the hypernatremia. Both cases are also described as ‘polyuric syndrome.’ Preclinically, DEX can inhibit vasopressin,^{23 23} and DEX-dosed patients have been shown to have a high urine output.^{24,31} The authors of the two FAERS literature cases also mentioned that the patients’ hypernatremia, polyuria and low urine osmolality were similar to what is seen in diabetes insipidus. Diabetes insipidus can be due to lack of vasopressin which can cause polyuria and subsequent hypernatremia.³² Additionally, we found another literature case (not in FAERS) of polyuria with DEX, but without hypernatremia; the authors also discussed DEX’s negative effect on vasopressin as a mechanism of action.³³

In the rash cases, DEX appeared to be a contributor based upon temporality and positive dechallenge. The DEX FAERS cases of rashes is new safety information as the sponsor’s proposed label only mentions *increased sweating* (Section 6.2: Skin and Appendage Disorders). The rash-related events were described in a number of different ways, some of which are not completely described in the MedDRA terminology (Appendix 7.6). An example is ‘wheal and flare’ (mentioned in the two literature reports).^{25,26,34} *Wheal and flare* is most commonly used to describe a positive allergen skin test.³⁵ Other descriptions from the

³⁰ Although the 6 mcg/kg/hr dosage exceeds that recommended, neither case reported any systemic events such as bradycardia or hypotension.

³¹ Leino K, Hynynen M, Jalonen J, Salmenpera M, et al. Renal effects of dexmedetomidine during coronary artery bypass surgery: a randomized placebo-controlled study. *BMC Anesthesiology*. 2011;11:9:1-10.

³² Verbalis JG. Diabetes insipidus. *Rev. Endocr. Metab. Dis.* 2003;4:177-185.

³³ Pratt A, Aboudra M, Lung L. Polyuria related to dexmedetomidine. *Anesth Analg.* 2013;117:150-2.

³⁴ ‘Wheals’ was also mentioned in one of the non-literature cases.

³⁵ Wheal: skin surface becomes elevated and reddened, due to inflammatory mediator release and vasodilation. Flare: spreading out of the wheal showing erythema. Carr TF, Saltoun CA. Chapter 2: Skin testing in allergy. *Allergy Asthma Proc.* 2012;33:suppl:S6-S8.

cases for these events such as *rash, pruritus and urticaria*, which are contained in the MedDRA terminology, can sufficiently characterize the FAERS data.

Most (4/5) of the QT prolongation cases had a positive dechallenge which suggests that DEX was a contributor to the event. Excessive dosing was not an issue for the three adult cases as most (2/3) were within the recommended range. Although there is no dosing recommendation for the two pediatric cases (off-label), both were within that recommended for adults. We also found two small (up to 23 patients) pediatric studies showing a QTc increase after DEX sedation (0.7 mcg/kg/hr in both).^{36,37} It is not uncommon for DEX to be used as part of a multi-drug regimen. This is evident in that all five FAERS cases reported other drugs in addition to DEX. Although in all of these cases, at least one of these other drugs is labeled for QT prolongation, the positive dechallenge cases provides sufficient basis for adding QT prolongation to the Postmarketing Experience section of the label.

For epileptic seizures, we identified a single literature report¹⁶ of a neonate. The DEX treatment of this patient is off-label,³⁸ and there is limited safety information for pediatrics or neonates.³⁹ Although DEX appeared to have played a role in this case, as far as we know, the patient did not end up with a diagnosis of epilepsy (or any other seizure disorder). The sponsor's proposed labeling already mentions seizures (as the MedDRA PT *convulsion*). After considering this neonatal case, the current labeling is sufficient.

5 CONCLUSION

Our FAERS review for dexmedetomidine (DEX) found 20 cases encompassing DAAAP's five event groups of interest: 1) fatalities reporting brain injury, bradycardia or hypotension, 2) QT prolongation, 3) hypernatremia, 4) epileptic seizures and 5) rash. DEX appeared to contribute to the events in all 20 cases. These cases reported DEX use in both non-intubated and intubated patients. Current labeling for seizures is sufficient based on the single literature case reviewed. The remaining cases provide new safety information that is not described in the sponsor's proposed labeling.

³⁶Hammer GB, Drover DR, Cao H, Jackson E, et al. The effects of dexmedetomidine on cardiac electrophysiology in children. *Anesth and Analges*. 2008;106:79-83.

³⁷Char D, Drover DR, Motonoga KS, Gupta S. The effects of ketamine on dexmedetomidine-induced electrophysiologic changes in children. *Ped Anesth*. 2013;23:898-905.

³⁸Precedex is only approved for adults; same for (proposed) HQ Specialty's DEX (NDA 206628).

³⁹Su F, Hammer GB. Dexmedetomidine: pediatric pharmacology, clinical uses and safety. *Exp Opin Drug Safety*. 2011;10:55-66.

6 RECOMMENDATIONS

The sponsor's proposed labeling should be modified as follows:

Label Section	Modification
5.2 Warnings: hypotension, bradycardia, and sinus arrest	Mention that hypotension and bradycardia can be <i>fatal</i>
6.2 Adverse Reactions: Postmarketing Experience	
Heart Rate and Rhythm Disorders	add QT prolongation
Renal Disorders	add polyuria
Metabolic and Nutritional Disorders	add hypernatremia
Skin and Appendages Disorders	add pruritus, rash, urticaria

7 APPENDICES

7.1 SPONSOR'S PROPOSED DEXMEDETOMIDINE LABELING (SELECTED SECTIONS)

WARNINGS AND PRECAUTIONS (SECTION 5)

Hypotension, Bradycardia, and Sinus Arrest (Section 5.2)



(b) (4)

ADVERSE REACTIONS (SECTION 6)

POSTMARKETING EXPERIENCE (SECTION 6.2)

The following adverse reactions have been identified during post approval use of dexmedetomidine hydrochloride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypotension and bradycardia were the most common adverse reactions associated with the use of dexmedetomidine hydrochloride during post approval use of the drug.

Table 1: Adverse Reactions Experienced During Post-approval Use of Dexmedetomidine Hydrochloride

Body System	Preferred Term
(b) (4)	

DOSAGE AND ADMINISTRATION (SECTION 2)

DOSAGE INFORMATION (SECTION 2.2)

Table 2: Dosage Information

INDICATION	DOSAGE AND ADMINISTRATION
Initiation of Procedural Sedation	(b) (4)
Maintenance of Procedural Sedation	(b) (4)

7.2 FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid trade names or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7.3 UNIQUE PTS (N=27) FROM DEXMEDETOMIDINE FAERS REPORTS (N=352) THAT WERE VERBATIM OR RELATED TO DAAAP'S EVENT GROUPS OF INTEREST

Index	Event group of interest	PT	Index	Event group of interest	PT
1	Bradycardia and or hypotension	Bradycardia	15	Seizure	Myoclonus
2	Bradycardia and or hypotension	Hypotension	16	Skin rash	Angioedema
3	Brain injury	Brain death	17	Skin rash	Blister
4	Brain injury	Coma	18	Skin rash	Drug eruption
5	Brain injury	Hypoxic-ischaemic encephalopathy	19	Skin rash	Drug reaction with eosinophilia and systemic symptoms
6	Brain injury	Neurological decompensation	20	Skin rash	Erythema
7	Hypernatraemia	Hypernatraemia	21	Skin rash	Necrosis
8	Hypernatremia	Blood sodium increased	22	Skin rash	Pruritus
9	Hypernatremia	Hypernatraemia	23	Skin rash	Purpura
10	QT prolongation	Electrocardiogram QT prolonged	24	Skin rash	Rash
11	QT prolongation	Long qt syndrome	25	Skin rash	Rash pruritic
12	QT prolongation	Torsade de pointes	26	Skin rash	Skin necrosis
13	Seizure	Convulsion	27	Skin rash	Urticaria
14	Seizure	Epilepsy			

7.4 FAERS CASE SERIES (N=20) FOR DEXMEDETOMIDINE AND EVENTS OF INTEREST: LINE LISTING

Case Id and version #	Mfr control#	Event	Country	DEX indication per proposed label
6699195; 1	L08-USA-02187-01	Brain death, bradycardia, hypotension (Fatal)	United States	Yes
9928922; 1	1828486	Brain death, hypotension (Fatal)	Italy	No
7418166; 2	602438	Bradycardia, hypotension (Fatal)	Australia	Unknown
8694324; 1	1324523	Bradycardia (Fatal)	United States	No
8717925; 1	BR-ASTRAZENECA-2012SE55750	Bradycardia (Fatal)	Brazil	Yes
7677739; 1	Direct report	Bradycardia, hypotension (Fatal)	United States	Yes
6596731; 2	08H-163-0313971-00	QT prolongation	United States	No
7998254; 1	930717	QT prolongation	Canada	Yes
9254944; 1	1678593	QT prolongation	United States	No
10028447; 1	2167017	QT prolongation	United States	Unknown
9416267; 1	1796622	QT prolongation	Ireland	No
8718282; 2	1344827	Seizure	Japan	No
9289002; 1	1706440	Hypernatremia	United States	No
8440861; 1	2012AP000359	Hypernatremia	United States	No
6973672; 1	231473	Rash	United States	Yes
10591443; 1	IN-BAXTER-2014BAX067188	Rash	India	Yes
7635498; 7	JP-PFIZER INC-2010098000	Rash	Japan	Unknown
7850739; 1	513798	Rash	Japan	No
10477341; 1	2534220	Rash	Japan	Unknown
9916479; 1	2191283	Rash	United Kingdom	Yes

7.5 FAERS DEXMEDETOMIDINE CASES OF RASH-RELATED EVENTS (N=6)

Case ID	Literature report and citation	Verbatim description of event[#]	FAERS MedDRA PT Coding
6973672	Yes; Ludwig et al. 2009	'Wheal-and-flare' rash', ...eruption of rash	Pruritus, rash, urticaria
10591443	Yes; Marodkar et al. 2014	'Wheal and flare type of rash', allergic reaction, allergic rash	Hypersensitivity, urticaria
7635498	Yes; Yukiko 2011	Skin eruption, erythema, vermeil to dark purple in color with pigmentation and purpura, multiple exanthemas, itching	Drug reaction with eosinophilia and systemic symptom
7850739	No	Wheals, allergic reaction	Hypersensitivity, urticaria
10477341	No	Urticaria	Urticaria
9916479	No	Severe rash which was very itchy	Rash pruritic

†As described in Section 3.5

#From narrative

7.6 MEDRA TERMINOLOGY STATUS FOR ‘WHEELS’ AND ‘WHEAL AND FLARE’⁺

Verbatim description	Lower level term (LLT)	Preferred Term (PT)
‘wheal’ and ‘flare’	evoked a flare & wheal reaction	skin test positive
‘wheal’	wheals	urticaria
‘flare’	dermatitis flare-up	dermatitis
	atopic-flare-up	dermatitis atopic

⁺‘Wheals’ (Case ID 7850739) and ‘wheal and flare’ (Case ID 6973672; 10591443) were mentioned as rash descriptions in three FAERS cases.

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

/s/

MARTIN L POLLOCK
05/05/2015

SARA L CAMILLI
05/05/2015

SCOTT E PROESTEL
05/05/2015

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: March 11, 2015

To: Allison Meyer, Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: Samuel M. Skariah, Team Leader (OPDP)

Subject: NDA 206628
OPDP labeling comments for dexmedetomidine

OPDP acknowledges receipt of your December 19, 2014, consult request for the proposed Package Insert (PI) for dexmedetomidine. Reference is made to the March 11, 2015 email response from DAAAP, confirming that a Complete Response (CR) letter would be issued. Therefore, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DAAAP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions, please contact Sam Skariah at (301)796-2774 or sam.skariah@fda.hhs.gov.

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

/s/

SAMUEL M SKARIAH
03/11/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: February 27, 2015 **Date Consulted:** February 3, 2015

From: Miriam Dinatale, D.O., Medical Officer
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND Associate Director
Division of Pediatric and Maternal Health

To: Division of Anesthesia, Analgesia and Addiction Products (DAAAP)

Drug: Dexmedetomidine Hydrochloride Injection, 400mcg/4ml and 1000mcg/10ml

NDA: 206628

Applicant: HQ Specialty Pharma

RLD: Precedex (dexmedetomidine hydrochloride) Injection and Injection Concentrate,
NDA 21038, Hospira, Inc.

Subject: Pregnancy and Lactation labeling

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

Materials Reviewed:

- DPMH consult request dated February 3, 2015, DARRTS Reference ID 3696492
- Sponsor's submitted background package for Dexmedetomidine Hydrochloride, NDA 206628

- Clinical Review: Dexmedetomidine. February 5, 2015. Reference ID 3698154
- Pharmacology/Toxicology Review: Dexmedetomidine. February 6, 2015. Reference ID 3698294

Consult Question:

DAAAP is requesting DPMH assistance in completing the review of the pregnancy and lactation section of labeling and conversion to the Pregnancy and Lactation Labeling Rule format.

REGULATORY HISTORY

On May 12, 2014, HQ Specialty Pharma submitted a 505(b)(2) New Drug Application (NDA) 206628 for Dexmedetomidine HCl Injection, a selective alpha2-adrenergic agonist, for the proposed indication of sedation of non-intubated patients prior to and/or during surgical or other procedures. Precedex, NDA 21038, is the reference listed drug that was approved in the U.S. on December 17, 1999, and has the following indications: 1.) sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting and 2.) sedation of non-intubated patients prior to and/or during surgical and other procedures. The proposed NDA differs from the reference product because of the addition of two preservatives (methylparaben and propylparaben) to this product. The applicant is relying on the Agency’s previous findings of safety and the relevant pharmacology, pharmacokinetics, and toxicology information in the label of the reference product, Precedex.¹

The Division of Anesthesia, Analgesia and Addiction Products (DAAAP) consulted the Division of Pediatric and Maternal Health (DPMH) on February 3, 2015, to provide input for appropriate labeling of the pregnancy and lactation subsections of Dexmedetomidine labeling and conversion to the Pregnancy and Lactation Labeling Rule format.

BACKGROUND

Dexmedetomidine and Mechanism of Action

Dexmedetomidine, a selective alpha2-adrenergic agonist, has been shown to have analgesic and sympatholytic properties. The sedative properties of the drug are produced by stimulation of presynaptic α_2 receptors, which results in a presynaptic decrease in norepinephrine release and an inhibition of postsynaptic activation; overall this serves to attenuate central nervous system excitation. Because the effects of dexmedetomidine are not mediated by the γ -aminobutyric acid (GABA)-mimetic system, it provides sedation, analgesia and anti-shivering properties.²

Pregnancy and Lactation Labeling

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”³ also known as the Pregnancy and

¹ Woo, Newton. Pharmacology/Toxicology Review: Dexmedetomidine, NDA 206628. February 6, 2015. Reference ID 3698294

² Palanisamy, et al. Intravenous dexmedetomidine as an adjunct for labor analgesia and cesarean delivery anesthesia in a parturient with a tethered spinal cord. International Journal of Obstetric Anesthesia. 2009; 18 (3): 258-261.

³ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule⁴ format to include information about the risks and benefits of using these products during pregnancy and lactation.

DISCUSSION

Nonclinical Experience

The applicant did not perform additional nonclinical studies for dexmedetomidine and relied on nonclinical information from the published literature to satisfy nonclinical requirements. Overall, the pharmacology/toxicology review noted that in animal reproduction studies there were no teratogenic effects in rats following subcutaneous administration of dexmedetomidine at doses equal to the maximum recommended human dose (MHRD) during organogenesis or in rabbits following intravenous administration of dexmedetomidine hydrochloride at doses equal to half the MHRD during organogenesis. Fetal toxicity (post-implantation losses and reduced live pups), however, was reported in rats given doses equal to the MHRD. Another study reported low birth weights in the offspring of rats given dexmedetomidine hydrochloride at doses that were less than the MHRD from day 16 of gestation through nursing. At doses less than the MHRD, rat offspring also showed delayed motor development.⁵

Reviewer Comments:

Overall, there were no teratogenic effects observed in a reproductive toxicology study conducted with dexmedetomidine hydrochloride dosed throughout organogenesis in rats and rabbits. However, an increase in post-implantation loss and reduced live pups were observed in rats given doses equal to the MHRD. Lower pup weights were observed in another reproductive toxicology study with dexmedetomidine hydrochloride conducted after organogenesis through weaning in rats with repeated subcutaneous administration at doses less than the MRHD.

In humans, dexmedetomidine is typically dosed once during surgery and is not given in repeated doses throughout the course of pregnancy as was seen in animal reproduction studies. It would be unlikely to see similar effects in humans as seen in animals given the indicated use in humans.

Dexmedetomidine and Pregnancy

The sponsor did not conduct studies with dexmedetomidine in pregnant women. A search of the scientific literature for available published human pregnancy data for dexmedetomidine was performed to update the Pregnancy subsection of labeling for this application. A limited number of case reports were found, but there is no evidence of controlled trials. A review TERIS notes that “there are no data on the use of dexmedetomidine in pregnant women. The effects, if any, on the developing fetus are unknown. The manufacturer only suggests dexmedetomidine therapy

⁴ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

⁵ Pharmacology/Toxicology Review: Dexmedetomidine. February 6, 2015. Reference ID 3698294

during pregnancy when necessary for the health of the mother.”⁶ The reports that follow are cases that were found in published literature and were not provided by the sponsor.

In a case study by Neumann, *et al.*, a 35 year-old female with spinal muscular atrophy (SMA) type III⁷ presented for urgent cesarean section after premature spontaneous rupture of membranes at 35 weeks gestation. The patient also had a past medical history of thoracosacral spinal fusion and severe restrictive lung disease. Dexmedetomidine is frequently used in patients with SMA to facilitate fiberoptic intubation. The patient was given dexmedetomidine 1 mcg/kg intravenously (IV) over 10 minutes followed by an infusion of 1 mcg/kg/hour. Halfway through the initial placement of the flexible fiberoptic intubating bronchoscope the patient became anxious, and the scope was removed, and a 0.5mcg/kg bolus of dexmedetomidine was given. Dexmedetomidine was given for a total of 1.84 mcg/kg over 38 minutes. Intermittent fetal heart tones were normal and remained unchanged during the procedure. The infant was delivered 68 minutes after discontinuation of the dexmedetomidine infusion (positioning difficulties required time for the surgeons to maximize exposure to the lower abdomen). At the time of delivery the maternal central venous dexmedetomidine concentration was 710 pg/ml, umbilical arterial concentration was 540 pg/ml and umbilical venous concentration was 543 pg/ml. The Apgar score⁸ was 6 at one minute and 8 at 5 minutes. The umbilical arterial and venous blood gas revealed a pH of 7.35 for both. The infant had an initial oxygen saturation of 88% and required assisted ventilation for 3 minutes requiring supplemental oxygen and then room air. Neurobehavioral and physical examinations of the infant were normal at 15 minutes.⁹

In another case report by Palanisamy, *et al.*, a 31 year-old female with a history of spina bifida occulta and a tethered spinal cord (reaching L5-S1) presented for elective induction of labor at 40 weeks gestation. Given her medical history, neuraxial blockade was not recommended, and the patient elected to use IV patient-controlled analgesia (IVPCA). When fentanyl infusion failed to work the patient was started on dexmedetomidine infusion as an adjuvant to IVPCA fentanyl. The patient was given a 0.5 mcg/kg loading dose of dexmedetomidine over 10 minutes and then placed on an continuous dexmedetomidine infusion of 0.2 mcg/kg/hour. Maternal blood pressure did not change from baseline, oxygen saturation remained above 95%, and the fetal heart rate remained between 150-160 beats per minute with moderate variability. The patient went on to have a cesarean section for prolonged first stage of labor and presumed chorioamnionitis and delivered a healthy baby boy with Apgar scores of 7 and 8 at one and five minutes. The infant was taken to the neonatal intensive care unit (NICU) for observation.

⁶ TERIS is the TERatology Information Service located at University of Washington. It is an online database designed to assist physicians or other healthcare professionals in assessing the risks of possible teratogenic exposures in pregnant women. Accessed February 12, 2015.

http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/

⁷ SMA, an inherited motor neuron disease, causes progressive degeneration of spinal cord anterior horn cells. It is characterized by diffuse voluntary muscle weakness and subsequent muscle atrophy, respiratory muscle insufficiency and scoliosis. These patients present multiple problems for the anesthesiologist including airway difficulties, respiratory compromise and spinal abnormalities.

⁸ Apgar score: a quick test performed on a baby at one and five minutes after birth that examines the infant's breathing effort, heart rate, muscle tone, reflexes and skin tone.

⁹ Neumann, *et al.* Dexmedetomidine for awake fiberoptic intubation in a parturient with spinal muscular atrophy type III for cesarean delivery. *Int J Obstet Anesth.* 2009 Oct;18(4):403-7.

Maternal and umbilical cord blood samples were collected; however, the medical team was unable to find a laboratory willing to measure serum concentrations of dexmedetomidine. The infant had an unremarkable 24-hour NICU stay and was discharged home three days later without any significant issues.¹⁰

In a case report by Machareth de Souza, *et al.*, a 19 year-old female at 27 weeks gestation presented with a ruptured cerebral aneurysm. Anesthesia for her surgery was maintained with propofol, alfentanil, rocuronium, and dexmedetomidine (0.7 mcg/kg/hour initially and then gradually decreased to 0.4 mcg/kg/hour). The patient was hemodynamically stable during the procedure (blood pressure of 110/60mmHg) as was the fetus who maintained a stable heart rate on periodic monitoring. The patient recovered with no underlying neurological sequelae and went on to deliver a healthy infant via cesarean section at 37 weeks gestation.¹¹

In a study by Ala-Kokko, *et al.*, placentas from normal term pregnant women were obtained following vaginal deliveries. A single cotyledon placental perfusion system was used to compare the perfusion of clonidine and dexmedetomidine. The average dexmedetomidine concentration achieved after the initial bolus was 3.1 nmol/l. Overall, both dexmedetomidine and clonidine were rapidly transported from the maternal circulation to the placenta. However, less dexmedetomidine was transported from the placenta to the fetal circulation as compared to clonidine, which may be due to the higher lipophilicity of dexmedetomidine resulting in greater placental retention. This suggests that at least after acute administration, such as during labor, the placenta might restrict the amount of dexmedetomidine reaching the fetal circulation.¹²

Reviewer Comments:

Although animal reproduction studies in rats showed an increase in post-implantation loss, reduced live pups, and lower pup weights, the rats were given repeated doses of dexmedetomidine from organogenesis through weaning. The relevance of these animal findings in humans is unknown, since women receiving dexmedetomidine would only be receiving a single dose of the drug during surgery instead of multiple doses as was seen in animal studies.

In an in vitro human placenta study, placental transfer of dexmedetomidine was observed when dexmedetomidine was administered subcutaneously; therefore, fetal exposure should be expected in humans. Overall, the infants exposed to dexmedetomidine in the case studies reviewed above, did not have serious side effects from in utero exposure to dexmedetomidine; however, one infant did require a brief period of assisted ventilation at birth.

¹⁰ Palanisamy, et al. Intravenous dexmedetomidine as an adjunct for labor analgesia and cesarean delivery anesthesia in a parturient with a tethered spinal cord. International Journal of Obstetric Anesthesia. 2009; 18 (3): 258-261.

¹¹ Machareth de Souza, et al. Dexmedetomidine in general anesthesia for surgical treatment of cerebral aneurysm in pregnant patient with specific hypertensive disease of pregnancy. Case Report. Rev Bra Anesthesiol. 2005; 55 (2): 212-6.

¹² Ala-Kokko, et al. Transfer of clonidine and dexmedetomidine across the isolated perfused human placenta. Acta Anaesthesiol Scand. 1997; 41: 313-319.

Dexmedetomidine and Lactation

There were no formal lactation studies of dexmedetomidine in nursing mothers conducted by the applicant. The Drugs and Lactation Database (LactMed)¹³ was searched for available lactation data on the use of dexmedetomidine, and no information was found. TERIS noted that “the effects of dexmedetomidine on the nursing infant are unknown. There are no studies on the use of dexmedetomidine during lactation; therefore, it is not known if dexmedetomidine is present in human milk.”¹⁴

In a lactation study done in Harlan Sprague Dawley rats, subcutaneous radiolabeled dexmedetomidine was injected into lactating rats at a dose of 0.015 mg/kg. The maximum drug exertion into rat milk occurred at four hours post-dosing, and milk/plasma ratios were all less than one, indicating no drug accumulation in rat milk. See table below for further information.¹⁵

Mean Concentrations of Radioactivity in Milk and Plasma, and
Milk: Plasma Concentration Ratios for Lactating Rats following a Subcutaneous
0.015 mg/kg Dose of [³H]Dexmedetomidine.HCl

Hours After Dose	ng EqBase/g		Milk:Plasma Ratio
	Plasma*	Milk	
0.5	1.45	0.88	0.59
1	1.74	1.12	0.65
2	2.44	1.56	0.64
4	3.31	1.57	0.48
8	1.93	1.34	0.70
24	0.18	0.16	0.87
72	0.03	nd	nd

*Average of premilk and postmilk values
All numbers have been rounded off to two decimal places
nd = not detected The last column was mislabeled in the submission.

Reviewer Comments:

Although dexmedetomidine is excreted into but does not accumulate in rat milk, it is difficult to predict whether this would be true in humans since drug presence and accumulation in breast milk is species specific. Therefore, there is no information to base a clear recommendation. Thus, this reviewer recommends that a lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk for approximately 5 half-lives after receiving dexmedetomidine hydrochloride in order to minimize potential drug exposure to a breastfed infant because this drug is not intended to be administered chronically.

¹³ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

¹⁴ http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/

¹⁵ NDA 21038, Precedex, Overall Toxicology Summary. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21-038_Precedex_pharmr_P4.pdf. Accessed: February 12, 2015.

CONCLUSIONS AND RECOMMENDATIONS

Dexmedetomidine labeling has been updated to comply with the PLLR. A review of the literature for relevant data revealed no new data with dexmedetomidine use in pregnant or lactating women. DPMH has the following recommendations for dexmedetomidine labeling:

- **Pregnancy, Section 8.1**
 - The “Pregnancy” subsection of dexmedetomidine labeling was formatted in the PLLR format to include the “Risk Summary” and “Data” subsections.¹⁶
- **Lactation, Section 8.2**
 - The “Lactation” subsection of dexmedetomidine labeling was formatted in the PLLR format to include the “Risk Summary” and “Clinical Considerations” subsections.¹⁷

DPMH DEXMEDETOMIDINE HCL LABELING

DPMH discussed labeling recommendations with DAAAP on February 19, 2015, and DPMH labeling recommendations are below. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here. (See Appendix A for the applicant’s proposed pregnancy and lactation labeling.)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no studies conducted with dexmedetomidine hydrochloride in pregnant women to inform any drug-associated risks. A published *in vitro* human placenta study reported placental transfer of dexmedetomidine hydrochloride. No teratogenic effects were observed in a reproductive toxicology study conducted with dexmedetomidine hydrochloride dosed throughout organogenesis in rats with subcutaneous administration at doses approximately equal to the maximum recommended human dose (MRHD), and in rabbits dosed throughout organogenesis with intravenous administration at doses approximately one-half the human exposure at the MRHD. However, an increase in post-implantation loss and reduced live pups were observed in rats. Lower pup weights were observed in another reproductive toxicology study with dexmedetomidine hydrochloride conducted after organogenesis through weaning in rats with repeated subcutaneous administration at doses less than the MRHD [see Data]. The background risk in the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

¹⁶ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

¹⁷ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1-Risk Summary.

Data

Animal Data

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

8.2 Lactation

Risk Summary

There is no information regarding the presence of dexmedetomidine hydrochloride in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Radio-labeled dexmedetomidine administered subcutaneously to lactating female rats was excreted in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for dexmedetomidine hydrochloride and any potential adverse effects on the breastfed infant from dexmedetomidine hydrochloride or from the underlying maternal condition.

Clinical Considerations

A lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk for 10 hours (approximately 5 half-lives) after receiving dexmedetomidine hydrochloride in order to minimize potential drug exposure to a breastfed infant.

APPENDIX A – Applicant’s Proposed Pregnancy and Nursing Mothers Labeling

(b) (4)

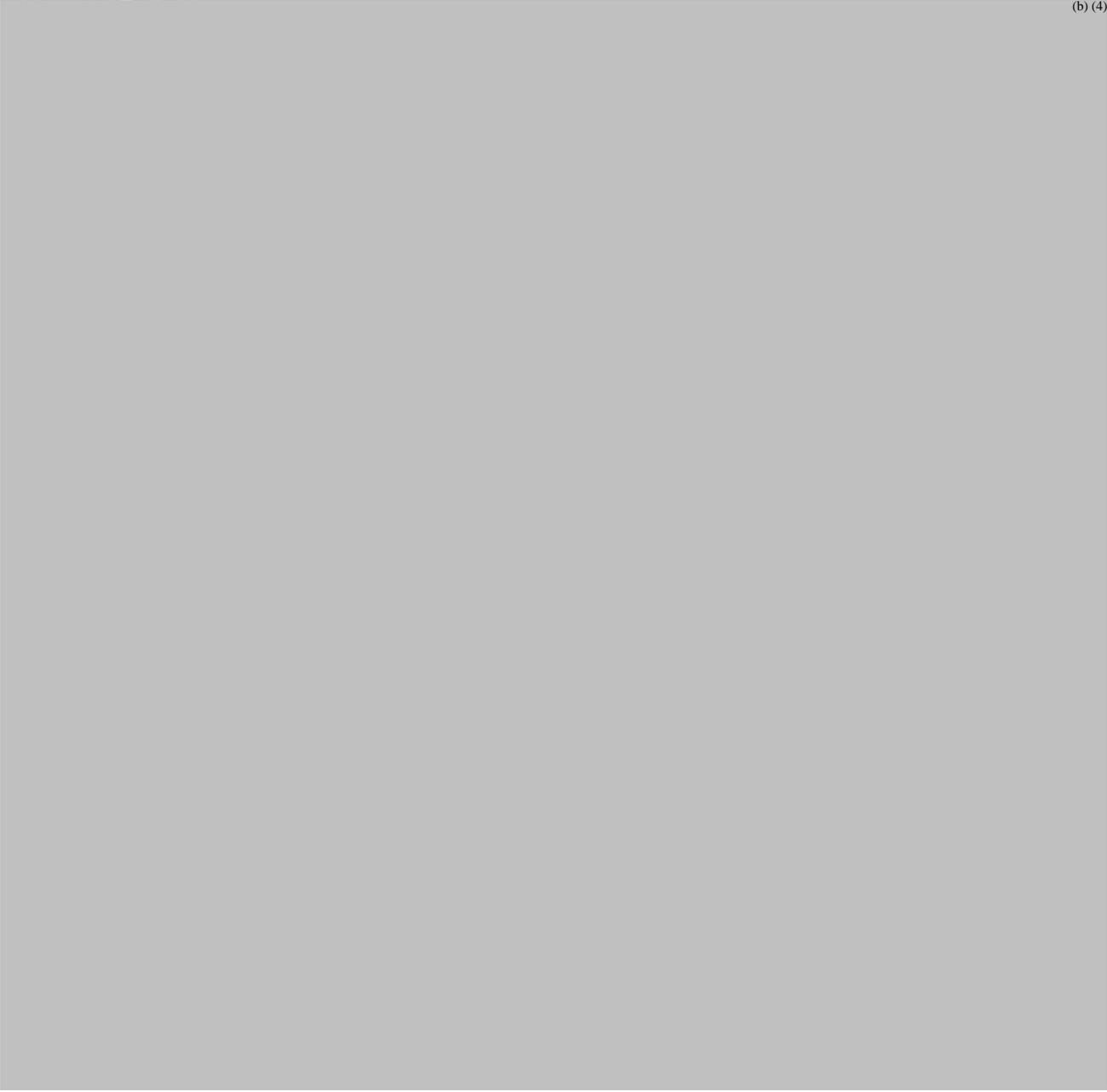
A large rectangular area of the document is completely redacted with a solid grey fill, covering the majority of the upper half of the page.

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

(b) (4)

A very large rectangular area of the document is completely redacted with a solid grey fill, covering the entire lower half of the page and extending upwards from the '8.1 Pregnancy' section header.

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

/s/

MIRIAM C DINATALE
02/27/2015

TAMARA N JOHNSON
02/27/2015

LYNNE P YAO
03/02/2015

**Selected Requirements of Prescribing Information
REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 206628

Application Type: New NDA

Name of Drug/Dosage Form: dexmedetomidine hydrochloride injection

Applicant: HQ Specialty Pharma

Receipt Date: May 12, 2014

Goal Date: March 12, 2015

1. Regulatory History and Applicant's Main Proposals

HQ Specialty Pharma submitted NDA 206628 for dexmedetomidine hydrochloride injection, 400 mcg/4mL and 1000 mcg/10 mL, for procedural sedation. This is a 505(b)(2) application that references Precedex as the listed drug. No studies were ever conducted under an IND. Preliminary responses were given in writing to a PIND meeting request.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

Selected Requirements of Prescribing Information

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.
Comment: None
- NO** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.
Comment: The length is more than 1/2 page. A waiver was not submitted.
- Yes** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
Comment: None
- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.
Comment: None
- yes** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.
Comment:
- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.
Comment: None
- yes** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required

Selected Requirements of Prescribing Information

• Revision Date	Required
-----------------	----------

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment: none

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment: None

Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment: The name of the drug product "dexmedetomidine hydrochloride injection" is not in UPPER CASE letters.

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment: None

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: None

Boxed Warning (BW) in Highlights

- n/a 12. All text in the BW must be **bolded**.

Comment: None

- n/a 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment: None

- n/a 14. The BW must always have the verbatim statement “***See full prescribing information for complete boxed warning.***” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment: None

- n/a 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “***See full prescribing information for complete boxed warning.***”).

Selected Requirements of Prescribing Information

Comment: *None*

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment: *New Application*

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment: *None*

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment: *None*

Indications and Usage in Highlights

- yes** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment: *Pharmacologic class is not indicated.*

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment: *Single dosage form*

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment: *None*

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment: *None*

Patient Counseling Information Statement in Highlights

Selected Requirements of Prescribing Information

yes 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment: *Pateint Counsleing Information Statment is missing.*

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *None*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment: None
- yes** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment: The heading is not bolded.
- yes** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment: BW heading is not bolded
- yes** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment: The section headings are in UPPERCASE, but they are not bolded.
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment: None
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment: None
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment: None

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: None

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment: None

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment: None

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment: None

BOXED WARNING Section in the FPI

- n/a** 36. In the BW, all text should be **bolded**.

Comment:

- n/a** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment: None

CONTRAINDICATIONS Section in the FPI

- yes** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment: None

- yes** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment: Postmarketing Eceprince Section is not included.

PATIENT COUNSELING INFORMATION Section in the FPI

- yes** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment: *None*

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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

/s/

ALLISON MEYER
02/05/2015

PARINDA JANI
02/06/2015

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: February 4, 2015

Requesting Office or Division: Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)

Application Type and Number: NDA 206628

Product Name and Strength: Dexmedetomidine Hydrochloride Injection
400 mcg/4 mL and 1,000 mcg/10 mL (100 mcg/mL)

Submission Date: February 2, 2015

Applicant/Sponsor Name: HQ Specialty Pharma

OSE RCM #: 2014-1140-1

DMEPA Primary Reviewer: James Schlick, RPh, MBA

DMEPA Acting Team Leader: Vicky Borders-Hemphill, PharmD

1 PURPOSE OF MEMO

The Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) requested that we review the revised container labels and carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSIONS

The revised container labels and carton labeling are acceptable from a medication error perspective.

¹ Schlick J. Label and Labeling Review for Dexmedetomidine (NDA 206628). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 JAN 12. 18 p. OSE RCM No.: 2014-1140.

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

/s/

JAMES H SCHLICK
02/04/2015

BRENDA V BORDERS-HEMPHILL
02/05/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: January 12, 2015

Requesting Office or Division: Division of Analgesia, Anesthesia, and Addiction Products (DAAAP)

Application Type and Number: NDA 206628

Product Name and Strength: Dexmedetomidine Hydrochloride Injection
400 mcg/4 mL and 1,000 mcg/10 mL (100 mcg/mL)

Product Type: Single

Rx or OTC: Rx

Applicant/Sponsor Name: HQ Specialty Pharma

Submission Date: May 12, 2014

OSE RCM #: 2014-1140

DMEPA Primary Reviewer: James Schlick, MBA, RPh

DMEPA Acting Team Leader: Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

HQ Specialty Pharma submitted this 505(b) (2) NDA for approval of Dexmedetomidine Injection for procedural sedation. Thus, the Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) consulted DMEPA to evaluate the container labels, carton labeling, and insert labeling from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D N/A
ISMP Newsletters	E
Other	F N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the similarities and differences between the proposed product and the Reference Listed Drug (RLD), Precedex (NDA 201038). We determined that both products have the same route and rate of administration, dose, frequency, dosage form, and storage conditions as the RLD. However, the strengths and indications between the two products are different. The proposed product includes a 400 mcg/4 mL and 1,000 mcg/10 mL multiple-dose vial whereas the RLD includes a 200 mcg/2 mL single-dose vial and a 200 mcg/50 mL and 400 mcg/100 mL single-dose bottle. Also, the proposed product does not include the indication for Adult Intensive Care unit Sedation, where the RLD has this indication.

We assessed the differences between the products to determine if they are prone to medication errors if simultaneously marketed. We determined that the product differences between the proposed product and the RLD should not pose a risk for medication errors. We also determined that strengths of the proposed multiple-dose vials are supported by the indications and dosing of the product.

We also assessed whether the container and closure of the proposed product was prone to medication error. The loading dose and maintenance dose for both the proposed product and RLD requires dilution in a piggyback before use. Thus, it is unlikely that a healthcare practitioner will draw up the total volume of the 4 mL and 10 mL vial and administer it as a bolus injection. Moreover, the 10 mL vial is unlikely to be confused with the 200 mcg/50 mL and 400 mcg/100 mL ready-to-use bottles due to volume differences. Thus, the volume differences minimize the risk for the 10 mL vial to be infused directly without further dilution. Lastly, the need to dilute the solution further in a piggyback before administering the product should prevent cross contamination between patients if multiple procedural sedations are performed using the multiple-dose vial.

Our search of the FAERS database identified two cases relevant to this review (see Appendix B). In both cases the root cause could not be identified. However, we reviewed the container labels, carton and insert labeling to determine if the errors could be attributed to a lack of information or a lack of clarity. We determined that no changes to the labels and labeling are recommended at this time given the information reviewed. We will continue to monitor for overdose errors.

We also identified a statement on the carton labeling “The container closure is not made with natural rubber latex.” We contacted ONDQA via email on December 8, 2014 to discuss this statement and we determined that DMEPA will defer to ONDQA on this statement. Additionally, because the statement is on the back panel of the carton labeling, we are not concerned that the presence of the statement will introduce clutter to important information on the principal display panel.

Our review of the container labels, carton labeling, and insert labeling for this product identified additional areas of vulnerability that may be subject to confusion and can be further optimized. This includes the addition of background colors to further differentiate between strengths on the container labels and carton labeling, the inclusion of a “(b) (4)” statement on the container label, increasing the prominence of the “(b) (4)” statement on the container label, and general revisions to Section 3 and Section 16 in the insert labeling. We provide recommendations to address these in Sections 4.1 below.

4 CONCLUSION & RECOMMENDATIONS

We find the addition of this product to the market acceptable. The proposed labels and labeling for this product can be improved to increase the readability and prominence of important information on the label and add important information to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Section 3; Dosage Form and Strength –Highlights of Prescribing and Full Prescribing Section

1. We provide recommendations in tracked changes in Appendix G.3 to optimize the language for these sections.

B. Section 16; How Supplied Section- Full Prescribing Information

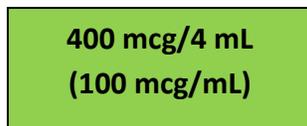
1. We provide recommendations in tracked changes in Appendix G.3 to optimize the language for this section.

4.2 RECOMMENDATIONS FOR THE HQ SPECIALTY PHARMA

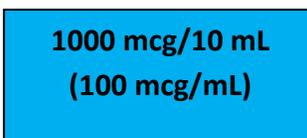
We recommend the following be implemented prior to approval of this NDA:

A. CONTAINERR LABELS AND CARTON LABELING

1. To help differentiate between the two product strengths (400 mcg/4 mL and 1,000 mcg/10 mL) and to mitigate product selection errors, incorporate a boxed background color for each strength. Ensure that the background colors are not similar in color to improve the differentiation between strengths, and ensure that the strength statement has adequate contrast with the background color. For example:



400 mcg/4 mL
(100 mcg/mL)



1000 mcg/10 mL
(100 mcg/mL)

B. Container Labels

1. Include the statement at the top of the principal display panel “4 mL Multi-Dose Vial” and “10 mL Multi-Dose Vial” to alert healthcare practitioners that the product is a multi-dose vial.
2. Increase the font size statement “Must be diluted” to increase the prominence of this important information.

C. Carton Labeling

1. Revise the statement “ (b) (4) ” on the 400 mcg/4 mL principle display panel to read “4 mL Multi-Dose Vial” to mitigate dosing errors. The statement should include the total volume of the solution (b) (4) . We have identified post-marketing error cases where confusion has occurred around the total contents of the (b) (4) , different from the total solution amount, has been used on the principal display panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

Table 2. Relevant Product Information for Dexmedetomidine Injection and the Listed Drug		
Product Name	Dexmedetomidine Injection	Precedex
Initial Approval Date	N/A	December 17, 1999
Active Ingredient	Dexmedetomidine	Dexmedetomidine
Indication	(b) (4)	
Route of Administration	Intravenous infusion	Intravenous infusion
Dosage Form	Solution for Injection	Solution for Injection
Strength	400 mcg/4 mL and 1,000 mcg/mL (100 mcg/mL)	200 mcg/2 mL 200 mcg/50 mL and 400 mcg/100 mL single use bottles

(b) (4)

<p>Dose and Frequency</p>	<p>Procedural Sedation-For adult patients: a loading infusion of 1 mcg/kg over 10 minutes. For less invasive procedures such as ophthalmic surgery, a loading infusion of 0.5 mcg/kg given over 10 minutes may be suitable.</p> <p>Alternative Doses- For awake fiberoptic intubation in adult patients: a loading infusion (b) (4)</p>	<p>(b) (4)</p>
<p>How Supplied/Container Closure</p>	<p>400 mcg/4 mL Multiple-dose clear glass vial 1000 mcg/10 mL Multiple-dose clear glass vial Packaged in cartons containing 4 vials per carton</p>	<p>Procedural Sedation-For adult patients: a loading infusion of 1 mcg/kg over 10 minutes. For less invasive procedures such as ophthalmic surgery, a loading infusion of 0.5 mcg/kg given over 10 minutes may be suitable.</p> <p>Alternative Doses- For awake fiberoptic intubation in adult patients: a loading infusion of 1 mcg/kg over 10 minutes.</p> <p>200 mcg/2 mL Single-dose clear glass vial 200 mcg/50 mL and 400 mcg/100 mL in clear glass bottles for single-use only.</p>
<p>Storage</p>	<p>Room temperature</p>	<p>Room temperature</p>

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Dexmedetomidine Injection that HQ Specialty Pharma submitted on May 12, 2014, and the listed drug (LD), Precedex.

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on December 8, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter²

Table 3: FAERS Search Strategy	
Date Range	October 28, 2013 (date of last search in OSE review# 2013-1918) to December 1, 2014
Product	Dexmedetomidine [active ingredient] Precedex[product name]
Event (MedDRA Terms)	Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Quality Issues (NEC)[HLT]

B.2 Results

Our search identified 2 cases, of which 2 described errors relevant for this review.

The first case (Case# 9789672) described a situation where the nurse incorrectly programmed the infusion pump and gave the whole Precedex infusion bag as a bolus. The patient died as a result of the overdose, and no root cause for the error was given. We reviewed the dosing and administration sections to determine if there is confusion related to bolus dosing and maintenance dosing of Precedex. We determined that the bolus and maintenance dosing are clearly delineated. In this case, it appears the pump was programmed incorrectly; thereby reflecting a performance deficit of the provider. Thus, DMEPA does not recommend any labeling changes based on these cases at this time.

The second case (Case# 10411894) described an error where a Precedex bag was prepared and labeled with the correct drug and fluid, but had an insulin infusion sticker accidentally applied directly above the hospital label. This error was not caught by the pharmacist or nurse involved in the case. The patient accidentally received the Precedex because the nurse thought this was the insulin infusion bag that the patient was also prescribed to receive. There was no adverse event since the patient was in sedation prior to administration to the unit. No root cause was

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

reported in the case. It appears that this case was a result of confusion due to internal hospital policies and labeling practices. Therefore, we did not further evaluate this case.

B.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

Case #	FDA Recd Date	Narrative	MFR Ctrl #
10411894	8/26/2014	<p>Description: This is a report of a medication error witnessed in the hospital. There was an order for Insulin Regular (Humilin R) 100 units in 100mL of 0.9 NaCl. The label on the Insulin IV bag was INCORRECT. The IV bag actually contained Precedex (Dexmedetomidine) 400mcg qs to 100 mL NS, which the bag clearly stated, and an Insulin Regular label was placed above where the bag said Precedex. So the initially error occurred during labeling. Then, as the pharmacist checked the IV bag before being brought to the floor, the error was not caught So the bag was brought to the floor and about half of the bag was administered to the patient before a nurse noticed the label error. there was no adverse event to the patient. The patient was on sedation prior to administration.</p> <p>Medication administered to or used by the patient: Yes</p> <p>Outcome: there was no adverse event to the patient. The patient was on sedation prior to administration.</p> <p>Where did the error occur: Hospital</p> <p>When and how was error discovered: Then, as the pharmacist checked the IV bag before being brought to the floor, the error was not caught. So the bag was brought to the floor and about half of the bag was administered to the patient before a nurse noticed the label error.</p>	N/A

Case #	FDA Recd Date	Narrative	MFR Ctrl #
9789672	12/27/2013	<p>Spontaneous report from the USA describing a case of fatal cardiac arrest, the pump was accidentally set bolus and not to maintenance infusion dose, patient received all the Precedex in a very short period of time and patient received a large amount of Precedex.</p> <p>A healthcare professional reported that a male patient (age unknown) received Dexmedetomidine Hydrochloride (Precedex; lot number, dose and frequency unknown, bolus) for an unknown indication on 28 Oct 2013. Medical history and concomitant medications were unknown.</p> <p>On 28 Oct 2013, the patient was in the ICU and received Dexmedetomidine Hydrochloride. It was reported there was a nursing error in the use of the product because the pump was accidentally set bolus and not to maintenance infusion dose. Accordingly, the patient received all the Precedex in a very short period of time and patient received a large amount of Precedex. Laboratory tests, diagnostic procedures and treatment were unknown. The reporter stated that due to the infusion of high dose of Precedex, the patient went to cardiac arrest and died.</p> <p>The patient died on an unknown date in 2013. Cause of death was reported as cardiac arrest. It was unknown if an autopsy was performed. The reporter's opinion of causality was unknown. Overall case causality: Possible</p> <p>The medication errors are not related as these are due to human error and not due to the pharmacologic effect of the suspect drug.</p> <p>The fatal cardiac arrest is possible. Temporally related and a potential sequela of the aforementioned medication errors.</p> <p>- (b) (4) (19 Dec 2013)</p>	2093016

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L Drive on December 8, 2014 using the terms, Precedex and Dexmedetomidine to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified 4 previous reviews¹²³⁴, and we confirmed that our previous recommendations were implemented or considered.

¹ Walker, M. Suitability Petition for Dexmedetomidine. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2012 MAR 22. 13 p. OSE RCM No.: 2012-2872.

² Winiarski, A. Label and Labeling Review for Precedex (NDA 021038). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 JUN 14. 9 p. OSE RCM No.: 2013-1314.

³ Kapoor, R. Label and Labeling Review for Precedex (NDA 021038). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 DEC 17. 12 p. OSE RCM No.: 2013-1918.

⁴ Holquist, C and Dallas, S. Label and Labeling Memo for Precedex (NDA 021038). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013-JUL-13. 8 p. OSE RCM No.: 2013-1949.

APPEARS THIS WAY ON ORIGINAL

APPENDIX E. ISMP NEWSLETTERS

E.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on December 1, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care Newsletter
Search Strategy and Terms	Match Any of the Words: Precedex; Dexmedetomidine

E.2 Results

Our search did not yield any articles or cases related to this review.

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

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

/s/

JAMES H SCHLICK
01/10/2015

BRENDA V BORDERS-HEMPHILL
01/12/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 206628	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: n/a Established/Proper Name: Dexmedetomidine Hydrochloride Dosage Form: Injection Strengths: 400ug/4mL; 1000ug/10mL		
Applicant: HQ Specialty Pharma Agent for Applicant (if applicable):		
Date of Application: May 12, 2014 Date of Receipt: May 12, 2014 Date clock started after UN:		
PDUFA Goal Date: March 12, 2015		Action Goal Date (if different):
Filing Date: July 11, 2014		Date of Filing Meeting: June 12, 2014
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): <ul style="list-style-type: none"> • sedation of non-intubated patients prior to and/or during surgical and other procedures <div style="background-color: #cccccc; width: 100%; height: 20px; margin-top: 5px;"></div>		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		
Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

	<input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
--	---

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 119008				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i>					
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
N021038	Precedex	M-61		June 17, 2016	
N021038	Precedex	Ped		December 17, 2016	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i>		<input type="checkbox"/>	<input checked="" type="checkbox"/>		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content	
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455	<input type="checkbox"/>	<input checked="" type="checkbox"/>		This is a literature

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<p>included with authorized signature per 21 CFR 54.4(a)(1) and (3)?</p> <p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				based NDA. The sponsor has not conducted any clinical trials and is not using any literature that from trial with which they have a financial interest.
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 12, 2014

BLA/NDA/Supp #: 206628

PROPRIETARY NAME: n/a

ESTABLISHED/PROPER NAME: Dexmedetomidine Hydrochloride

DOSAGE FORM/STRENGTH: Injection 400ug/4mL; 1000ug/10mL

APPLICANT: HQ Specialty Pharma

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): sedation of non-intubated patients prior to and/or during surgical and other procedure (b) (4)

BACKGROUND: This is a 505(b)(2) application that references Precedex as the listed drug. No studies were ever conducted under an IND. Preliminary responses were given in writing to a PIND meeting request.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Allison Meyer	y
	CPMS/TL:	Parinda Jani	n
Cross-Discipline Team Leader (CDTL)	Christopher Breder		y
Clinical	Reviewer:	Amelia Lockett	Y
	TL:	Christopher Breder	Y
Social Scientist Review (for OTC products)	Reviewer:	NA	N
	TL:	NA	N
OTC Labeling Review (for OTC products)	Reviewer:	NA	N
	TL:	NA	n
Clinical Microbiology (for antimicrobial products)	Reviewer:	NA	N

	TL:	NA	n
Clinical Pharmacology	Reviewer:	Srikanth Nallani	Y
	TL:	Yun Xu	Y
Biostatistics	Reviewer:	NA	N
	TL:	Janice Derr	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Newton Woo	Y
	TL:	Adam Wasserman	Y
Statistics (carcinogenicity)	Reviewer:	NA	N
	TL:	NA	N
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	NA	N
	TL:	NA	n
Product Quality (CMC)	Reviewer:	Xiaoben Shen	Y
	TL:	Julia Pinto	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Jessica Cole	N
	TL:		
CMC Labeling Review	Reviewer:	NA	N
	TL:	NA	N
Facility Review/Inspection	Reviewer:	NA	N
	TL:	NA	N
OSE/DMEPA (proprietary name)	Reviewer:	NA	N
	TL:	NA	N
OSE/DRISK (REMS)	Reviewer:	NA	N
	TL:	NA	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	NA	N
	TL:	NA	n

--	--	--	--

Bioresearch Monitoring (OSI)	Reviewer:	NA	N
	TL:	NA	N
Controlled Substance Staff (CSS)	Reviewer:	NA	n
	TL:	NA	N
Other reviewers	Lisa Skarupa, OSEPM		y
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO BE studies
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO If no, was a complete EA submitted? <input type="checkbox"/> YES <input type="checkbox"/> NO If EA submitted, consulted to EA officer (OPS)? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments:</p>	
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p>

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	NA
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Rigoberto Roca, MD, Deputy Division Director	

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 10/9/14

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>

ACTIONS ITEMS

<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and

	the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

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

/s/

ALLISON MEYER
09/18/2014

PARINDA JANI
09/19/2014