CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206628Orig1s000

SUMMARY REVIEW

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

Summary Review for Regulatory Action

Date	October 21, 2015
From	Rigoberto Roca, M.D.
Subject	Deputy Division Director Summary Review
NDA No.	206628
Applicant Name	HQ Specialty Pharma Corporation
Date of Original Submission	May 12, 2014 Complete Response letter issued March 12, 2015
Date of Complete Response Submission	April 21, 2015
PDUFA Goal Date	October 21, 2015
Proprietary Name / Established (USAN) Name	Dexmedetomidine hydrochloride injection
Dosage Forms / Strength	400 mcg/4mL 1000 mcg/mL
Proposed Indication	Sedation of non-intubated patients prior to and/or during surgical and other procedures
Action	Approval

Material Reviewed/ Consulted OND Action Package, including:	
Medical Officer Review	Amelia Luckett, MD
OPS/NDMS Microbiology Review	Jessica Cole, PhD; Dupeh Palmer, PhD
Project Management Staff	Allison Meyer; Parinda Jani
OMP/OPDP	Koung Lee; Jessica Fox; Samuel Skariah
OSE/DMEPA	James Schlick, MBA, RPh Vicky Borders-Hemphill, PharmD
OSE/DPV II	Martin Pollock, PharmD; Sara Camilli, PharmD; Scott Proestel, MD

CDTL = Cross-Discipline Team Leader
DMEPA = Division of Medication Error Prevention and Analysis
DPV II = Division of Pharmacovigilance II
NDMS = New Drug Microbiology Staff
OMP = Office of Medical Policy
OND = Office of New Drugs ONDQA = Office of New Drug Quality Assessment
OPS = Office of Pharmaceutical Sciences
OPDP = Office of Professional Drug Promotion
OSE = Office of Surveillance and Epidemiology

1. Introduction

The Applicant, HQ Specialty Pharma, submitted a 505(b)(2) application for dexmedetomidine hydrochloride, using Precedex® (NDA 21038) as the reference drug. The two formulations are very similar, except for the presence of two preservatives in the Applicant's formulation: [redacted] (b) (4). Due to the presence of these two preservatives, the Applicant was not able to file this application as a generic drug. Due to inadequate information about the preservative system, the application was issued a Complete Response letter on March 12, 2015. The Applicant submitted information to address the deficiency on April 21, 2015.

This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling requested by the Applicant. No primary review was required for this resubmission.

2. Background

Dexmedetomidine is an α_2-adrenergic agonist, originally approved for marketing in 1999 for the intravenous sedation of mechanically ventilated and intubated patients. A subsequent supplemental application added the additional indication of sedation of non-intubated patients prior to and/or during surgical and other procedures. Due to unexpired patents held by Hospira, the Applicant is only seeking the second indication.

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

3. Chemistry, Manufacturing, and Controls (CMC)

General Product Considerations

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

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

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

> The dexmedetomidine hydrochloride drug substance is manufactured by (b) (4) in (b) (4) per DMF (b) (4). The DMF has been last reviewed by this reviewer on 22-Jan- 2015 and deemed adequate. The drug substance manufacturer site EES status is acceptable.
>
> Specifications for dexmedetomidine hydrochloride drug substance include both USP and ICH requirements. Collectively they include appearance, identification, assay, impurities, heavy metals, loss on drying, residue on ignition, residual solvents, microbial limits and bacterial endotoxin. The drug substance is packaged in (b) (4). The drug substance stability data was referenced to DMF (b) (4), which is adequate to support its use in the NDA. It has a retest date of (b) (4) months.
>
> The drug product is available as 100 µg/mL injection solution filled as 4 mL (in 5 mL vial) and 10 mL (in 10 mL vial) packaging configurations. The excipients include methylparaben, propylparaben, and sodium chloride. All excipients are of compendial grades. The vials are made of USP Type 1 tubular glass. The vials are stoppered with (b) (4) rubber stopper (b) (4) The drug product is manufactured by (b) (4) in (b) (4). The drug product manufacturing site EES status is acceptable.
>
> The drug product specifications include appearance, identification, pH, assay, degradation products, particulate matter, extractable volume, sterility and bacterial endotoxins. The drug product primary stability studies were conducted on 3 batches for each packaging configuration. Up to 24 months of stability data is provided for the product stored under long term (25°C/60% RH) storage conditions and 6 months of stability data is provided for products stored under accelerated conditions (40°C/75% RH). For the tested quality attributes, appearance, assay, API related impurities and degradation products, particulate matter, container closure integrity, sterility and bacterial endotoxins results remained relatively stable and showed no trend during the time periods studied for all product strength/packaging configuration combinations and under all storage conditions. pH stayed relatively unchanged under long term storage conditions, it decreased under accelerated storage conditions although it remained well within specification. The assay of the two preservatives decreased over time but still within specification by 24 months. Consequently, their degradation product (b) (4) (b) (4) increased over time and reached (b) (4)% by month 24 when stored at 25°C/60% RH. This is well within the specification of no more than 1.0% of the total preservatives and deemed acceptable by pharm/tox. Overall, the provided stability data supports the applicant's proposed 36 month product expiry.

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

Product Quality Microbiology

Dr. Cole reviewed the product quality microbiology data that was submitted in response to the deficiency noted in the Complete Response letter issued on March 12, 2015. Dr. Cole's final assessment of the submitted information was that the product meets the USP <51> requirements at the minimum preservative levels in the specification. Therefore, the deficiency has been adequately addressed and Dr. Cole's recommendation was for approval of the application.

Facilities Review/Inspections

The facilities inspection during the first review cycle did not find anything that would preclude approval.

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Outstanding or Unresolved Issues

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

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

In addition, the deficiency noted in the Complete Response letter of March 12, 2015 has been adequately addressed with this submission. I concur with Drs. Shen, Pinto, Cole and Palmer that there are no product quality issues that would preclude approval.

4. Nonclinical Pharmacology/Toxicology

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

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

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

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

Outstanding or Unresolved Issues

I concur with the conclusions reached by Drs. Newton and Mellon that there are no pharmacology/toxicology issues that would preclude approval of this supplement. I also concur with their request to have the Applicant conduct a leachable assessment as a post-marketing requirement.

5. Clinical Pharmacology/Biopharmaceutics

There were no clinical pharmacology data submitted it in the original application. The Applicant requested a biowaiver from doing an in vivo bioequivalence study. The data and justification

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were reviewed by the biopharmaceutics team, found to be acceptable, and the Applicant's request was granted during the first review cycle.

There were no clinical pharmacology or biopharmaceutics deficiencies noted during the first review cycle; therefore, no additional clinical pharmacology data were required, or submitted for review, in this resubmission.

Outstanding or Unresolved Issues
There are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

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

7. Clinical/Statistical – Efficacy

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

Outstanding or Unresolved Issues
There are no unresolved efficacy issues that would preclude approval.

8. Safety

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

Dr. Luckett's review during the first review cycle details her findings after her review of the document, as well as her review of the literature citations found in the document. Her conclusions at the end of the first review cycle were that there were no new risks identified that would have precluded approval of this application.

In addition, the review team consulted the Office of Surveillance and Epidemiology for an assessment of the FDA Adverse Event Reporting System (FAERS) database for all adverse events from 2008 to the present. Their findings were that, and Dr. Luckett concurs, there are adverse events reported in the literature that warrant inclusion in "Section 6.2, Postmarketing Experience" of the package insert.

Lastly, the Applicant has submitted an update to their report of a literature review seeking to identify new adverse events that was submitted during the first review cycle. The update did not

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contain any new information that would alter the conclusions reached during the first review cycle.

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

9. Advisory Committee Meeting

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

10. Pediatrics

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

11. Labeling

The carton and container labels were reviewed, comments sent to the Applicant, and final agreed-upon carton and container labels were submitted during the first review cycle. The review team reviewed the proposed package insert and made modifications as appropriate. The package insert was sent to the Applicant during this review cycle and an agreement has been reached.

As noted above, representatives from the Office of Surveillance and Epidemiology, and the Office of Prescription Drug Promotion were consulted and their recommendations were incorporated during the discussion of the label during this review cycle. This included the addition to the WARNINGS AND PRECAUTIONS section that bradycardia and hypotension can have a fatal outcome, and the addition of QT prolongation, hypernatremia and rash to the ADVERSE EVENTS/Postmarketing Experience section.

12. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action
Approval.

Risk:Benefit Assessment

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I concur with the review team that the Applicant has now submitted adequate information to demonstrate that the multi-dose product is adequately preserved. This application can be approved at this time.

Recommendation for Postmarketing Risk Management Activities

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

> Conduct an adequate leachable safety assessment for the (b) (4) 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.

Recommendation for other Postmarketing Study Commitments

None.

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/s/

RIGOBERTO A ROCA
10/21/2015