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RESEARCH**

APPLICATION NUMBER:

201657Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 201-657	Reviewer: Elsbeth Chikhale, PhD	
Submission Date:	April 7, 2011		
Division:	Division of Metabolism and Endocrinology Products	Team Lead: Angelica Dorantes, PhD	
Applicant:	Hospira Inc.	Acting Supervisor: Angelica Dorantes, PhD	
Trade Name:	None proposed	Date Assigned:	April 28, 2011
Established Name:	Paricalcitol	Date of Review:	December 13, 2011
Indication:	Prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease stage 5.	Type of Submission: Original New Drug Application	
Formulation/ strengths	Solution for Injection/ 2 mcg/1 mL vial, 5 mcg/1 mL vial, and 10 mcg/ 2 mL vial		
Route of Administration	IV injection		
Type of Review:	Biowaiver Request		
<u>SUBMISSION:</u>			
<p>The proposed drug product is a sterile solution for IV injection containing paricalcitol as the active ingredient. Paricalcitol is a synthetically manufactured analog of calcitriol, the active metabolite of vitamin D. The proposed drug product is packaged in multi-dose vials of 2 mcg/1 mL vial, or 5 mcg/1 mL vial, or 10 mcg/2 mL vial. This application is an electronic NDA, filed as a 505(b)(2) application, with Zemplar as the reference listed drug (RLD). The difference between the proposed product and the RLD is in the amounts of the excipients, propylene glycol and alcohol (40% and 10% in the new proposed drug product vs. 30% and 20% in Zemplar). The ratio (b)(4) was modified to ensure complete solubilization of the active drug. The reference drug product was approved by the FDA under NDA 20-819 on 4/17/1998, for the prevention and treatment of renal osteodystrophy and secondary hyperparathyroidism associated with chronic renal failure.</p>			
<u>BIOPHARMACEUTIC INFORMATION:</u>			
<p>In this NDA submission, the Applicant is requesting a waiver of the <i>in vivo</i> bioequivalence study requirement as allowed under 21 CFR 320.22(b)(1)(i) and (ii). The applicant claims that the bioequivalence of the proposed drug product and the RLD is self-evident.</p>			
<u>Assessment of Biowaiver Request</u>			
<p>The compositions for the formulations of the proposed Hospira drug product and the RLD product are as follows:</p>			

Component	Hospira Quantity per Milliliter (mL)	Innovator Quantity per Milliliter (mL)	Function	Reference to Standards
Paricalcitol	2 mcg Or 5 mcg	2 mcg Or 5 mcg	Active ingredient	USP
Alcohol (b) (4)	(b) (4)	(b) (4)	(b) (4)	USP
Propylene Glycol	(b) (4)	(b) (4)	(b) (4)	USP
Water for Injection	(b) (4)	(b) (4)	Vehicle	USP/Ph Eur
Total Volume	1.00 mL	1.00 mL		
q.s. = Quantity sufficient				

The diluent of the RLD (Zemplar) consists of (b) (4) % water, 20% alcohol, and 30% propylene glycol (from the product labeling). The applicant, Hospira, proposes to use (b) (4) different concentrations for these (b) (4) % water, 40% alcohol, and 10% propylene glycol. According to CFR 320.22(b), for certain drug products the in vivo bioavailability (BA) or bioequivalence (BE) of the drug product may be self-evident and the Agency can waive the requirement for the submission of in vivo BA/BE data of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident if the drug product meets the following:

- Is a parenteral solution intended solely for administration by injection, and
- Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

The proposed drug product is a parenteral solution for administration by injection, and the proposed drug product has the same concentration of active ingredient (paricalcitol), and has the same dosage form, route of administration and indication as the RLD. However, the inactive ingredients of the proposed product and the reference product are different. Although, the CFR requires that the active and inactive ingredients for the test product are the same as the reference product, the difference in the inactive ingredients ((b) (4) propylene glycol) are not expected to impact the amount of drug delivered to the site of action, since this is an injectable dosage form administered as a bolus dose. Therefore, we consider that the in vivo BA/BE of the proposed Paricalcitol Injection is self-evident, and the Applicant's request for a biowaiver for their proposed Paricalcitol product is acceptable and the biowaiver is granted.

RECOMMENDATION:

A waiver of the *in vivo* bioequivalence study requirement is granted. From the Biopharmaceutics perspective, NDA 201-657 for Paricalcitol Solution for Injection (2 mcg/1 mL vial, 5 mcg/1 mL vial, and 10 mcg/ 2 mL vial) is recommended for approval.

Signature

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Signature

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

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/s/

ELSBETH G CHIKHALE
12/13/2011

ANGELICA DORANTES
12/13/2011

CLINICAL PHARMACOLOGY FILING CHECKLIST FOR NDA 20-2231

NDA Number: 20-1657

Applicant: Hospira Inc.

Stamp Date: April 7, 2011

Drug Name: Paricalcitol

NDA Type: Standard

On **initial** overview of the NDA application for RTF:

	Content Parameter	Yes	No	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?			The sponsor requested an in vivo bioequivalence waiver between their paricalcitol injection and ZEMPLAR [®] , the reference product.
2	Has the applicant provided metabolism and drug-drug interaction information?			NA
Criteria for Assessing Quality of an NDA				
Data				
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?			NA
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			NA
Studies and Analyses				
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			NA
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?			NA
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?			NA
8	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?			NA
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			NA
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			NA
11	Is the appropriate pharmacokinetic information submitted?			NA
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			NA

**CLINICAL PHARMACOLOGY
FILING CHECKLIST FOR NDA 20-2231**

General				
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?			This NDA does not contain clinical pharmacology and biopharmaceutical data.
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?			NA
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?			NA
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			NA
17	Was the translation from another language important or needed for publication?			NA

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

S. W. Johnny Lau, R.Ph., Ph.D.

Reviewing Pharmacologist

Date

Jayabharathi Vaidyanathan, Ph.D.

Acting Team Leader

Date

**CLINICAL PHARMACOLOGY
FILING CHECKLIST FOR NDA 20-2231**

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
General Information About the Submission				
Information		Information		
NDA	20-1657	Brand Name	To-be-determined	
OCP Division	2	Generic Name	Paricalcitol	
Medical Division	DMEP	Drug Class	Vitamin D analog	
OCP Reviewer	S.W. Johnny Lau	Indication(s)	Prevent & treat secondary hyperparathyroidism with chronic kidney disease Stage 5	
OCP Team Leader	Jayabharathi Vaidyanathan	Dosage Form	Sterile aqueous solution for intravenous injection	
Date of Submission	7-APRIL-2011	Dosing Regimen	0.04 µg/kg to 0.1 µg/kg as bolus no more frequently than every other day any time during dialysis. Dose may be increased by 2 to 4 µg at 2 to 4 week intervals.	
Estimated Due Date of OCP Review	3-Jan-2012	Route of Administration	Intravenous	
PDUFA Due Date	7-Feb-2012	Sponsor	Hospira Inc.	
Division Due Date	10-Jan-2012	Priority Classification	Standard	
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Comments (Study number)
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	X			Annotated labeling
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
In vivo mass balance:				
In vitro isozyme characterization:				
In vitro metabolite identity:				
In vitro metabolism inhibition:				
In vitro metabolism induction:				
In vitro mechanism of uptake in human liver				
In vitro plasma protein binding:				
Blood/plasma ratio:				
Pharmacokinetics (e.g., Phase I) -				
Dose proportionality, healthy volunteers – fasting & non-fasting single and multiple doses:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
pediatrics:				
gender & geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:				
Phase 3:				
PK/PD:				
Phase 2, dose ranging studies:				
Phase 2				

**CLINICAL PHARMACOLOGY
FILING CHECKLIST FOR NDA 20-2231**

Phase 3 clinical STUDIES (placebo controlled):				
Phase 3 clinical STUDIES (uncontrolled):				
Population Analyses -				
Meta-analysis:				
NONMEM:				
Population PK/PD analysis				
II. Biopharmaceutics				
Absolute bioavailability:				
Bioequivalence studies – traditional design				
Relative bioavailability				
alternate formulation as reference:				
Food-drug interaction studies:				
Absorption site				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Phenotype studies:				
Chronopharmacodynamics				
Pediatric development plan				
Literature References				
QT prolongation assessment				
Total Number of Studies				
Fileability and QBR comments				
	“X” if yes	Comments		
Application fileable?	X	Provided OND Biopharmaceutics grants the in vivo bioavailability waiver to the sponsor’s paricalcitol injection product, otherwise it may be a refusal to file		
Comments to be sent to firm?				
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CLINICAL PHARMACOLOGY FILING CHECKLIST FOR NDA 20-2231

Filing Memo

CLINICAL PHARMACOLOGY

NDA: 20-1657
Compound: Paricalcitol
Sponsor: Hospira Inc.
Submission Date: April 7, 2011
From: S.W. Johnny Lau, R.Ph., Ph.D.

Background

The sponsor is developing paricalcitol injection (2 and 5 µg/mL strengths) that has the same active ingredient, dosage form, strength, route of administration, and conditions of use as ZEMPLAR[®] manufactured by Abbott Laboratories. The sponsor had a pre-NDA teleconference with the Division of Metabolism and Endocrinology Products on July 29, 2010 for the following objectives:

- Obtain the Agency's agreement to file this 505(b)(2) application with an abbreviated stability package.
- Understand the Agency's expectations regarding the reporting of stopper extractables.
- Obtain the Agency's concurrence to use a waiver to meet the requirements for in vivo Bioavailability or Bioequivalence.

Clinical Pharmacology Findings

Formulation comparison of the sponsor's paricalcitol injection and Zemplar[®] follows:

Ingredients	Hospira's Paricalcitol Injection	Abbott's ZEMPLAR [®]
Each vial contains:		
Paricalcitol, USP, µg/mL	2 or 5	2 or 5
Propylene Glycol, USP, % (v/v)	10	30
Alcohol, USP, % (v/v)	40	20
Water for Injection, USP	q.s.	q.s.

Essentially, the sponsor reduced (b) (4) % propylene glycol and added (b) (4) % alcohol to the Zemplar[®] formulation and form their paricalcitol injection. The paricalcitol injection will have 2 strengths (2 and 5 µg/mL) and fill volume configurations (1 mL for the 2 and 5 µg/mL strengths and 2 mL for the 5 µg/mL strength) in multiple dose vials.

The sponsor requested a waiver of in vivo Bioavailability or Bioequivalence for their paricalcitol injection.

The sponsor provided annotated labeling for review.

The sponsor only provided Quality and Nonclinical (toxicology) data to support NDA 20-1657.

The sponsor did not provide any clinical study and data to support NDA 20-1657.

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/s/

S. W. JOHNNY W LAU
07/29/2011

JAYABHARATHI VAIDYANATHAN
07/29/2011

BIOPHARMACEUTICS FILLING REVIEW
Office of New Drugs Quality Assessment

Application No.:	NDA 201-657	Reviewer: Elsbeth Chikhale, PhD	
Submission Date:	April 7, 2011		
Division:	Division of Metabolism and Endocrinology Products	Team Lead: Angelica Dorantes, PhD	
Sponsor:	Hospira Inc.	Supervisor: Patrick Marroum, PhD	
Trade Name:	Paricalcitol Injection	Date Assigned:	April 28, 2011
Established Name:	Paricalcitol	Date of Review:	June 3, 2011
Indication:	Prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease stage 5.	Type of Submission: Original New Drug Application- 505(b)(2)	
Formulation/ strengths	Solution for injection/ 2 mcg/mL vial, 5 mcg/mL vial, and 10 mcg/ 2 mL vial		
Route of Administration	IV injection		

SUBMISSION:

The proposed drug product is a sterile solution for IV bolus injection containing paricalcitol as the active ingredient. Paricalcitol is a synthetically manufactured analog of calcitrol, the metabolically active form of vitamin D. The proposed drug product is packaged in vials of 2 mcg/mL vial, or 5 mcg/mL vial, or 10 mcg/2 mL vial. This application is an electronic NDA, filed as a 505(b)(2) application, with Zemplar as the reference listed drug (RLD). The difference between the proposed product and the RLD is in the amounts of the excipients propylene glycol and alcohol (40% and 10% in the new product vs. 30% and 20% in Zemplar).

BIOPHARMACEUTIC INFORMATION:

In this 505(b)(2) NDA submission, the applicant is requesting a waiver of the *in vivo* bioequivalence study requirement as allowed under 21 CFR 320.22(b)(1)(i) and (ii). The applicant claims that the bioequivalence of the proposed drug product and the RLD is self-evident.

The compositions for the formulations of the proposed Hospira drug product and the RLD product are as follows:

Component	Hospira Quantity per Milliliter (mL)	Innovator Quantity per Milliliter (mL)	Function	Reference to Standards
Paricalcitol	2 mcg Or 5 mcg	2 mcg Or 5 mcg	Active ingredient	USP
Alcohol (b)(4)	(b)(4)		Vehicle	USP
Propylene Glycol (b)(4)				USP
Water for Injection				USP/Ph Eur
Total Volume	1.00 mL	1.00 mL		
q.s. = Quantity sufficient				

The RLD diluent consists of (b)(4)% water, 20% alcohol, and 30% propylene glycol (from the product labeling). The applicant, Hospira, proposes to use (b)(4) different amounts: (b)(4)% water, 40% alcohol, and 10% propylene glycol.

The review of this submission will consist on the evaluation of the overall information supporting the biowaiver request. Please note that if during the review cycle the other reviewing disciplines (i.e., clinical and pharmacology/toxicology, etc.) do not have any safety concerns regarding the injection of a 40% alcohol solution, the biowaiver for the proposed Paricalcitol Injection product may be granted.

RECOMMENDATION:

The ONDQA/Biopharmaceutics team has reviewed NDA 201-657 for filing purposes. The sponsor has submitted a reviewable submission. There are no comments to be conveyed to the sponsor at this time.

NDA 201-657 is filable from a Biopharmaceutics perspective.

Signature

Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Signature

Biopharmaceutics Team Leader or Supervisor
Office of New Drugs Quality Assessment

cc: NDA 201-657

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/s/

ELSBETH G CHIKHALE
06/03/2011

ANGELICA DORANTES
06/03/2011