CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207174Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

12/3/14 (panorama)

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 207-174	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Date:	4/1/2014; 9/19/14		
Division:	DMEP	**Team Leader:** Tapash Ghosh, Ph.D.	
Applicant:	Accord Healthcare Inc.	**Acting Supervisor:** Paul Seo, Ph.D.	
Trade Name:	Paricalcitol Injection	**Date Assigned:**	4/2/2014
Generic Name:	Paricalcitol Injection	**Date of Review:**	12/2/2014
Indication:	the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease (CKD) Stage 5	**Type of Submission:** 505(b)(2) NDA	
Formulation/strengths:	Solution for Injection; 2 mcg/mL and 5 mcg/mL		
Route of Administration:	IV		

SUMMARY:

This submission is a 505(b)(2) New Drug Application for Paricalcitol Injection, 2 mcg/mL and 5 mcg/mL. The proposed indication is for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease (CKD) Stage 5.

The Applicant is requesting a waiver from requirements of submission of evidence demonstrating *in-vivo* bioequivalence for the proposed product to the reference product ZEMPLAR® (paricalcitol) Injection (NDA 20819 of AbbVie Inc.).

The Biopharmaceutics review of this NDA focuses on the evaluation and acceptability of the data/information supporting the biowaiver for the proposed product.

RECOMMENDATION:

A waiver from conducting an *in vivo* bioequivalence study is granted for Paricalcitol Injection, 2 mcg/mL and 5 mcg/mL. Thus, Paricalcitol Injection, 2 mcg/mL and 5 mcg/mL is recommended for approval from the Biopharmaceutics perspective.

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Tapash Ghosh, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Dr. Paul Seo

ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

1. Background

Drug Substance

The chemical structure of paricalcitol is illustrated in Figure 1.

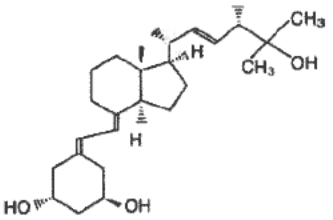

Figure 1. Chemical structure of paricalcitol

Drug Product

The proposed drug product is a clear aqueous solution intended solely for intravenous administration (refer to Table 1).

Table 2. Composition pf Paricalcitol Injection 2 mcg/mL (1 mL) and 5 mcg/mL (1mL and 2 mL)

Ingredients	**2 mcg/mL**	**5 mcg/mL**		**Function**	**Reference to quality standards**
	Quantity per 1 mL	**Quantity per 1 mL**	**Quantity per 2 mL**		
Paricalcitol	2.0 mcg[1]	5.0 mcg[1]	10.0 mcg[1]	Active	USP
Propylene Glycol	0.30 mL[2]	0.30 mL[2]	0.60 mL[2]	(b) (4)	USP & Ph.Eur#
Alcohol (Ethanol)	0.35 mL[3]	0.35 mL[3]	0.70 mL[3]	(b) (4)	USNF & Ph.Eur#
					USP & Ph.Eur#
					USNF & Ph.Eur#
Packaging material description of Paricalcitol Injection, 2 mcg/mL (1 mL) and 5 mcg/mL (1 mL and 2 mL)					
Container description	2 mL, clear glass vial (type I)				
Closure description	(b) (4) rubber stopper (b) (4)				

2. Biowaiver

The Applicant is requesting a waiver from requirements of submission of evidence demonstrating *in-vivo* bioequivalence for the proposed product to the reference product ZEMPLAR® (paricalcitol) Injection (NDA 20819 of AbbVie Inc.).

The active ingredient, route of administration, dosage form and strength of the proposed drug product is the same as those of the reference product ZEMPLAR®. The proposed product will contain the same concentration of the active ingredient as the reference product. However, the proposed drug product will differ from the formulation of the reference product in terms of its quantitative composition of excipient. The proposed product contains inactive

ingredient alcohol (ethanol) in a concentration which is different from that in the reference product. The comparison of the proposed and reference formulations is provided in Table 2.

Table 2. Comparative Formulations of Accord's Proposed Product and the Reference Product

Ingredients	Quantity per 1 mL			
	Accord's Paricalcitol Injection 2 mcg/mL	RLD Product: Zemplar® Injection 2 mcg/mL	Accord's Paricalcitol Injection 5 mcg/mL	RLD Product: Zemplar® Injection 5 mcg/mL
Active Ingredient				
Paricalcitol	2 mcg/mL	2 mcg/mL	5 mcg/mL	5 mcg/mL
Inactive Ingredients				
Propylene Glycol	30 % v/v	30 % v/v	30 % v/v	30 % v/v
Alcohol (Ethanol)	35 % v/v	20 % v/v	35 % v/v	20 % v/v
				(b) (4)

Reviewer's Assessment:

The Applicant has not provided comparative pH and osmolality data to justify why the formulation differences would not affect the safety and/ or effectiveness of the proposed product. The following IR comment was conveyed to the Applicant on September 8, 2014.

> **Provide your proposed drug product's osmolality and pH values and the analytical procedure/s used to measure them. Also provide the same information of your reference product.**

In a submission dated September 19, 2014, the Applicant provided comparative pH and osmolality data (refer to Tables 3-5).

Table 3. Comparative pH Data

Reference Product				
Product Name	**Batch No.:**	**Exp. Date:**	**pH**	**Marketed for**
Zemplar 2 mcg/ml, 1 ml	88-300-DK	04/2012	7.40	AbbVie Inc. North Chicago, IL 60064, U.S.A.
Zemplar, 5 mcg/ml, 1 ml	86-453-DK	02/2012	7.21	
Zemplar, 5 mcg/ml, 2 ml	21-540-DK	09/2014	7.90	
Applicant's Product				
Product Name	**Batch No.:**	**Mfg. Date:**	**pH**	**Marketed for**
Paricalcitol injection, 2 mcg/ml, 1 ml	N02228	02/2012	8.28	Accord Healthcare, Inc.
	N07904	07/2012	8.32	
	P04901	04/2013	7.93	
Paricalcitol injection, 5 mcg/ml, 1 ml	N07969	07/2012	8.42	
	N07953	07/2012	8.27	
	N07962	07/2012	8.28	
Paricalcitol injection, 5 mcg/ml, 2 ml	N07970	07/2012	8.25	
	N07954	07/2012	7.36	
	N07966	07/2012	8.19	

Table 4. Comparative Osmolality Data

Parameter	Reference Product (Zemplar)		Applicant's Product (Paricalcitol Injection)	
	2 mcg/ml, 1 ml	5 mcg/ml, 2 ml	2 mcg/ml, 1 ml	5 mcg/ml, 2 ml
Batch No.	88-300-DK	21-540-DK	P04901	N07954
Osmolality (mOsm/Kg) (1 mL product diluted to 10 mL with water)	783.7	808.7	1105	1122
Osmolality after multiplying with dilution factor (mOsm/Kg)	7837	8087	11050	11220
Osmolarity* (mOsm/L)	7829	8079	10995	11164

* Osmolarity values are calculated considering the density of Reference product = 0.999 g/mL and Applicant product = 0.995 g/mL of the diluted solution

Table 5. Calculation of Blood Osmolarity after Administration of the Proposed and Reference Products

2 mcg/ml strength	Applicant's product	Reference product
Osmolarity	10995 mOsm/L	7829 mOsm/L
Maximum Product being injected for 11 mcg dose	0.0055 L	00.0055 L
mOsmoles of solute/0.0055 L of product	60.5 mOsm/0.0055 L	43.1 mOsm/0.0055 L
Total mOsmoles of solute in 5.020 L of blood after Injection	1510.5 mOsmoles (1450 +60.5)	1493.1 mOsmoles (1450 + 43.1)
Total Theoritical Blood volume after Injection	5.0055 L	5.0055 L
Blood Osmolarity after Injection	302 mOsm/L	298 mOsm/L

5 mcg/ml strength	Applicant's product	Reference product
Osmolarity	11164 mOsm/L	8079 mOsm/L
Maximum Product being injected for 11 mcg dose	0.0022 L	0.0022 L
mOsmoles of solute/0.0022 L of product	24.6 mOsm/0.0022 L	17.8 mOsm/0.0022 L
Total mOsmoles of solute in 5.008 L of blood after Injection	1474.6 mOsmoles (1450 + 24.6)	1467.8 mOsmoles (1450 + 17.8)
Total Theoritical Blood volume after Injection	5.0022 L	5.0022 L
Blood Osmolarity after Injection	307 mOsm/L	293 mOsm/L

Note: The blood osmolarity is approximately 290 mOsm/L and the average volume of blood in human body is 5 Liter. Thus, the total solutes in the blood are 1450 mOsm/5 L.

Reviewer's Assessment:

The data in Table 3 shows that the pH of the Applicant's product and the reference product is comparable. The data in Table 4 demonstrates that the osmolality of applicant's product is slightly higher compared to reference product. However, the data in Table 5 shows that there is no significant difference in blood osmolarity after intravenous administration of the Applicant's product and the reference product.

Thus, a waiver from conducting an in vivo bioequivalence study is granted for the proposed product due to the following reasons:

1. ***The proposed product is a parenteral solution intended solely for administration by injection.***
2. ***The proposed product contains the same active ingredient in the same concentration as the reference product, ZEMPLAR® (paricalcitol) Injection.***
3. ***The difference in concentration of the inactive ingredients in the proposed product and the reference product, ZEMPLAR® (paricalcitol) Injection, should not affect the safety and/or effectiveness of paricalcitol as demonstrated by the similar pH and osmolality data.***

Kareen Riviere -S

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Tapash K. Ghosh -S

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