CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207174Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	207174
Supporting document/s:	1
Applicant's letter date:	4/01/2014
CDER stamp date:	4/01/2014
Product:	Paricalcitol Injection
Indication:	Prevention/treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5
Applicant:	Accord Health Care Inc.
Review Division:	DMEP
Reviewer:	Parvaneh Espandiari, Ph.D.
Supervisor/Team Leader:	Karen Davis-Bruno, Ph.D.
Division Director:	Jean-Marc Guettier, M.D.
Project Manager:	Meghna M Jairath, Pharm.D.

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of [NDA 207174] are owned by [Accord Health Care Inc.] or are data for which [Accord Health Care Inc] has obtained a written right of reference.

Any information or data necessary for approval of [NDA 207174] that [Accord Health Care Inc.] does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of [NDA 207174].

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1 Executive Summary

1.1 Introduction

The Sponsor proposed a new drug application (new formulation of Paricalcitol) under section 505(b)(2) for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease (CKD) Stage 5. The listed drug (LD) is Zemplar™ (NDA 020819, owned by Abbott Laboratories) for the same indication and for the same patient population. The safety profile of the Zemplar has been well established; therefore, nonclinical (pharmacology, pharmacokinetics and toxicology) studies for the new formulation are relying on the previous findings of the safety and efficacy for Zemplar.

The new formulation has the same active ingredient (paricalcitol) and inactive ingredient (propylene glycol) of the LD; however, it has different level of alcohol (35% v/v vs. 20% v/v in Zemplar). The level of alcohol is within Inactive Ingredients Guidance (IIG) limits for other marketed i.v. products and additional toxicity/safety studies are not required for qualification of the inactive ingredient for the new formulation.

The Sponsor conducted a 4-week repeat-dose toxicity study in rats with a 2-week recovery period to assess the potential toxicity of the new formulation to the approved LD Zemplar.

1.2 Brief Discussion of Nonclinical Findings

Results of the nonclinical study suggested similar TK and/or toxicity profile between the new formulation of Paricalcitol to the approved LD of Zemplar.

1.3 Recommendations

None

1.3.1 Approvability

Yes

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Section 8.1 Pregnancy

Same as the LD (Zemplar)

Section 8.3 Nursing Mothers

Same as the LD (Zemplar)

Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Same as the LD (Zemplar)

2 Drug Information

2.1 Drug

CAS Registry Number: 131918-61-1

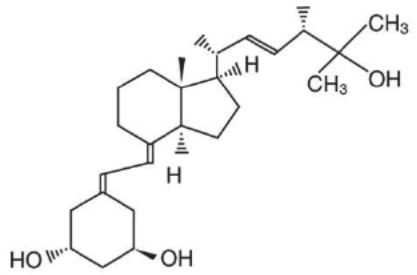
Generic Name: Analog of (b) (4) the metabolically active form of vitamin D

Code Name: NA

Chemical Name: (b) (4)

Molecular Formula/Molecular Weight: $C_{27}H_{44}O_3$/416.64 g/mol

Structure or Biochemical Description:



Pharmacologic Class: Vitamin D (b) (4) the metabolically active form of vitamin D

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 20819 (Zemplar™); DMF (b) (4) (Paricalcitol); ANDA 090,829; ANDA 091; ANDA 091,412108; NDA 018,044; NDA 018,874; NDA 020,862; PIND 113078; IND (b) (4); IND 020,889; IND 031,423; IND (b) (4) IND (b) (4); IND (b) (4); IND (b) (4); IND (b) (4); IND (b) (4); IND (b) (4); IND (b) (4); IND (b) (4); IND (b) (4); IND (b) (4); and IND (b) (4).

2.3 Drug Formulation

The proposed new formulation has different alcohol level compared to the LD (35% vs, 20% in LD). Alcohol is approved for use in concentrations up to 49% in i.v. infusion and injection dosage forms (FDA database, for Inactive Ingredient Search for Approved Drug Products). Sponsor's Tables:

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]		USNF & Ph.Eur#
	(b) (4)	(b) (4)	(b) (4)		(b) (4)

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)

USP: United States Pharmacopoeia
USNF: United States National Formulary
Ph. Eur: European Pharmacopoeia

(b) (4)

We are committing reference quality standards for the excipients USP/USNF grade only.

Comparative formulations of Accord's proposed product and Listed Drug

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)

Formulation comparison & IIG limit of excipients:

Ingredients	Amount in % (Accord)	Amount in % (RLD)	IIG levels in %	Remarks
Propylene Glycol	30 %	30 %	82.04 %	Below IIG Limit
Alcohol (Ethanol)	35 %	20 %	80.00 %	Below IIG Limit

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

The Sponsor refers to the DMF (b) (4) for Paricalcitol.

2.6 Proposed Clinical Population and Dosing Regimen

- Patients with secondary hyperparathyroidism associated with chronic kidney disease Stage 5
- The recommended initial dose is 0.04 mcg/kg to 0.1mcg/kg (2.8 to 7 mcg) as bolus dose no more frequently than every other day at any time during dialysis.

2.7 Regulatory Background

On August 5, 2011, the Sponsor requested a meeting to discuss the new paricalcitol injection formulation development program for the prevention and treatment of secondary hyperparathyroidism associated with CKD under 505(b)(2) application. See below for PIND (113078) T-con on October 29, 2011:

> **Sponsor Question 4:** The proposed product is an injection that contains the same concentration of the active ingredient as in the reference listed drug, Zemplar®. The inactive ingredients that will be used are listed in the Inactive Ingredient Database (IIG), and have been previously approved for use in the same route of administration, at levels above those reflected in the formulation for Accord's proposed product.
>
> Since Accord intends to rely on the agency's finding of safety for the Reference Listed Drug, Zemplar® and in light of the previously approved levels of the inactive ingredients contained in the proposed formulation, Accord believes that no additional toxicological studies would be required for the NDA. Does the agency agree?
>
> **FDA Preliminary Comment: No, we do not agree. Concerning the inactive ingredient, the level of (b) (4) alcohol is within Inactive Ingredients Guidance (IIG) limits for other marketed products and additional toxicity/safety studies are not required for qualification of the inactive ingredient in your formulation. However, the manufacturing process for your paricalcitol product is likely to differ from that of the listed drug (LD) Zemplar and therefore the impurities/degradants profile might also differ. These differences may require qualification with comparative bridging toxicology studies.**

The 505(b)(2) approval pathway may be used for a product that is sufficiently similar to an approved product to permit reliance, where scientifically justified, on certain existing information (including the FDA's finding of safety and/or effectiveness for an approved drug product) for approval of a new drug application. You should establish a bridge between the proposed product and the LD to demonstrate that such reliance is scientifically justified. An assessment of similarity between these two products may include comparative physiochemical and biological studies, bridging toxicology studies which allow for a comparison between the products, pharmacokinetic/pharmacodynamic and or clinical data as appropriate. You must establish that reliance on the FDA's prior finding of safety and/or effectiveness for the LD is scientifically appropriate for your product and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the LD. A bridging nonclinical toxicology study (GLP) using a head-to-head comparison between the Accord product and the LD with toxicokinetics and the recovery period in a relevant species is recommended to address these concerns.

Meeting Discussion: Sponsor inquired about doing a toxicity study. We stated that a study is needed to link and compare the proposed product to the listed drug and to identify any impurities/degradants which exceed the USP monograph. Sponsor further inquired the details of what needs to be included in the toxicity study. We stated that a repeat dose toxicity study for either one or three months in a single relevant species (preferably rodents) with GLP standard endpoints and the recovery time.

On April 1, 2014, the Sponsor submitted NDA207174 application under section 505(b)(2) for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5.

3 Studies Submitted

A 7-Day dose range finding study in rats "Repeated Dose 7-Day Dose Range Finding Toxicity Study of Paricalcitol Injection Through Intra Venous Bolus Injection in Wistar Rats".
A 4-week repeat dose toxicity study in rats "Repeated Dose 28-Day Study of Paricalcitol Injection with Toxicokinetics Through Intravenous Bolus Injection in Wistar Rats".

3.1 Studies Reviewed

All

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

None

4 Pharmacology

4.1 Primary Pharmacology

No new information.

Paricalcitol, a synthetically manufactured [redacted] (b) (4) active form of vitamin D. Its biological actions are mediated through binding of the vitamin D receptor (VDR), which results in

the selective activation of vitamin D responsive pathways. Vitamin D and Paricalcitol have been shown to reduce parathyroid hormone levels by inhibiting PTH synthesis and secretion.

4.2 Secondary Pharmacology

No new information.

4.3 Safety Pharmacology

No new information.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No new information.

5.2 Toxicokinetics

TK data is included in the toxicity study.

6 General Toxicology

A 7-Day dose range finding study was performed with paricalcitol injection (i.v.) in rats to select dose levels for the actual bridge toxicity study between the new formulation and the approved LD (Zemplar). Based on results of this study, the 4-week repeat dose toxicity study in rats with a 2-week recovery period was conducted with the new paricalcitol formulation (up to 3µg/kg) and the approved LD (at 3µg/kg/day). Findings of this study showed consistency between the toxicity profiles and TK data of the new formulation to the LD.

6.2 Repeat-Dose Toxicity

Study title: Repeated Dose 28-Day Toxicity Study of Paricalcit9l Injection with Toxicokinetics through Intravenous Bolus Injection in Wistar Rats	
Study no.:	411-1-02-7977
Study report location:	eCTD
Conducting laboratory and location:	(b) (4)
Date of study initiation:	December 12, 2013
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Paricalcitol; lot#: N07970; and purity 100.40% Zemplar; lot#: 21-540-DK; and purity 97.1%

Key Study Findings:

Toxicity profiles and TK data were similar for both new formulations and the approved LD.

Methods	
Frequency of dosing:	Three times/week
Dose volume:	Paricalcitol: 0, 0.3, 1.5 and 3µg/kg/day; Zemplar: 3µg/kg/day; Recovery groups: 0 and 3µg/kg/day
Formulation/Vehicle:	Normal Saline (Sodium Chloride 0.9% w/v)

Species/Strain:	Wistar rats
Number/Sex/Group:	10/sex/group
Age:	8-9 weeks
Weight:	Males: ~236g; Females:~176g
Satellite groups:	10/sex/group
Unique study design:	Recovery groups= 10/sex/group
Deviation from study protocol:	None

Observations and Results

Mortality

None

Clinical Signs

Unremarkable

Body Weights

Unremarkable

Feed Consumption

Unremarkable

Hematology

Unremarkable

Clinical Chemistry

Increased serum levels of calcium (ss at HD in males and at MD in females) and phosphorus (ss at HD in both genders) were noted in new paricalcitol formulation treated animals. In the comparator treated animals, the serum calcium and phosphorus decreased in males. These changes are related to the pharmacological effects of paricalcitol and not noted in the Recovery study.
Tables below were modified from Sponsor's Tables:
In Males:

Parameters	Main Groups									
	G1 (N=10)		G2 (N=10)		G3 (N=10)		G4 (N=10)		G5 (N=10)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Calcium (mg/dL)	10.52	0.27	10.60	0.29	10.71	0.19	11.04↑↑	0.42	10.22↓	0.16
Phosphorus (mg/dL)	6.77	0.28	7.28↑	0.47	7.62↑↑	0.42	8.33↑↑	0.58	6.17↓	0.40

In Females:

Parameters	Main Groups									
	G1 (N=10)		G2 (N=10)		G3 (N=10)		G4 (N=10)		G5 (N=10)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Calcium (mg/dL)	10.41	0.31	10.52	0.26	10.93↑	0.36	10.69	0.46	10.79	0.31
Phosphorus (mg/dL)	5.63	0.49	6.04	0.89	6.63↑↑	0.76	6.68↑↑	0.53	7.00↑↑	0.86

Dose: G1: 0; G2: 0.3; G3: 1.5; G4:3; G5: 3 µg/kg b.wt.

Urinalysis

Unremarkable

Gross Pathology

Unremarkable

Organ Weights

Unremarkable

Histopathology

Adequate Battery: Yes, the histopathological evaluation was performed only for tissues that were treated with control or HD (3µg/kg/day of Paricalcitol or Zemplar) groups.

Peer Review: Yes

Histopathological findings:

Kidneys: At HD, increased mineralization in the cortex was reported only for male rats with both formulations as follows: paricalcitol (1/10) and LD (2/10). In addition, hyperplasia (transitional epithelium) and pelvis with inflammatory cells (epithelial/subepithelial) were noted only in HD treated females with new formulation. However, these findings in the kidneys are less concerning because of the subjects not having normal renal function.
Tails: lesions were noted in different treated groups which were related to the method of test administration.

The rest of microscopic lesions in different organs were at lower rate and according to the Sponsor these changes were considered to be spontaneous or incidental in rats of this age (Sponsor's Tables):

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Toxicokinetics

In general TK data for both formulations was similar for both time points (Day 1 and Day 28). Paricalcitol C_{max} increased with a dose levels in both Day 1 and 28 and was similar in both treated male and female rats. However, AUC and $t_{1/2}$ of paricalcitol were higher in treated males compared to treated females (Sponsor's Table):

(b) (4)

Dosing Solution Analysis

According to the Sponsor, the results of dose formulation samples collected on days 1 and 28 for Paricalcitol Injection and comparator were within the range of + 10 % of nominal concentration.

7 Genetic Toxicology

No genotoxicity studies were submitted

8 Carcinogenicity

No carcinogenicity studies were submitted

9 Reproductive and Developmental Toxicology

No reproductive studies were conducted

11 Integrated Summary and Safety Evaluation

Paricalcitol, a synthetically manufactured (b) (4) active form of vitamin D. Its biological actions are mediated through binding of the vitamin D receptor, which results in the selective activation of vitamin D responsive pathways. Vitamin D and Paricalcitol have been shown to reduce parathyroid hormone levels by inhibiting PTH synthesis and secretion.

The Sponsor proposed a new drug application under section 505(b)(2) for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5. The approval listed drug for this NDA is Zemplar™ (NDA 020819) for the same indication.

The new formulation has the same active ingredient (paricalcitol) and inactive ingredient (propylene glycol) as the approved LD; however, it has different level of alcohol (35% v/v vs. 20% v/v in Zemplar). The level of alcohol is within Inactive Ingredients Guidance (IIG) limits for other marketed i.v. products and additional toxicity/safety studies are not required for qualification of the inactive ingredient for the new formulation. In addition, The Sponsor conducted a 4-week repeat-dose toxicity study in rats with a 2-week recovery period to assess the potential toxicity of the new formulation to the LD.

In general, results of this study showed no mortality, clinical signs, or treatment-related effects on body weight, food consumption, clinical pathology (hematology, coagulation, and urine parameters), organ weights, or necropsy findings. Increases (ss) in levels of serum calcium and phosphorus (in dose response) were reported in treated animals with the new formulation. These changes are related to the pharmacological effects of paricalcitol (hypercalcimes, hyperphosphatemia). Histopathological evaluation was performed only for tissues from animals that were treated at control or HD groups. In these tissues, calcification was reported only for HD treated males for both formulations (paricalcitol: 1/10; LD: 2/10). In addition, in kidneys, hyperplasia (transitional epithelium) and pelvis with inflammatory cells (epithelial/ subepithelial) were noted in the HD new formulation treated females. These findings in the kidneys are less concerning because of the subjects not having normal renal function. In tails, histopathological

findings (necrosis, inflammation) were reported in all treated animals (including control), which related to the method of test administration for tail vein injection.

TK data was similar in both formulations. The C_{max} for the new formulation increased with a dose levels in both Day 1 and 28 and was similar in both treated male and female rats. However, AUC and $t_{1/2}$ of paricalcitol were higher in treated males compared to treated females, which coordinate to calcification that was reported in males only.

Findings of this study suggested no significant TK or toxicity profile differences between the Accord paricalcitol formulation and the approved LD of Zemplar.

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/s/

PARVANEH ESPANDIARI
12/16/2014

KAREN L DAVIS BRUNO
12/16/2014

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 207174 **Applicant:** Accord Health Care Inc. **Stamp Date:** 4/01/2014

Drug Name: Paricalcitol Injection; 2 mcg/mL (1 mL) and 5 mcg/mL (1 mL and 2 mL) **NDA Type:** 505(b)2 **Indication:** Prevention/Treatment of secondary hyperparathyroidism with CKD Stage 5

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		The submission is in CTD format
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		Section 4.2.3. Toxicology
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?		X	Requested the bridge tox study between the new formulation and LD was submitted.

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		The proposed labeling is the same as the labeling of the LD and data express human dose multiples in mg/m^2.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		Reference to the DMF # (b) (4)
11	Has the applicant addressed any abuse potential issues in the submission?		X	
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			NA

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ____Yes, this application is fileable____

If the NDA/BLA is not fileable from the pharmacology/toxicology 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.

Parvaneh Espandiari, Ph.D

Reviewing Pharmacologist Date

Karen Davis-Bruno, Ph.D

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

PARVANEH ESPANDIARI
04/14/2014

KAREN L DAVIS BRUNO
04/15/2014
filing