CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207174Orig1s000

CHEMISTRY REVIEW(S)

Recommendation:
Approval

NDA 207174
Review #2
Review Date (see page 3)

Drug Name/Dosage Form	paricalcitol injection
Strength	2 mcg/mL, 5 mcg/mL, and 10 mcg/2 mL
Route of Administration	Intravenous through a hemodialysis vascular access port
Rx/OTC Dispensed	Rx
Applicant	Accord Healthcare

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Resubmission	05-AUG-2015

Quality Review Team
(including reviewers from the previous review cycle)

DISCIPLINE	REVIEWER	DIVISION/OFFICE
Application Technical Lead	Suong Tran	New Drug Products I/ONDP
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Drug Substance	Xavier Ysern	New Drug API/ONDP
Drug Product	Xavier Ysern	New Drug API/ONDP
Biopharmaceutics	Kareen Riviere	Biopharmaceutics/ONDP
Microbiology	Jessica Cole	Microbiology Assessment/OPF
Facility	Steven Fong	Inspectional Assessment/OPF

Executive Summary

I. Recommendation

The recommendation from the Office of Pharmaceutical Quality (including the manufacturing inspection recommendation) is for approval. There is no unresolved deficiency.
Labeling comments were finalized in the first review cycle (Complete Response on 29-JAN-2015). If necessary, the adequacy of the current labeling would be verified during the multi-disciplinary OND-managed labeling review.

This NDA received a Complete Response action on 29-JAN-2015 due to GMP deficiencies at the testing site [redacted] (b) (4)
The resubmission only includes information on a new testing site [redacted] (b) (4) to replace the deficient site. There is no other CMC information in the resubmission. The new testing site is found acceptable by the Office of Pharmaceutical Quality on 12-JAN-2016 (attached to this Executive Summary).

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues: not applicable
2. Action letter language: not applicable
3. Benefit/Risk Considerations: The benefit/risk ratio is minimal because 1) patients have another FDA-approved product (Zemplar) currently available in the U.S. with the same active ingredient, and 2) the new product, subject of this review, would not not be marketed as a generic option, thus negating any potential savings for patients.

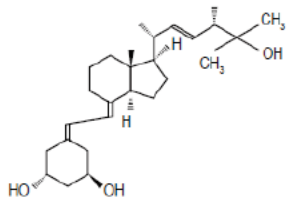
B. Recommendation on Post-Marketing Commitments, Agreements, and/or Risk Management Steps- not applicable

II. Summary of Quality Assessment

A. Drug Substance

1. **Chemical Name or IUPAC Name/Structure**:

19-nor-1α,3β,25-trihydroxy-9,10-secoergosta- 5(Z),7(E),22(E)-triene with the following structural formula:



See Chemistry Reviews from the previous review cycle for the following information:
2. **Properties Relevant to Drug Product Quality**
3. **List of starting materials**

4. **Suppliers of starting materials**
5. **Summary of Synthesis**
6. **Process**
7. **Container Closure**
8. **Retest Period & Storage Conditions**

B. Drug Product

1. **Strength**: 2 mcg/mL, 5 mcg/mL, and 10 mcg/2 mL
2. **Description/Commercial Image**: sterile, clear, colorless liquid
3. **Summary of Product Design**: [see Chemistry Reviews from the previous review cycle]
4. **List of Excipients**: alcohol, 35 % (v/v) and propylene glycol, 30 % (v/v).
5. **Process**: [see Chemistry Reviews from the previous review cycle]
6. **Container Closure**: single-use 1-mL and multiple-use/dose-2 mL glass vials with rubber stoppers.
7. **Expiration Date & Storage Conditions**: 24 months at room temperature. After the first use of the multiple-use/dose vial: up to 7 days at room temperature, protected from light.
8. **List of co-packaged components**: not applicable

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	PARICALCITOL INJECTION
Non Proprietary Name of the Drug Product	paricalcitol injection
Non Proprietary Name of the Drug Substance	paricalcitol
Proposed Indication(s) including Intended Patient Population	prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5
Duration of Treatment	chronic
Maximum Daily Dose	individualized dosing, see the CDTL's memo
Alternative Methods of Administration	none

D. Biopharmaceutics Considerations: see Biopharmaceutics Reviews from the previous review cycle

E. Novel Approaches: not applicable

F. Any Special Product Quality Labeling Recommendations: not applicable

G. Life Cycle Knowledge Information: see Chemistry Reviews from the previous review cycle

OVERALL ASSESSMENT AND SIGNATURE: EXECUTIVE SUMMARY

Application Technical Lead Signature: I concur with the primary reviewers' conclusions.

Suong T. Tran -S

Digitally signed by Suong T. Tran -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Suong T. Tran -S, 0.9.2342.19200300.100.1.1=1300101829
Date: 2016.01.13 09:53:53 -05'00'

Suong (Su) Tran, PhD, Quality/CMC Lead, OPQ

Overall Manufacturing Inspection Recommendation http://panorama.fda.gov/task/view?ID=55c3977d0271a10759f0abf85a0...

My Work Projects Reporting Timesheet

NDA 207174-Orig1-Resubmission/Class 2(12) » Manufacturing Facility Inspection

Overall Manufacturing Inspection Recommendation

Edit Task | Task Actions

Task Summary Task Details Issues Task Email Form Updates Application History

Inspection Management Form

Inspection Management Form | As of 9:29 AM

Inspection Management Form

NDA 207174-Orig1-Resubmission/Class 2(12)

INTAS PHARMACEUTICALS LIMITED | (b) (4)
Facility -

INTAS PHARMACEUTICALS LIMITED |
DRUGS | Approve Facility -

(b) (4)

(b) (4)

INTAS PHARMACEUTICALS LIMITED | (b) (4) Approve
Facility -

(b) (4)

Overall Manufacturing Inspection Recommendation

- Approve
- Withhold

Cancel

Assigned To

OPF Reviewer

Steven Fong

IM - OPF Reviewer

Edit Assignment

This was done on
Jan 12, 2016
(Yesterday)

Status
Complete

Requested by

DARRTS Integration

This task is waiting on
Facilities

Last Update
Jan 12, 2016

Submitted On
Aug 6, 2015

Reference Number
5336312

1/27/15
(panorama)

NDA 207-174

Paricalcitol Injection 2mcg/mL and 5 mcg/mL

Accord Healthcare Inc.

Xavier Ysern, PhD
ONDQA/ DNQA III/ Branch VII

CMC Review for DMEP

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III. List of Deficiencies To Be Communicated

[*There are no deficiencies to be communicated to the Applicant*]

Chemistry Review Data Sheet

1. NDA: 207-174

2. Review #: 1

3. Review Date: 07-Jan-2015

4. Reviewer: Xavier Ysern, PhD

5. Previous Documents:

Previous Documents	Document Date
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6. Submission(s) Being Reviewed:

Submission(s) Reviewed		Document Date
Amendment	Serial 009 eCTD 0008 (Labeling/ Package Insert)	08-Dec-2014
Amendment	Serial 008 eCTD 0007 (Labeling/Container-Carton)	02-Dec-2014
Amendment	Serial 007 eCTD 0006 (Quality/ Response to IR)	24-Sep-2014
Amendment	Serial 006 eCTD 0005 (Quality/ Response to IR)	19-Sep-2014
Amendment	Serial 004 eCTD 0003 (Labeling/ Package Insert)	20-Jun-2014
Original	Serial 001 eCTD 0000	01-Apr-2014

7. Name and Address of Applicant:

Name: Accord HealthCare Inc.
Sabita Nair/ Director Regulatory Affairs
Tel: 1-919-941-7880; Fax:1-919-941-7881; e-mail: snair@intaspharma.com
Address: 10099 Slater Road, Suite 210-B/ Durham, NC 27703/ USA
USA Representative: ACIC Fine Chemicals, Inc.
Ms. Aman Panag/ Regulatory Affairs Associate - Pharmaceutical Development
Tel: 1-800-265-6727; Fax: 519-751-1378; Email Address: apanag@acic.com
11772 West Sample Road, Coral Springs, Florida, 33065, U.S.A.

8. Drug Product Name/ Code/ Type:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Paricalcitol Injection
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority: Chem. Type: 5 Submission Priority: Standard

9. Legal Basis for Submission: 505 (b)(2) Reference listed drug (RLD) Zemplar® (NDA 20819)

10. Pharmacological Category: Indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5.

11. Dosage Form: Injection

12. Strength/Potency: [redacted] (b) (4) (1 mL) and 5 µg/mL (1 mL and 2 mL) [redacted] (b) (4) = 1 mcg = 10^{-6} g]

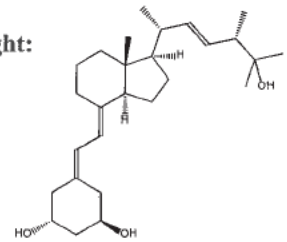
13. Route of Administration: Injection as a bolus through a hemodialysis vascular access port (not directly into a vein)

Chemistry Review Data Sheet

14. Rx/OTC Dispensed: Rx

15. SPOTS (Special Products On-Line Tracking System): Not a SPOTS product

16. Chemical Name, Structural Formula, Molecular Formula, Molecular Weight:



Paricalcitol

CAS: 131918-61-1
Molecular formula: $C_{27}H_{44}O_3$
Molecular weight: 416.64 g/mol

(b) (4)

17. Related/Supporting Documents:

A. DMFs:

DMF #	Holder	Item Referenced	Code[a]	Status[b]	Date Review Completed	LOA Date
(b) (4)		Paricalcitol	3	Adequate	NA	20-Mar-2014
		(b) (4)	4	Adequate	NA	24-Feb-2014
			4	Adequate	NA	03-Mar-2014

[a] Action codes for DMF Table: 1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF; 3 – Reviewed previously and no revision since last review
4 – Sufficient information in application; 5 – Authority to reference not granted
6 – DMF not available; 7 – Other (explain under "Comments")
[b] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Document	Application Number	Description
--	--	--

18. Status:

ONDC:

Consults/ CMC Related Reviews	Recommendation	Date	Reviewer
Biometrics	NA		
Manufacturing Facilities	Pending (see Panorama)		Steven Hertz
Pharm/Tox	Pending		Dr. Parnavaneh Espandary
Biopharm	Pending		Dr. Kareen Riviere
LNC	NA		
Methods Validation	Revalidation by Agency Laboratories is not recommended		Part of this review
EA	Adequate		Part of this review
Microbiology	Pending		Dr. Jessica Cole

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application can be approved from the CMC perspective. At this time, an overall recommendation for the commercial manufacturing and testing facilities listed in the NDA has not been issued.

- Shelf life prior to single-use of the drug product: 24 months at the recommended storage condition: store 25 °C protected from light.
- In-use period (multi-dose presentation 5 mcg/mL, 2 mL): 7 days stored at room temperature (up to 30 °C) protected from light.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- Drug Substance (Paricalcitol, [redacted] (b) (4))

Paricalcitol [redacted] (b) (4) the active form of vitamin D_2 (ergocalciferol). The information on the quality of the drug substance paricalcitol is incorporated by reference to [redacted] (b) (4) DMF [redacted] (b) (4) DMF [redacted] (b) (4) is an approved and currently active Type II DMF that is also reference by approved generic paricalcitol drug products.

Paricalcitol is a lipophilic molecule with limited water solubility (< 0.05 mg/mL) but is freely soluble in alcohol. The drug substance is white to almost off-white powder [redacted] (b) (4) Since the proposed drug product is a solution, polymorphism is not an issue. The drug substance is a chiral molecule with multiple chiral centers [redacted] (b) (4) It is [redacted] (b) (4) light [redacted] (b) (4) sensitive as well as susceptible to degradation [redacted] (b) (4) conditions. Paricalcitol drug substance meets USP compendial requirements.

- Drug product (Paricalcitol Injection 2 mcg/mL and 5 mcg/mL, Accord HealthCare Inc.)

The drug product Paricalcitol Injection 2 mcg/mL and 5 mcg/mL is submitted as a 505(b)(2) drug product. AbbVie Inc.'s Zemplar® (NDA 20819) is the reference listed drug (RLD). In addition to the API, paricalcitol, Paricalcitol Injection contains propylene glycol, ethanol [redacted] (b) (4) The formulation of Paricalcitol Injection differs from that of the RLD only in the amount of ethanol (35 % versus 20 % in the RLD). None of the excipients exceed the Agency's inactive ingredient database limit for this route of administration (injection).

Drug product's manufacture involves the preparation of the solution for injection [redacted] (b) (4) (b) (4)

Excipients meet compendial requirements. 2 mL USP Type I clear glass vials conform USP <660> for "Glass containers for Pharmaceutical use". Rubber stopper comply with the USP <381> requirements (Elastomeric Closures for Injection). In addition, a leachable study has been carried out by the Applicant (3.2.P.2 Appendix-02). Adequacy of the container closure system and compatibility of the excipients is supported by the stability data.

Executive Summary

Drug product specifications include description, identification (by HPLC and UV), clarity and color of solution, bacterial endotoxin, particulate matter, [redacted] (b) (4) content, assay, purity (content impurities [redacted] (b) (4) [redacted] (b) (4) maximum single unknown, and total impurities), container content, sterility, content of propylene glycol and alcohol, limit of [redacted] (b) (4) (meet USP <467>).

Comparative analysis of Paricalcitol Injection and RLD reveal no differences among impurity profiles. Stability studies fully support the requested 24 month shelf-live stored at 25 °C protected from light. In use study, to qualify the vial for multiple punctures for withdrawal of doses at different times showed that the drug product (10 mcg/2 mL 2 mL multi-dose presentation) remained stable for at least 24 days (duration of the study).

The drug product is available in: (1) Single-dose 2 mcg/mL, 1 mL: 2 mL, clear glass vial (type I) with [redacted] (b) (4) [redacted] (b) (4) rubber stopper [redacted] (b) (4) and [redacted] (b) (4) aluminum seals with [redacted] (b) (4) flip-off cap, (2) Single use 5 mcg/mL, 1 mL: 2 mL, clear glass vial (type I) with [redacted] (b) (4) rubber stopper [redacted] (b) (4) and [redacted] (b) (4) aluminum seals with [redacted] (b) (4) flip-off cap, and (3) Multi-dose 5 mcg/mL, 2 mL (10 mcg/2 mL): 2 mL, clear glass vial (type I) with [redacted] (b) (4) rubber stopper [redacted] (b) (4) and [redacted] (b) (4) aluminum seals with [redacted] (b) (4) flip-off cap.

The CMC review team performed risk assessment on the factors that can impact product quality and concluded that the potential risk to overall product quality is acceptable (low risk, see table below for an executive summary of the risk assessment). No additional risk mitigation necessary.

Executive Summary Risk Assessment

From Initial Risk Assessment			Review Assessment		
Product attribute/ CQA	*Factors that can impact the CQA*	*Risk[a]*	*Final Risk Ranking*	*Risk evaluation*	*Life cycle considerations/ comments*
Assay (Paricalcitol)	Formulation Container closure Raw materials Process parameters Scale/ equipment Site	Low	Low	Acceptable	90.0 – 110.0 % Drug product final weight is linked to assay and is controlled by in-process specifications. Applicant's batch release and validation data indicate that assay values controlled tightly. Mixing parameters are adequate. Paricalcitol is a solution and hence dissolution is not an issue.
Assay (Propylene Glycol and Ethanol)		Low	Low	Acceptable	[redacted] (b) (4) (Propylene Glycol) (Ethanol) Mixing parameters are adequate. The drug product is a solution and dissolution is not an issue.
Related Compounds, and Impurities		Low	Low	Acceptable	Limits as per USP monograph for Paricalcitol Injection
Microbiological (Sterility and Endotoxin)		Medium	Low	Acceptable	Controlled by validated sterilization and qualified environment used for filling. [redacted] (b) (4)
Appearance Limits of aluminum Residual Solvent Leachable/Extractables		Low Low Medium Medium	Low Low Low Low	Acceptable Acceptable Acceptable Acceptable	Clear solution [redacted] (b) (4) Meets USP <467> Option-1 requirements [redacted] (b) (4)
Particulate matter		Medium	Low	Acceptable	[redacted] (b) (4) Maximum [redacted] (b) (4) per container USP<788> Maximum [redacted] per container

B. Description of How the Drug Product is Intended to be Used

Paricalcitol is an active form of vitamin D indicated for the prevention and treatment of secondary hyperparathyroidism in patients with chronic kidney disease (CKD). Its mechanism of action is 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 parathyroid hormone (PTH) levels by inhibiting PTH synthesis and secretion and so should be effective for the treatment of secondary hyperparathyroidism in patients with CKD (proposed indication). Although the drug product is a ready to use solution for direct intravenous administration (no reconstitution and dilution is require prior to administration), according to Dosage and Administration paricalcitol injection should be administered as a bolus through a hemodialysis vascular access port at any time during dialysis.

C. Basis for Approvability or Not-Approval Recommendation

The information on the quality of the drug substance, paricalcitol, has been adequately provided by cross reference to DMF (b) (4)

The Application has been submitted as a 505(b)(2). Information on the quality of the drug product Paricalcitol Injection has been adequately provided, in particular the Pharmaceutical Development Section is fully detailed . Quality Target Product Profile (QTPP) of the finished product is fully documented and justified.

Based in the information provided, from the CMC viewpoint this NDA is recommended for approval.

III. Administrative

A. Reviewer's Signature	Xavier Ysern, PhD	Chemist/ CDER/ ONDQA/ DNDQA III/ Branch VII
B. Endorsement Block	Danae Christodoulou, PhD	Acting Branch Chief/ ONDQA/ DNDQA III/ Branch VII
C. CC Block	Meghna Jairath	Project Manager/ CDER/ OND/ ODE II/ DMEP

39 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling and Package Insert *Pending*

- Package Insert

The CMC pertinent sections of the package insert, section 3 "Dosage Forms and Strengths", section 11 "Description", and section 16 "How Supplied", appear adequate.

- Labeling

Draft copies of the immediate and carton labels (Figures A-1 and A-2, respectively) have been provided. These labels appear adequate.

(b) (4)

Comment: The review of the labelling submissions is multidisciplinary and is still ongoing.

B. Environmental Assessment or Claim of Categorical Exclusion *Satisfactory*

Pursuant to 21 CFR 25.31(a) and 25.15(d), Accord claims a categorical exclusion from the requirement of an environmental Impact Analysis statement and states that to the Accord knowledge, no extraordinary circumstances exist.

- Accord meets the requirements of 21 CFR 25.31 (a) because Paricalcitol Injection 2 mcg/mL (1 mL) and 5 mcg/mL (1 mL and 2 mL) will be administered at the same dosage level, for the same duration and for the same indication as reference listed drug, ZEMPLAR® (paricalcitol) Injection; NDA # 020819 of AbbVie Inc., USA.
- Accord is unaware of any other data that would establish that Paricalcitol Injection 2 mcg/mL (1 mL) and 5 mcg/mL (1 mL and 2 mL) may be toxic to organism in the environment at expected levels of exposure.
- In addition, Accord certifies that, it is in compliance with all federal, state and local environmental protection requirements and that it has a certified waste disposal program.

C. **Establishment Inspections** *Pending*

Overall manufacturing inspection recommendation is still pending (see Panorama).

Xavier J. Ysern -S

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Date: 2015.01.27 11:49:03 -05'00'

Danae D. Christodoulou -A

Digitally signed by Danae D. Christodoulou -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300132624, cn=Danae D. Christodoulou -A
Date: 2015.01.27 12:31:52 -05'00'

ONDQA Initial Quality Assessment (IQA) and Filing Review for new NDA

1. NEW DRUG APPLICATION NUMBER: 207174
2. DATES AND GOALS:

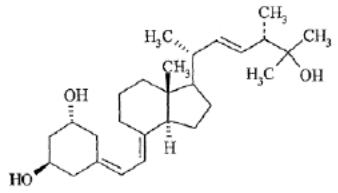
Letter Date: 4/01/2014	Submission Received Date : 4/01/2014
PDUFA Goal Date: 2/01/2015	NDA is not part of "The Program"

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	None proposed
Established Name (USAN):	Paricalcitol Injection
Dosage Form:	Solution
Route of Administration	Intravenous injection
Strength/Potency	2 mcg/mL (1 mL vials) or 5 mcg/mL (1 mL and 2 mL vials)
Rx/OTC Dispensed:	Rx

4. INDICATION: Prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease stage 5.
5. DRUG SUBSTANCE STRUCTURAL FORMULA:

Chemical Name(s): (b) (4)



Molecular Formula: $C_{27}H_{44}O_3$

Molecular Weight: 416.64 g/mol

6. NAME OF APPLICANT (as indicated on Form 356h): (b) (4)
7. SUBMISSION PROPERTIES:

Review Priority (select one)	Standard
Submission Classification:	5
Application Type:	505(b)(2)
Breakthrough Therapy	No
Clinical Division	Division of Metabolism and Endocrinology Products CMC Lead: Suong (Su) Tran

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		x	
Establishment Evaluation Request (EER)	x		To be sent by the ONDQA PM
Pharmacology/Toxicology		x	
Methods Validation			To be determined by Primary Reviewer

Environmental Assessment			To be determined by Primary Reviewer
CDRH		x	
Other			

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes
Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? No

Biopharmaceutics: See the Biopharmaceutics filing review attached at the end of this IQA.

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes
Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? No

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? Yes
Are there potential Microbiology review issues to be forwarded to the Applicant with the 74-Day letter? See Microbiology Filing Review in DARRTS for details and for any potential Microbiology review issues.

ONDQA Initial Quality Assessment (IQA) and Filing Review
For new NDA

CMC Summary:
Critical Issues and Complexities

Summary of Critical CMC Issues Previously Discussed with the Applicant (if any):			
None			
Critical CMC Issues or Complexities (note issues or if there are none)			
None			
Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
No	No	No	No

Is a team review recommended?		
Yes	No	Suggested expertise for team
x		Microbiology (sterile product) Biopharmaceutics (biowaiver request) CMC (drug product)

Summary or Highlights of the Application ***(not already mentioned in other sections)***

- The NDA is a 505(b)(2) application for Paricalcitol Injection, with the approved Zemplar as referenced product. The two products differ in formulation: the new product has 35% ethanol compared to Zemplar which has 20% [redacted] (b) (4). The new product cannot be submitted in an ANDA [redacted] (b) (4).
- The NDA includes a biowaiver request for the lack of any in vivo bridging study of the two products. The request will be evaluated by the ONDQA Biopharmaceutics team.
- The established name of the product is "paricalcitol" based on the dosage strength, which is acceptable per current CDER's policy on nomenclature.

Drug Substance

Paricalcitol is a small synthetic molecule drug substance. Reference is made to the DMF [redacted] (b) (4) for all CMC information on the drug substance. A copy of the approved drug substance specification is copied at the end of this review. . The referenced DMF has been reviewed in support of other approved applications. The primary reviewer will evaluate any new information in the DMF submitted since the most recent review.

Drug Product

Composition. A copy of the product composition is included at the end of this review. The product is for direct IV injection (no dilution/reconstitution). There is no overfilling indicated, which will be confirmed by the reviewer. Excipients are within FDA's IIG limits for the same dosage form and route of administration.

Manufacture. The manufacturing process is [redacted] (b) (4)

Master batch records are included in the NDA for the commercial manufacturing process (complying with 505(b)(2) regulations).

Drug product specification. . A copy of the drug product specification is included at the end of this review. The attributes are standard for this type of dosage form (injectable solution). The limit on an unknown impurity is [redacted] (b) (4)%, which meets the ICH identification and qualification thresholds for the maximum daily dose ([redacted] (b) (4)). The reviewer will confirm that the specified impurities that comply with the USP monograph are appropriate for this product (the limit of [redacted] (b) (4)% for each meets the ICH qualification threshold). The limit on Total Impurities is [redacted] (b) (4)%, which is comparable to other approved products.

Container closure system. The primary container closure system is a Type I clear glass vial and with a rubber closure and aluminum flip-off seal. The applicant states that the rubber closure complies with applicable USP testing requirements. The primary stability batches were packaged in the commercial container closure system. The Pharmaceutical Development section includes reports on the qualification of the rubber closure.
Stability. The NDA includes at least 12-month data at 25 °C/60% RH and 6-month data at 40 °C/75% RH for the primary stability batches: three batches of the 2 mcg/mL in 1mL vials, three batches of the 5 mcg/mL in 2 mL vials, and three batches of the 5 mcg/mL in 1mL vials. All vials were stored inverted and upright. Stability data are also provided from the photostability study and in-use study (in the Pharmaceutical Development report). The primary stability batches were manufactured by the full scale commercial process (they are the same as the process validation batches). The reviewer will determine the final expiry based on all available data and per ICH Q1E Evaluation of Stability Data.
Comparability protocol. A protocol is included in the NDA for an alternate drug substance source, which will be evaluated by the reviewer with consult from the Post Marketing Branch.

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

B. FACILITIES*				
*	**If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.**			
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		

6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			N/A

	Parameter	Yes	No	Comment
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment or claim of categorical exclusion been provided?	x		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?			Referencing quality information in DMF (b) (4).
13.	Does the section contain identification and controls of critical steps and intermediates of the DS			Referencing quality information in DMF (b) (4).
14.	Does the section contain information regarding the characterization of the DS?			Referencing quality information in DMF (b) (4).
15.	Does the section contain controls for the DS?			Referencing quality information in DMF (b) (4).
16.	Has stability data and analysis been provided for the drug substance?			Referencing quality information in DMF (b) (4).
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?	x		
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	x		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	x		

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE
(b) (4)	II	(b) (4)	Paricalcitol, USP	20-MAR-2014
	III		(b) (4)	03-MAR-2014
	III			24-FEB-2014

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

Appendix 1. Composition of Drug Product

Table 1: Unit composition [Paricalcitol Injection 2 mcg/mL (1 mL) and 5 mcg/mL (1 mL 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]		USNF & Ph.Eur#
(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.

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PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	NDA 207-174
Submission Date	4/1/2014
Product name, generic name of the active	Paricalcitol Injection
Dosage form and strength	IV Injection; 2 mcg/mL and 5 mcg/mL
Applicant	Accord Healthcare Inc.
Clinical Division	DMEP
Indication	the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease (CKD) Stage 5.
Type of Submission	505(b)(2)
Biopharmaceutics Reviewer	Kareen Riviere, Ph.D.
Biopharmaceutics Team Leader	Tapash Ghosh, Ph.D.
Biopharmaceutics Supervisor (acting)	Richard Lostritto, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	**Yes**	**No**	**Comment**
1.	Does the application contain dissolution data?		x	Not Applicable.
2.	Is the dissolution test part of the DP specifications?		x	Not Applicable.
3.	Does the application contain the dissolution method development report?		x	Not Applicable.
4.	Is there a validation package for the analytical method and dissolution methodology?		x	Not Applicable.
5.	Does the application include a biowaiver request?	x		
6.	Is there information provided to support the biowaiver request?	x		
7.	Does the application include a IVIVC model?		x	Not Applicable.
8.	Is information such as BCS classification mentioned, and supportive data provided?			
9.	Is information on mixing the product with foods or liquids included?		x	Not Applicable.
10.	Is there any in *vivo* BA or BE information in the submission?		x	Not Applicable.

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
11.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
12.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	-	-	
13.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		-	

{See appended electronic signature page}

Kareen Riviere, Ph.D. — 5/13/14
Biopharmaceutics Reviewer — Date
Office of New Drug Quality Assessment

{See appended electronic signature page}

Tapash Ghosh, Ph.D. — 5/13/14
Biopharmaceutics Team Leader — Date
Office of New Drug Quality Assessment

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

INITIAL BIOPHARMACEUTICS ASSESSMENT

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

The proposed drug product is a clear aqueous solution intended solely for intravenous administration. The active ingredient, route of administration, dosage form and strength of the proposed drug product is the same as those of the RLD ZEMPLAR®. Accord's proposed product will contain the same concentration of the active ingredient as the Reference Listed Drug. However, the proposed drug product will differ from the formulation of the RLD 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 Listed Drug. The formulation comparison of Accord's formulation with RLD is provided in Table 1.

Table 1: Comparative Formulations of Accord's Proposed Product and Reference 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)

The Biopharmaceutics review will focus on the evaluation and acceptability of the data/information supporting the biowaiver for the proposed product.

RECOMMENDATION:

The ONDQA Biopharmaceutics team has reviewed NDA 207-174 for filing purposes. We found this NDA **fileable** from a Biopharmaceutics perspective. The Applicant has submitted a reviewable submission.

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

/s/

SUONG T TRAN
05/14/2014

KAREEN RIVIERE
05/14/2014

TAPASH K GHOSH
05/14/2014

DANAE D CHRISTODOULOU
05/16/2014