

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205917Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Application Number(s)	205-917
Priority or Standard	Standard
Submit Date(s)	June 7, 2013
Receipt Date(s)	October 18, 2013
user fee received	
Revised PDUFA Goal due to major amendment	November 18, 2014
Division / Office	DMEP/ODEII
Reviewer Name(s)	William Lubas, M.D., Ph.D.
Review Completion Date	October 21, 2014
Established Name	Paricalcitol
(Proposed) Trade Name	(Paricalcitol) Injection
Therapeutic Class	Bone-Vitamin D
Applicant	Hikma Pharmaceuticals Co LTD c/o Exela Pharma Sciences LLC
Formulation(s)	injection
Dosing Regimen	 (b) (4) no more frequently than every other day
Indication(s)	Prevention and Treatment of Secondary Hyperparathyroidism
Intended Population(s)	Patients on Hemodialysis

Template Version: March 6, 2009

## Table of Contents

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>	<b>6</b>
1.1	Recommendation on Regulatory Action .....	6
1.2	Risk Benefit Assessment.....	6
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	6
1.4	Recommendations for Postmarket Requirements and Commitments .....	6
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND .....</b>	<b>6</b>
<b>4</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES .....</b>	<b>7</b>
4.1	Chemistry Manufacturing and Controls .....	7
4.2	Clinical Microbiology.....	8
4.3	Preclinical Pharmacology/Toxicology .....	8
4.4	Biopharmaceuticals .....	9
<b>5</b>	<b>SOURCES OF CLINICAL DATA.....</b>	<b>9</b>
<b>6/7</b>	<b>REVIEW OF EFFICACY AND SAFETY .....</b>	<b>9</b>
<b>9</b>	<b>APPENDICES .....</b>	<b>10</b>

## Table of Tables

Table 1 Paricalcitol Formulations .....	6
Table 2 Toxicokinetic Data .....	8

## Table of Figures

Figure 1 Chemical Structure of Paricalcitol .....	7
---	---

## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

This application should be approved.

### 1.2 Risk Benefit Assessment

The information submitted in this application support the safety and efficacy of this 505(b)(2) product as described in the revised package insert.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

### 1.4 Recommendations for Postmarket Requirements and Commitments

None

## 2 Introduction and Regulatory Background

Paricalcitol, is a synthetically manufactured metabolically active form of vitamin D indicated for the prevention and treatment of secondary hyperparathyroidism in patients with chronic kidney disease (CKD). Paracalcitol is currently available in the US, as the active ingredient in Zemplar® injectable, in 1 and 2mL single dose Fliptop vials containing 2 or 5µg/mL solution. In this application, Hikma is submitting a 505(b)(2) application for another paricalcitol injectable with a novel formulation. Hikma, Paricalcitol contains the same active ingredient as Zemplar® (paricalcitol) injection, but has different amounts of (b) (4) propylene glycol and sorbitol.

**Table 1 Paricalcitol Formulations**

	<b>Abbott (Zemplar)</b>	<b>Hikma/Exela (Paricalcitol)</b>
% (b) (4) v/v	20	35
%propylene glycol	30	0
% water		(b) (4)
% Sorbitol v/v	0	7

The original application was submitted 7 June 2013. However, the sponsor did not include a user fee in the original submission so the receipt date for the application was not listed until 18, Oct. 2013 when the user fee was finally received. Filing issues with

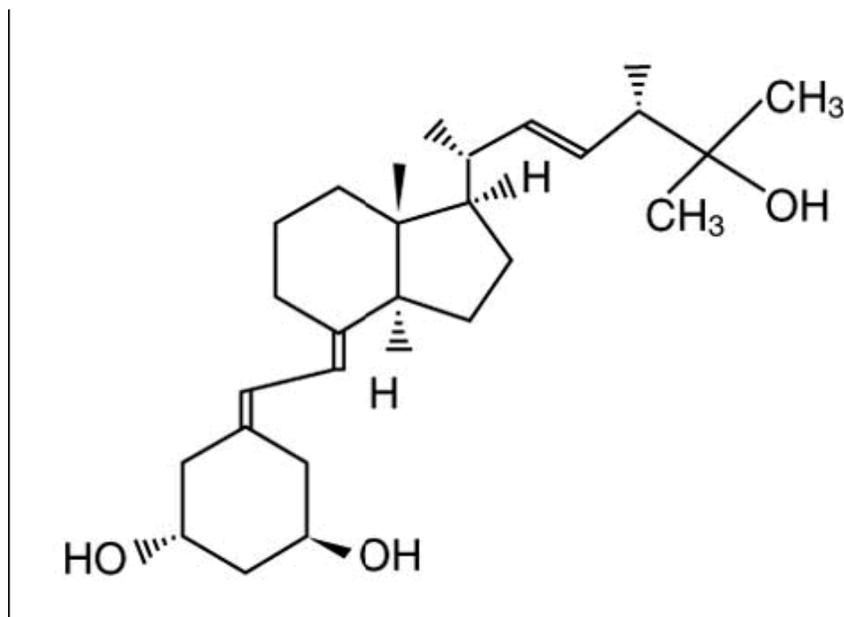
respect to CMC were identified and an information request was sent to the sponsor in a letter dated 31 Dec 2013. The sponsor's formal response to the information request was not submitted until 2 July 2014 necessitating a 3 month clock extension for a major amendment. The current PDUFA due date is 18 Nov. 2014.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

Paricalcitol is a synthetic, biologically active vitamin D2 analog with modifications to the side chain (D2) and the A (19-nor) ring. Paricalcitol Injection, will be available as a sterile, colorless, solution in 1 or 2mL glass vials sealed with (b) (4) rubber stoppers and will be further packaged in a single unit carton. The 2mcg/mL presentation is supplied as a 1.0 mL single-dose vial. The 5mcg/mL presentation is supplied as both a 1.0 mL and a 2.0mL single-dose vial. The drug product has a shelf life of 24 months when stored at  $25 \pm 2^\circ\text{C}/60\% \text{RH}$ . Paricalcitol Injection is intended for intravenous use without further dilution and is meant for single use only and does not contain any preservative.

**Figure 1 Chemical Structure of Paricalcitol**



The Chemistry Review was performed by Dr. Muthukumar Ramaswamy. The sponsor's response to the original information request was found acceptable as all CMC

deficiencies were adequately resolved. The chemistry review recommends approval of the current application.

#### 4.2 Clinical Microbiology

The drug product is formulated (b) (4) 2mL glass vials. The vials are stoppered and secured with aluminum over seals. Sealed units are (b) (4) The microbiology review by Dr. Robert Mello stated that the applicant had demonstrated adequate controls over the manufacturing process to mitigate the sterility and (b) (4) to the final drug product and recommended approval for these single use vials.

#### 4.3 Preclinical Pharmacology/Toxicology

A 4-week intravenous rat toxicity study with a 2-week recovery period comparing Hikma's and Abbott's paricalcitol products was performed to comply with pharm/tox's request for a bridging study. The study was required even though the active ingredients in the products (b) (4) formulations are different with respect to the amount of (b) (4) propylene glycol and sorbitol which could potentially affect the efficacy and safety of the new product. The pharm/tox review by Drs. Espandiar and Davis-Bruno indicates no significant toxicokinetic or toxicity profile difference between the Hikma paricalcitol formulation and the approved listed drug of Zemplar.

Toxicokinetic data were similar for both compounds except for slightly higher C<sub>max</sub> in the Zemplar group compared to the paricalcitol group on Day 27.

**Table 2 Toxicokinetic Data**

Day	Test Article	Group	Dose (µg/kg)	Sex	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	C <sub>max</sub> (ng/mL)	AUC <sub>last</sub> (hr*ng/mL)	AUC <sub>0-∞</sub> (hr*ng/mL)
1	Paricalcitol	7	1	Male	0.250	2.63	16.2	34.8	53.8
				Female	0.083	1.49	18.9	25.9	30.3
	Paricalcitol	8	3	Male	0.083	2.44	49.7	92.7	133
				Female	0.083	1.28	53.1	68.6	76.6
	Zemplar	9	1	Male	0.083	2.57	15.3	27.6	41.2
				Female	0.083	1.59	18.2	23.6	28.6
	Zemplar	10	3	Male	0.083	2.00	55.7	90.4	116
				Female	0.083	1.36	62.0	69.6	79.1
27	Paricalcitol	7	1	Male	0.083	3.13	14.5	27.4	48.5
				Female	0.083	2.67	14.7	22.1	34.0
	Paricalcitol	8	3	Male	0.250	NR <sup>1</sup>	30.1	69.8	NR
				Female	0.500	NR	16.2	44.9	NR
	Zemplar	9	1	Male	0.083	3.28	28.8	28.1	48.2
				Female	0.083	1.48	17.3	21.6	25.1
	Zemplar	10	3	Male	0.083	1.84	67.1	88.8	115
				Female	0.250	2.33	26.3	44.9	65.0

<sup>1</sup>NR = Not reportable, due to poor goodness-of-fit ( $R^2 < 0.8$ ) for the elimination phase.

These differences at higher dose level did not affect the potential toxicity of the new formulation based on the histopathology incidences provided. Therefore, the pharm/tox review found the bridging study to be adequate and recommended approval of this product.

#### 4.4 Biopharmaceuticals

Dr. Noory reviewed the application and granted a biowaiver for this intravenous product.

### 5 Sources of Clinical Data

No clinical studies were included in this submission. Safety and efficacy were derived from literature relating to the currently approved product Zemplar (paricalcitol) Injection.

### 6/7 Review of Efficacy and Safety

Preclinical and *in vitro* studies from the literature have demonstrated that paricalcitol's biological actions are mediated through binding to the Vitamin D receptor, which results in the selective activation of Vitamin D responsive pathways. Paricalcitol therefore has been shown to reduce PTH levels by inhibiting PTH synthesis and secretion and so should be effective for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease.

The chemistry review showed the active ingredient, paricalcitol, in the Hikma product (b) (4) (b) (4) the paricalcitol in the currently approved and marketed Zemplar injectable. The observed differences in the pharmtox bridging animal study between Zemplar and the Hikma product did not correspond to any clinically relevant differences that would affect the safety or efficacy of this 505(b)(2) product. Therefore, no clinical trials were required as part of this submission.

However, as it was noted that the new formulation has a higher (b) (4) concentration (35%) than the innovator product (20%). Since (b) (4) could be potentially toxic to cells, this medical officer was concerned that the higher concentration of (b) (4) in the new formulation might be potentially toxic to endothelial cells if the product was directly injected into a vein or artery. This could be especially problematic if the endothelial toxicity affected the patency of the patient's AV fistula.

That said, it is possible to mitigate the potential toxicity by injecting the drug product directly into an injection port on the dialysis machine during dialysis. Given the flow rate in the dialysis machine is around 300mL/min or 5mL/sec a typical 1 mL (5 µg) bolus

injection, which should take at least one second to complete, should be adequately diluted in the hemodialysis machine tubing as it mixes with 5 mL of blood resulting in an <sup>(b) (4)</sup> concentration of no greater than 6% before it would gain access to a patient's circulation. Similar results would be expected for a typical 2 mL dose (10 µg) which should take at least 2 seconds to complete. To avoid this potential toxicity the sponsor has agreed to label the product to be injected into a port in the dialysis machine at any time during dialysis and not to be injected directly into a vein.

#### **Pediatrics-**

The sponsor is seeking a full waiver from the requirement for pediatric studies as the new formulation does not include a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration. This medical reviewer agrees that such a waiver is appropriate for this new formulation.

## **9 Appendices**

None

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

/s/  
-----

WILLIAM A LUBAS  
10/21/2014

DRAGOS G ROMAN  
10/21/2014



## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1  Indication:				
	Pivotal Study #2  Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	No clinical data submitted
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	No clinical data submitted
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	No clinical data submitted
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			X	No clinical data submitted
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	No clinical data submitted
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	Relying on Reference Listed Drug Zemplar
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	No clinical data submitted
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	No clinical data submitted
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?			X	No clinical data submitted
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	Due to the presence of sorbitol and a higher concentration of

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					(b) (4) (35% vs. 20%) compared to the RLD, Zemplar®, the sponsor submitted as a bridging study a 4-Week, 3-Times Weekly, Intravenous Toxicity and Toxicokinetic Study in Rats with a 14-Day Recovery Period
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	No clinical data submitted
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	This application did not trigger PREA.
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	Drug is unlikely to be abused.
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	No clinical data submitted
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	No clinical data submitted
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	No clinical data submitted
34.	Are all datasets to support the critical safety analyses available and complete?			X	No clinical data submitted
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	No clinical data submitted
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	No clinical data submitted
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	No clinical data submitted
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial			X	No clinical data

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Disclosure information?				submitted that requires financial disclosure
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	No clinical data submitted

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_\_ Yes \_\_\_**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

William Lubas MD, PhD  
 \_\_\_\_\_  
 Reviewing Medical Officer Date

Dragos Roman MD  
 \_\_\_\_\_  
 Clinical Team Leader Date

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

/s/  
-----

WILLIAM A LUBAS  
09/16/2013

DRAGOS G ROMAN  
09/17/2013