CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206628Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	206628/N000
Submission Date:	05/12/14 and 12/22/14
Generic Name:	Dexmedetomidine HCL
Formulation:	Injectable Injection
Strength:	0.1mg/mL (0.4mg/4mL and 1.0mg/10 mL vials)
Applicant:	HG Specialty Pharma Corporation
Type of submission:	505(b)(2)
Reviewer:	Tien-Mien Chen, Ph.D.

SYNOPSIS

Background

Hospira's Precedex (Dexmedetomidine HCL) Injectable Injection was approved on 12/17/99 under NDA 21038 with one strength (0.1mg/mL) in one vial size (2 mL vial). Dexmedetomidine HCL is a relatively selective alpha2-adrenergic agonist for sedation.

A pre-IND119008 meeting was held on 09/24/13 to discuss the drug development plan of (Dexmedetomidine HCL) Injectable Injection.

Current Submission

On 05/12/14, HG Specialty Pharma Corporation submitted an original NDA 206628 seeking approval for Dexmedetomidine HCL, an Injectable Injection with one strength (0.1mg/mL) in two different vial sizes (0.4mg/4mL and 1.0mg/10 mL vials). This is a 505(b)(2) submission referencing Precedex (Dexmedetomidine HCL), the RLD (reference listed drug). A biowaiver request was also submitted. Per Agency's request on 12/11/14, additional information on justification for biowaiver was provided on 12/22/14.

Biopharmaceutics Review

The Biopharmaceutics review is focused on the evaluation and acceptability on the similarity assessment of the formulations between the proposed DP and the RLD.

RECOMMENDATION

From the Biopharmaceutics perspective, the biowaiver request and justification for waiving the *in vivo* bioequivalence (BE) study are reviewed and found acceptable. Therefore, the biowaiver is granted and this NDA is recommended for approval from biopharmaceutics perspective. No comment needs to be sent to the Applicant.

Tienmien Chen -A

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02/05/15

Tien-Mien Chen, Ph.D.
ONDQA Biopharmaceutics Acting Biopharm Lead

Date

Tapash K. Ghosh -S

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02/05/15

Tapash Ghosh, Ph.D.
ONDQA Biopharmaceutics Acting Branch Chief

Date

CC: DARRTS/NDA No.206628/N000\PSeo

PRODUCT QUALITY - BIOPHARMACEUTICS ASSESSMENT

BACKGROUND

Hospira's Precedex (Dexmedetomidine HCL) Injectable Injection was approved on 12/17/99 under NDA 21038 with one strength (0.1mg/mL) and one vial size (2 mL vial). Dexmedetomidine HCL is a relatively selective alpha2-adrenergic agonist indicated for:

(1)Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Administer Precedex by continuous infusion not to exceed 24 hours.

(2) Sedation of non-intubated patients prior to and/or during surgical and other procedures.

A pre-IND 119008 meeting was held on 09/24/13 to discuss the drug development of (Dexmedetomidine HCL) Injectable Injection.

CURRENT SUBMISSION

On 05/12/14, HG Specialty Pharma Corporation submitted an original NDA 206628 seeking approval for Dexmedetomidine HCL, an Injectable Injection with one strength (0.1mg/mL), but in two different vial sizes (0.4mg/4mL and 1.0mg/10 mL vials). This is a 505(b)(2) submission referencing Precedex (Dexmedetomidine HCL), the RLD (reference listed drug). A biowaiver request was also submitted which stated that:

The basis for this request is that the bioequivalence of the product is self-evident, according to the following criteria outlined in 21 CFR § 320.22:

Upon the Agency's request in the 09/24/13 IND meeting, the Applicant submitted a side-by-side comparison of the formulations between the proposed and the RLD. Per Agency's request on 12/11/14, additional information on justification for waiving the *in vivo* BE study was provided on 12/22/14.

BIOPHARMACEUTICS REVIEW

The Biopharmaceutics review is focused on the evaluation and acceptability on the similarity assessment of the formulations between the proposed DP and the RLD.

The basis of submitting a 505(b)(2) is stated by the Applicant as follows:

1. The active ingredient for the proposed drug product is the same as that of the RLD.
2. The route of administration, dosage form and strength of the proposed drug product are the same as those of the RLD when administered.
3. Composition of the proposed product differs from that of the RLD listed herein and therefore it is not eligible to submit as an ANDA under Section 505(j) of the FDC Act.
4. The labeling for the proposed drug product is the same as that of RLD, with the exception of those changes outlined in the annotated labeling.

DISSOLUTION METHODOLOGY AND ACCEPTANCE CRITERION

No dissolution methodology and acceptance criterion are needed.

FORMULATION COMPARISONS

The side-by-side comparison table of the proposed DP (Test) and the RLD (Ref) drug DP is shown below.

Table 1. The Side-by-Side Comparison of the Proposed vs. the Reference Drug Products

Product:	Proposed Drug Product	Reference Listed Drug
Product Proprietary Name:	None	Precedex®
Product Established name	Dexmedetomidine HCl	Dexmedetomidine HCl
Conditions of Use:	(b) (4) - sedation of non-intubated patients prior to and/or during surgical and other procedures	- sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting - sedation of non-intubated patients prior to and/or during surgical and other procedures
Active Ingredient(s):	Dexmedetomidine HCl	Dexmedetomidine HCl
Inactive Ingredients:	methylparaben propylparaben sodium chloride WFI	Sodium Chloride WFI
Route of Administration:	Injectable	Injectable
Dosage Form:	IV (Infusion)	IV (Infusion)
Strength:	100 µg/mL in 4 mL vial 100 µg/mL in 10 mL vial	100 µg/mL in 2mL vial

The only difference in the composition between the Test and Ref is the preservatives (Methylparaben and Propylparaben) added to the proposed drug product (Test).

In the IND119008 meeting on 09/24/13, the Agency responded to the Applicant's question #7 as shown below.

7. *Does the Agency agree with the waiver of bioavailability or bioequivalence?*

FDA Response:
Your proposal for a biowaiver request for your proposed product is reasonable. However, the final determination of the acceptability of the waiver request for the CFR requirement to provide in vivo bioequivalence data for your proposed product will be made during NDA review.

We recommend that, in your NDA submission, you provide adequate scientific information/data supporting the bridging of your proposed product to the reference product with a side-to-side summary table comparing your proposed product to the reference product (including description, formulation, pH, osmolality, drug concentration, indication, etc.). For any difference(s) between your proposed product and the reference product, justify why this difference(s) would not affect the safety and/or effectiveness of your proposed product.

However, the Applicant did not provide adequate scientific information/data per Agency's requests (except the side-by-side comparison table, Table 1) to support the bridging with justification for waiving the BE study. On 12/11/14, the Agent sent another information request and the Applicant responded on 12/22/14 as shown below.

Request:
Provide your justification to address any differences between your proposed drug product (Test) and the RLD (Reference), (i.e., the differences in terms of preservatives, pH, and osmolality, will not affect the safety and/or effectiveness of your proposed drug product).

Response:

Justification to address differences is included in "Justification of Differences between Proposed Drug Product and RLD Section as shown below.

Table 2. Justification of Differences between Drug Product and RLD

Product:	Proposed Drug Product	Reference Listed Drug	Justification of Differences
Product Proprietary Name:	None	Precedex®	Not applicable
Product Established name	Dexmedetomidine HCl	Dexmedetomidine HCl	NONE
Conditions of Use:	(b) (4) - sedation of non-intubated patients prior to and/or during surgical and other procedures.	- sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting - sedation of non-intubated patients prior to and/or during surgical and other procedures.	NONE; (b) (4) (b) (4) it was stated in PIND response that review of the published literature, reference to FDA previous determination of clinical safety and efficacy by reference to the Precedex Injection NDA 021038, is sufficient to support a 505(b)(2) NDA filing.
Active Ingredient(s):	Dexmedetomidine HCl	Dexmedetomidine HCl	NONE; there are no differences in drug substance impurities. API Supplier for RLD and HQs proposed product are the same.
Inactive Ingredients:	methylparaben, propylparaben sodium chloride WFI	Sodium Chloride WFI	HQ proposed product has addition of parabens. The parabens are commonly used excipients used to retard microbial growth. Amount of excipients used in formulation are below the IID limits allowed and do not affect the safety of the drug product. Addition of the parabens introduces degradation product, (b) (4). The proposed limit for the (b) (4) in formulation is not more than (b) (4) exposure, which is about (b) (4) times less than the LD_{50}. Please refer to Module 4.2.3.7 for further details and Module 3.2.P.8.3 for stability.
Route of Administration:	Injectable	Injectable	NONE
Dosage Form:	IV (Infusion)	IV (Infusion)	NONE
Strength:	100 µg/mL in 4 mL vial 100 µg/mL in 10 mL vial	100 µg/mL in 2mL vial	HQ proposed product has alternate vial sizes; no impact on patient dosing
Specifications			
- pH	(b) (4)	4.5 – 7.0	Differences in pH specifications do not impact safety of drug product. Data shows pH results on average of 5 which is within range of RLD.
- Osmolality	Isotonic	Isotonic	NONE

Reviewer's Comments:
For the injection drug products, certain preservatives within a certain amount are allowed as long as the Pharm/Tox. certifies the acceptability. From the Biopharmaceutics perspective, the justification provided is considered adequate provided no other discipline has any issue. Therefore, the biowaiver is granted and the NDA 206628 is recommended for approval.

CLINICAL PHARMACOLOGY REVIEW

NDA: 206628	Submission Date(s): 5/12/2014
Brand Name	Dexmedetomidine Injection
Generic Name	Dexmedetomidine HCl Injection
Clinical Pharmacology Reviewer	Srikanth C. Nallani, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia, Analgesia and Addiction Products
Sponsor	HQ Specialty Pharma Corporation.
Relevant IND(s)	NA
Submission Type	505(b)(2)
Formulation; Strength(s)	Intravenous Injection
Indication	IV infusion for sedation.
Proposed Dosage Regimen	Administer as an IV bolus followed by infusion.

HQ Specialty Pharma Corporation submitted a 505(b)(2) NDA application for approval of dexmedetomidine HCl with reference to safety and efficacy established previously in an approved NDA 021038 Precedex. There is no Clinical Pharmacology Data in the NDA. The sponsor has submitted biowaiver request and the ONDQA Biopharm team agreed to biowaiver for the IV product.

Table: Differences in RLD and proposed formulation

4 mL Vial	**10 mL Vial**	**RLD: Precedex**
Dexmedetomidine	Dexmedetomidine	Dexmedetomidine
Methylparaben	Methylparaben	NA
Propylparaben	Propylparaben	NA
Sodium Chloride	Sodium Chloride	Sodium Chloride
WFI	WFI	WFI

Labeling: The clinical pharmacology section in the proposed product label is similar to Precedex product label. It is noteworthy that Precedex product label was recently updated (11/14/2014).

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/s/

SRIKANTH C NALLANI
01/22/2015

YUN XU
02/03/2015

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**206628**	**Brand Name**	**Dexmedetomidine HCl Injection**
OCP Division (I, II, III, IV, V)	**DCP2**	**Generic Name**	**Dexmedetomidine HCl Injection**
Medical Division	**DAAAP**	**Drug Class**	**Sedative**
OCP Reviewer	**Srikanth C. Nallani, Ph.D.**	**Indication(s)**	**Sedation**
OCP Team Leader	**Yun Xu, Ph.D.**	**Dosage Form**	**IV Injection**
Pharmacometrics Reviewer		**Dosing Regimen**	**Infusion**
Date of Submission	**5/12/2014**	**Route of Administration**	**Intravenous Injection**
Estimated Due Date of OCP Review	**2/5/2015**	**Sponsor**	**HQ Speciality Pharma Corp**
Medical Division Due Date	**3/12/2015**	**Priority Classification**	**Standard**
PDUFA Due Date	**3/12/2015**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies				**Biowaiver Requested**
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**0**	**0**		**Biowaiver Requested**

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	Biowaiver Requested
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate			X	

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	hyperlinks and do the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?			X	Biowaiver
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	Biowaiver Requested
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
__YES_____

HQ Speciality Pharma Corporation submitted a 505(b)(2) NDA application for approval of dexmedetomidine HCl with reference to safety and efficacy established previously in an approved NDA 021038 Precedex. There is no Clinical Pharmacology Data in the NDA. The sponsor has submitted biowaiver sought at Pre-IND meeting where Biopharm team agreed to biowaiver for IV product (PIND responses sent on 9/24/2013)

Labeling: The clinical pharmacology section in the proposed product label is similar to Precedex product label. It is noteworthy that Precedex product label was recently updated.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None Identified.

Srikanth C. Nallani, Ph.D.	6/27/2014
Reviewing Clinical Pharmacologist	Date
Yun Xu, Ph.D.	6/27/2024
Team Leader/Supervisor	Date

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

/s/

SRIKANTH C NALLANI
06/27/2014

YUN XU
06/27/2014