CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201657Orig1s000

CHEMISTRY REVIEW(S)

Final Addendum to Quality Reviews

To: **NDA 201657 (paricalcitol injection)**

Subject: **Final ONDQA recommendation**

The 21-APR-2014 NDA Resubmission is in response to the 06-FEB-2012 CR letter. The CR letter did not include any pending issue or deficiency from the CMC, Biopharmaceutics, and Microbiology reviews. The CR action was based on a "withhold" recommendation from Compliance/OMPQ regarding the drug product manufacturing site Hospira Inc., Rocky Mount NC.

- The resubmission contains no new CMC, Biopharmaceutics, or Microbiology information, and these review members confirmed that their reviews of the resubmission are not necessary (their previous recommendations for this NDA were for approval). Labeling revisions will be sent to the OND PM as part of the multi-disciplinary labeling review.
- The EES overall recommendation dated 14-MAY-2014 for this NDA is ACCEPTABLE (including the specific site Hospira Inc., Rocky Mount NC).

Conclusion:

Based on the CMC, Biopharmaceutics, and Microbiology reviews and the Compliance overall findings dated 14-MAY-2014, the ONDQA recommendation for this NDA is for APPROVAL.

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/s/

SUONG T TRAN
05/14/2014

DANAE D CHRISTODOULOU
05/16/2014

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 201657/000	**Sponsor:**	HOSPIRA INC
Org. Code:	510		275 NORTH FIELD DR DEPT 0389 BLDG H2 2
Priority:	5		LAKE FOREST, IL 60045
Stamp Date:	07-APR-2011	**Brand Name:**	PARICALCITOL INJECTION
PDUFA Date:	07-FEB-2012	**Estab. Name:**	PARICALCITOL INJECTION
Action Goal:		**Generic Name:**	
District Goal:	08-AUG-2011	**Product Number; Dosage Form; Ingredient; Strengths**	

001; SOLUTION, INJECTION; PARICALCITOL; 2MCG/1ML
002; SOLUTION, INJECTION; PARICALCITOL; 5MCG/1ML
003; SOLUTION, INJECTION; PARICALCITOL; 10MCG/2ML

FDA Contacts:	K. SHARMA	Project Manager	
	E. CHIKHALE	Review Chemist	301-796-1659
	S. TRAN	Team Leader	301-796-1764

Overall Recommendation:	WITHHOLD	on 03-JAN-2012	by EES_PROD
	WITHHOLD	on 03-JAN-2012	by EES_PROD
	WITHHOLD	on 27-APR-2011	by EES_PROD

Establishment:	**CFN:**	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE RELEASE TESTER		
	DRUG SUBSTANCE STABILITY TESTER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	11-APR-2011		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** 1021343 **FEI:** 1021343

HOSPIRA WORLDWIDE, INC
4285 NORTH WESLEYAN BLVD

ROCKY MOUNT, NC 278048612

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

DRUG SUBSTANCE RELEASE TESTER

FINISHED DOSAGE LABELER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** OAI ALERT

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-APR-2011

Decision: WITHHOLD

Reason: DISTRICT RECOMMENDATION

Profile: (b) (4) **OAI Status:** OAI ALERT

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-APR-2011

Decision: WITHHOLD

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** **FEI:** 3004591926

HOSPIRA WORLDWIDE, INC
375 N FIELD DRIVE

LAKE FOREST, IL 60045

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-APR-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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/s/

MEGHNA M JAIRATH
02/06/2012

NDA 201-657

TRADENAME™
(paricalcitol)
Injection

Hospira Inc.

Elsbeth Chikhale, Ph.D.
ONDQA – Div III – Branch VII

for
Division of Metabolism and Endocrinology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 201-657

2. REVIEW #: 2

3. REVIEW DATE: 19-DEC-2011

4. REVIEWER: Elsbeth Chikhale, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed:	Document Date:
Original	7-APR-2011
Amendment to original[1]	3-MAY-2011
Amendment to original[2]	22-JUL-2011
Amendment to original[3]	23-NOV-2011

1) The 5/3/11 amendment provides for updated labeling
2) The 7/22/11 amendment provides for a response to the CMC IR in the filling communication dated 6/20/11.
3) The 11/23/11 amendment provides for responses to the CMC IR letter dated 10/19/11.

7. NAME & ADDRESS OF APPLICANT:

Name:	Hospira, Inc.
Address:	275 North Field Dr., Lake Forest, IL 60045
Contact person:	Laurie Wojtko, Sr. Associate, Global Regulatory Affairs
Telephone:	(224) 212-6158

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Tradename™
b) Non-Proprietary Name (USAN): paricalcitol
c) Code Name/#:
d) Chem. Type/Submission Priority:

- Chem. Type: 5 (new formulation)
- Submission Priority: Standard

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(2) application. The reference drug is: Zemplar (paricalcitol) Injection (Abbott Laboratories).

10. PHARMACOL. CATEGORY:

Paricalcitol is a synthetic, biologically active vitamin D analog of calcitriol with modifications to the side chain (D2) and the A (19-nor) ring. Paricalcitol is indicated for the prevention and treatment of secondary hyperparathyrodism associated with chronic kidney disease Stage 5.

11. DOSAGE FORM: Injection

12. STRENGTH/PRESENTATIONS: 2 mcg/1 mL multi-dose vial
5 mcg/1 mL multi-dose vial
10 mcg/2 mL multi-dose vial

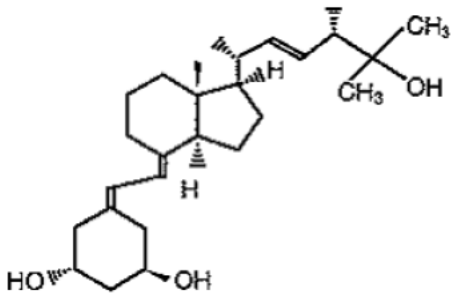
13. ROUTE OF ADMINISTRATION: I.V. injection

14. Rx/OTC DISPENSED: _x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product ___ Form Completed
__x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Paricalcitol:



Chemical name: (1α,3β,7E,22E)-19-Nor-9,10-secoergosta-5,7,22-triene-1α,3β,25-triol
CAS registration number: 131918-61-1
Molecular Formula: $C_{27}H_{44}O_3$

Molecular Weight: 416.64 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Paricalcitol Drug substance	3	Adequate	October 14, 2010	Reviewed by D. Chowdhury, Ph.D.

[1] 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 relevant revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other

[2] 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:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biopharmaceutics	Biowaiver granted	12/13/11	Elsbeth Chikhale, Ph.D.
Biometrics	N/A		
EES	Withhold	4/27/11	Office of Compliance
Pharm/Tox	N/A		
CDRH	N/A		
Clinical Pharmacology	N/A		
Methods Validation	FDA revalidation is not needed	10/20/11	Elsbeth Chikhale, Ph.D.
DMEPA - OSE	Labeling recommendations provided	12/6/11	Denise Baugh, Pharm.D.
DDMAC	Pending		
EA	Categorical exclusion granted (consult not needed)	10/20/11	Elsbeth Chikhale, Ph.D.
Microbiology	Pending		Robert Mello, Ph.D.

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 201-657

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view, the recommendation for this application is Complete Response (CR), because:

- The NDA has an overall withhold recommendation from the Office of Compliance regarding the cGMP status of the manufacturing and testing facilities.

In addition,

- An acceptable recommendation from Microbiology Consult Review is pending.

This review was finalized in DARRTS to meet the GRMP timelines.
Final labeling will be done in coordination with the clinical division.

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

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substances

1) **Drug Product**

The proposed drug product is a sterile, clear, colorless solution containing the active ingredient, paricalcitol, at a concentration on 2 mcg/mL or 5 mcg/mL in a mixture of the inactive ingredients, propyleneglycol (10%), alcohol (40%), and water for injection ((b) (4)%). The drug product is a solution for intravenous injection, indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease stage 5. The drug product will be available in 3 presentations: 2 mcg/1 mL, 5 mcg/1 mL and 10 mcg/2 mL in multi-dose vials. The drug product specifications include: clarity, fill volume, identification and assay for paricalcitol, color, (b) (4), degradation products, content of alcohol, content of propyleneglycol, particulate matter, sterility, limit of (b) (4), and bacterial endotoxin testing. The stability

data for the drug product support an expiry dating period of 12 months (stored at 25°C/40%RH) instead of the requested (b) (4) months. The drug product will be manufactured by Hospira, Inc., Rocky Mount, NC. This facility has received a withhold recommendation from the office of compliance on April 27, 2011. The drug product will be packaged in multi-dose glass vials with a rubber stopper and aluminum seal. After the first use, the drug product can be stored at room temperature. The provided stability data support the storage at room temperature and use of the drug product up to 28 days after the first use. Once the seal is broken, the drug product needs to be consumed or disposed within 28 days.

2) **Drug Substance:**
The drug substance, paricalcitol, USP, is a previously approved drug substance. It is a synthetically manufactured analog of calcitriol, the active metabolite of vitamin D. Paricalcitol is a white to almost white powder which is not soluble in water but which is soluble in (b) (4) propylene glycol and water. All information regarding the physicochemical properties, impurities, method of synthesis and purification, process controls, control of raw materials, container closure system and stability of paricalcitol, USP are provided in the Drug Master File (DMF) (b) (4) held by (b) (4). DMF (b) (4) was reviewed on 10/14/10 (review #2 by D. Chowdhury, Ph.D.) and found adequate to support an (b) (4) for a paricalcitol injection drug product. The drug substance also complies with the USP monograph. The drug substance, paricalcitol, USP will be manufactured by (b) (4). The retest period for paricalcitol, USP is (b) (4) months when stored at (b) (4) °C as described in DMF (b) (4).

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

The drug product is indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5. The initial dose is 0.04 mcg/kg to 0.1 mcg/kg (2.8 – 7 mcg) administered as a bolus no more frequently than every other day at any time during dialysis. The dose may be increased by 2 to 4 mcg at 2- to 4- week intervals. If an elevated calcium level or a Ca x P product greater than 75 is observed, the drug dosage should be immediately reduced or interrupted. The drug product should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. After initial vial use, the contents of the multi-dose vial remain stable for up to twenty-eight days when stored at controlled room temperature.

C. Basis for Approvability or Not-Approval Recommendation

From the CMC point of view, the recommendation is Complete Response (CR) based on the OC overall withhold recommendation for this NDA.

III. Administrative

A. Reviewer's Signature: in DARRTS

B. Endorsement Block: in DARRTS

C. cc Block: in DARRTS

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/s/

ELSBETH G CHIKHALE
12/19/2011

ALI H AL HAKIM
12/20/2011

NDA 201-657

TRADENAME™
(paricalcitol)
Injection

Hospira Inc.

Elsbeth Chikhale, Ph.D.
ONDQA – Div III – Branch VII

for
Division of Metabolism and Endocrinology Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 201-657

2. REVIEW #: 1

3. REVIEW DATE: 20-OCT-2011

4. REVIEWER: Elsbeth Chikhale, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed:	Document Date:
Original	7-APR-2011
Amendment to original[1]	3-MAY-2011
Amendment to original[2]	22-JUL-2011

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Address:	275 North Field Dr., Lake Forest, IL 60045
Contact person:	Laurie Wojtko, Sr. Associate, Global Regulatory Affairs
Telephone:	(224) 212-6158

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a) Proprietary Name: Tradename™
b) Non-Proprietary Name (USAN): paricalcitol
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- Chem. Type: 5 (new formulation)
- Submission Priority: Standard

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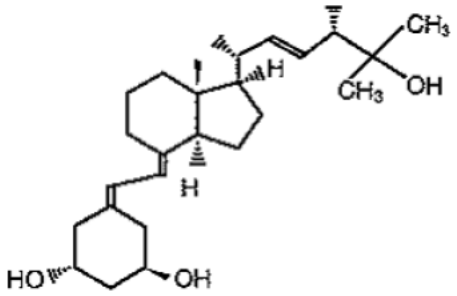
Paricalcitol:



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B. Other Documents:

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Biometrics	N/A		
EES	Withhold	4/27/11	Office of Compliance
Pharm/Tox	N/A		
CDRH	N/A		
Clinical Pharmacology	N/A		
Methods Validation	FDA revalidation is not needed	10/20/11	Elsbeth Chikhale, Ph.D.
DMEPA	Pending		
DDMAC	Pending		
EA	Categorical exclusion granted (consult not needed)	10/20/11	Elsbeth Chikhale, Ph.D.
Microbiology	Pending		Robert Mello, Ph.D.

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 201-657

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC point of view, the recommendation for this application is pending:

- Overall acceptable recommendation from the Office of Compliance regarding the cGMP status of the manufacturing and testing facilities.
- Acceptable responses to the information requests noted at the end of this review (pg.45).
- Acceptable recommendation from Microbiology Consult Review.

Final labeling will be done in coordination with the clinical division.

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

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substances

1) Drug Product

The proposed drug product is a sterile, clear, colorless solution containing the active ingredient, paricalcitol, at a concentration on 2 mcg/mL or 5 mcg/mL in a mixture of the inactive ingredients, propyleneglycol (10%), alcohol (40%), and water for injection (b) (4) %). The drug product is a solution for intravenous injection, indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease stage 5. The drug product will be available in 3 presentations: 2 mcg/1 mL, 5 mcg/1 mL and 10 mcg/2 mL in multi-use vials. The drug product specifications include: clarity, fill volume, identification and assay for paricalcitol, color, (b) (4), degradation products, content of alcohol, content of propyleneglycol, particulate matter, sterility, limit of (b) (4), and bacterial endotoxin testing. The stability data for the drug product support an expiry dating period of 12 months (stored at 25°C/40%RH) instead of the requested (b) (4) months. The drug product will be manufactured by Hospira, Inc., Rocky Mount, NC. This facility has received a

withhold recommendation from the office of compliance on April 27, 2011. The drug product will be packaged in multi-use glass vials with a rubber stopper and aluminum seal. After the first use, the drug product can be stored at room temperature. The provided stability data support the storage at room temperature and use of the drug product up to 28 days after the first use. Once the seal is broken, the drug product needs to be consumed or disposed within 28 days.

2) **Drug Substance:**

The drug substance, paricalcitol, USP, is a previously approved drug substance. It is a synthetically manufactured analog of calcitriol, the active metabolite of vitamin D. Paricalcitol is a white to almost white powder which is not soluble in water but which is soluble in (b) (4) propylene glycol and water. All information regarding the physicochemical properties, impurities, method of synthesis and purification, process controls, control of raw materials, container closure system and stability of paricalcitol, USP are provided in the Drug Master File (DMF) (b) (4) held by (b) (4) DMF (b) (4) was reviewed on 10/14/10 (review #2 by D. Chowdhury, Ph.D.) and found adequate to support an (b) (4) for a paricalcitol injection drug product. The drug substance also complies with the USP monograph. The drug substance, paricalcitol, USP will be manufactured by (b) (4). The retest period for paricalcitol, USP is (b) (4) months when stored at (b) (4) °C as described in DMF (b) (4).

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

The drug product is indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5. The initial dose is 0.04 mcg/kg to 0.1 mcg/kg (2.8 – 7 mcg) administered as a bolus no more frequently than every other day at any time during dialysis. The dose may be increased by 2 to 4 mcg at 2- to 4- week intervals. If an elevated calcium level or a Ca x P product greater than 75 is observed, the drug dosage should be immediately reduced or interrupted. The drug product should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. After initial vial use, the contents of the multi-use vial remain stable up to twenty-eight days when stored at controlled room temperature.

C. Basis for Approvability or Not-Approval Recommendation

From the CMC point of view, the recommendation is pending and will be finalized in review #2. A list of information requests is provided at the end of this

review and has been sent to the applicant by the ONDQA project manager on 10/19/11.

III. Administrative

A. Reviewer's Signature: in DARRTS

B. Endorsement Block: in DARRTS

C. cc Block: in DARRTS

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

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/s/

ELSBETH G CHIKHALE
10/20/2011

ALI H AL HAKIM
10/21/2011

Initial Quality/CMC Assessment
ONDQA

Division of Metabolism and Endocrinology Products

NDA:	**201657**
Applicant:	Hospira Inc.
Stamp Date:	07-APR-2011
PDUFA Date:	**07-FEB-2012**
Proposed Proprietary Name:	[none indicated]
Established Name:	Paricalcitol
Dosage form and strength:	Solution for injection 2 mcg/mL vial, or 5 mcg/mL vial, or 10 mcg/2 mL vial
Route of Administration:	IV injection
Indications:	Prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease stage 5.
CMC Lead:	Su **(**Suong) Tran, ONDQA
ONDQA Fileability:	**Yes**

Are there comments for the 74-day letter? Yes.

- **Indicate the location in the NDA of the stability data supporting the proposed in-use period "After first use and following multiple needle entries and product withdrawals, Paricalcitol multi-use vials are stable for up to 28 days when stored between 20-25 °C (68-77 °F)."**
- **In the Stability section of the NDA, you state that "Paricalcitol Injection is not light sensitive." However, in the Quality Summary Overall, you state that "The container/closure should protect the drug product from light based on the results of the formulation development…" Explain the two different statements regarding the photostability of the product.**
- **During a recent inspection of the "Hospira Inc., Highway 301 North, Rocky Mount NC 27801" manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.**

CONSULTS/ CMC RELATED REVIEWS	COMMENT
CBER	*Not applicable*
CDRH	*Not applicable*
EA	The categorical exclusion claim will be assessed by Primary Reviewer.
Compliance (DMPQ)	**"Withhold" overall recommendation on 27-APR-2011: GMP violations at the drug product manufacturer Hospira, Rocky Mount, NC** (see the 74-day letter comment on the first page of this review)
Methods Validation	*Validation may be requested of FDA labs after test methods are finalized.*
Microbiology	**Review of sterility assurance.**
OBP	*Not applicable*
ONDQA Biopharm	**Review of biowaiver request.**
OSE	*Labeling consult request will be sent as part of DMEP's request.*
Pharm/Tox	*Not applicable. Impurity and degradant limits are below ICH qualification thresholds and/or comply with compendial limits.*
QbD	*Not applicable*

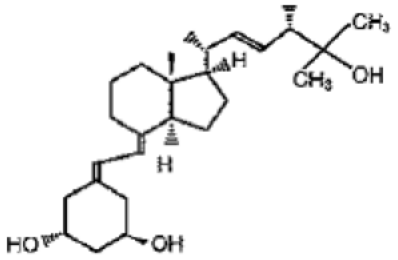
This is an electronic NDA, filed as a 505(b)(2) application, with Zemplar as the reference listed drug (RLD) listed in Form 356h. The difference between the 2 products is in the amounts of the excipients propylene glycol and alcohol (40% and 10% in the new product vs. 30% and 20% in Zemplar).

Reference is made to the DMF (b) (4) for the CMC information on the drug substance.

The drug product is a sterile solution for IV injection. The product will be packaged in multi-dose vials of 2 mcg/mL vial, or 5 mcg/mL vial, or 10 mcg/2 mL vial. The product is stored long-term at room temperature. The in-use period of the multi-dose vials is up to 28 days at room temperature.

Has all information requested during the IND phases, and at the pre-NDA meetings been included?
To be discussed in the itemized sections of this review.

Drug substance:

Chemical Abstracts Service (CAS) Index Name	(1α,3β,7E,22E)-19-Nor-9,10-Secoergosta-5,7,22-triene-1,3,25-triol
CAS Registry Number	131918-61
United States Adopted Name (USAN)	Paricalcitol
European Pharmacopoeia Name (EPN)	Paricalcitol
International Nonproprietary Name (INN)	Paricalcitol
Molecular Structure	
Molecular Formula	$C_{27}H_{44}O_3$
Molecular Weight	416.64 AMU

Physical Description: Paricalcitol is a white powder.

Solubility Characteristics: Paricalcitol is insoluble in water at room temperature, but soluble in most polar solvents e.g., (b) (4)

Polymorphism: A (b) (4)

Chirality: Produced as a single enantiomer

Reference is made to the DMF (b) (4) for all CMC information on the drug substance.

Review comments: The drug substance specification (copied on the next page) is the same as the current USP monograph for paricalcitol, with the addition of (b) (4) , with ICH limits). All the impurities and their limits are the same as in the monograph. 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.

Table 4. Specifications for Drug Substance

Test	Acceptance Criteria	Regulatory Analytical Procedure	Test Results Lot # 80-052-DP-00	Justification of Specification[3]
Appearance	White powder	Visual	White powder	
Identification (IR)	Corresponds to RS	USP IR <197K>	Pass	Complies with current USP General Chapter <197>
Identification (HPLC)	Corresponds to RS	USP	Pass	Complies with USP monograph
Loss on Drying	NMT (b) (4)% of its weight	USP <891> Thermal Analysis	(b) (4)%	Complies with USP monograph
Assay (HPLC)	97.0 % - 103.0 %, calculated (b) (4)	MTS.01007-7A [1,2,3] MTS.01008-7A [1,2]	(b) (4)%	Complies with USP monograph
Chromatographic Purity (HPLC)	Individual Impurity: NMT (b) (4)	USP	N.D.	Complies with USP monograph
	Total Impurities: NMT		N.D.	
(b) (4)				

1 IR = Infrared spectrum; HPLC = High performance liquid chromatography; NMT = Not More Than; N.D. = None detected;

2 In-house (non-USP) analytical procedure is provided in *Section 3.2.S.4.2 Analytical Procedures*

3 The validation data for the analytical procedure is provided in *Section 3.2.S.4.3 Validation of Analytical Procedures*

4 Full Justification of Specifications is provided in *Section 3.2.S.4.5 Justification of Specification*

Drug product

Table 7. Composition

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				USP
Water for Injection		(b) (4)	Vehicle	USP/Ph Eur
Total Volume	1.00 mL	1.00 mL		
q.s. = Quantity sufficient				

Review comments: (drug product specification starting on page 10)

- **Formulation development**. The RLD diluent consists of (b) (4)% water, 20% alcohol, and 30% propylene glycol (from the product labeling). The applicant developed a slightly different diluent consisting of the same solvents but at different amounts: (b) (4)% water, 40% alcohol, and 10% propylene glycol. Both excipients are compendial. This final diluent system was selected based on the desired solubility profile of the product.
- **Sterility assurance**. The OPS Microbiology Team will evaluate the sterility assurance of this product. The container closure system is labeled as (b) (4) and the applicant claims that the diluent system is antimicrobial.
- **Comparability of the product used in the clinical studies, stability studies, and commercial product**. Seven registration batches (3 batches of the 2 mcg/mL vial, 2 batches of the 5 mcg/mL vial, and 2 batches of the 10 mcg/2 mL vial) were manufactured with the commercial process, at (b) (4) commercial scale, with the commercial formulation. All batches were placed on stability as primary stability batches. No clinical/clin.pharm. study was conducted in support of this NDA.
- **Master batch records** are included in the NDA for the commercial manufacturing process (complying with 505(b)(2) regulations).
- **Limits on degradation products.** The limit on an unknown impurity is (b) (4)%, which meets the ICH identification and qualification thresholds for the maximum daily dose. Other impurities (b) (4) (b) (4) are the same as listed in the USP monograph for Paricalcitol Injection and with the same limit

of (b) (4)% for each specified impurity. As requested by FDA at the pre-NDA meeting, comparative data are provided for the impurities/degradants in the new product and the RLD. The data (copied below) show that the new product has lower levels of impurities than the RLD.

Table 5. Comparison of Potency and Impurities Results between Hospira and Reference Product (5 µg/mL)

	Hospira Paricalcitol 5 µg/mL (1 mL fill) Lot 80-101-DK	Hospira Paricalcitol 5 µg/mL (2 mL fill) Lot 80-104-DK	Zemplar® 5 µg/mL, (1 mL fill) Lot 735178E02[a]	Zemplar® 5 µg/mL, (2 mL fill) Lot 681958E07[b]
	% Potency (Initial)[c]		% Potency (Initial)	
	(b) (4)			
	% Potency (6 months (b) (4) inverted storage)		% Potency (6 months after initial)	
	(b) (4)			
	% Impurities (Initial)		% Impurities	
Specified Impurities (b) (4)	ND	ND	ND	ND
Unspecified Impurities	ND	ND	(b) (4)	
Total Impurities	0.0	0.0		
	% Impurities (6 months (b) (4) storage)		% Impurities (6 months after initial)	
Specified Impurities (b) (4)	ND	ND	ND	ND
Unspecified Impurities	(b) (4)			
Total Impurities	0.0	0.0	(b) (4)	

a Zemplar Lot 735178E02, Exp. Feb,2011, Comparison testing initiated 14 months prior to expiry

b Zemplar Lot 681958E07, Exp. Aug 2010, Comparison testing initiated 10 months prior to expiry

c Results are an average of 4 data points. All individual data points can be accessed in *3.2.P.8.3 Stability Data*.

- **Dissolution/Drug release.** This product is an immediate release injectable, no dissolution/drug release testing is necessary.
- **Manufacture**. The manufacturing process is typical of this dosage form, consisting of (b) (4)

- **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 all closures have been qualified using USP biological, physicochemical, and other tests, including extractables (see next bullet).

Table 17. Summary of the Container Closure System

Type	Description	Supplier	DMF
Glass Vial	Type I, Clear, 2 mL Vial	(b) (4)	(b) (4)
Closure	(b) (4)		
Seal			N/A [1]

1. Not considered a primary packaging component. A DMF reference is not applicable as there is no product contact with the seals.

- **Extractable/leachables**. The applicant states that the primary packaging components of this new product are the same as those of the RLD. However, this statement is not useful because 1) FDA cannot confirm that these components are the same (i.e., not authorized to check the referenced NDA), and 2) the diluents are different for the 2 products. As requested by FDA at the Pre-NDA meeting, the NDA includes a report on extractables/leachables (generated by using the drug product diluent, the proposed rubber stopper, and (b) (4) conditions), USP (b) (4) test results, and stability data. The primary CMC reviewer will evaluate the data and determine whether the applicant's proposal not to include leachable testing in the drug product specification would be acceptable.

Stability:

- As mentioned earlier, seven registration batches (3 batches of the 2 mcg/mL vial, 2 batches of the 5 mcg/mL vial, and 2 batches of the 10 mcg/2 mL vial) were manufactured with the commercial process, at (b) (4) commercial scale, with the commercial formulation. Each batch was packaged in the commercial container closure system. All batches were placed on stability as primary stability batches. The stability protocol includes testing for leachables and both inverted/upright positions for the sample storing, as requested by FDA at the Pre-NDA meeting.
- The applicant submitted 12-month data for the primary stability batches (at 25 °C/40% RH and 40 °C/25% RH). The primary reviewer will determine the final expiry based on all available data and per ICH Q1E Evaluation of Stability Data.
- Photostability data were obtained to support the claim that the product is not light-sensitive. However, in the QOS, the applicant states that " (b) (4)

[redacted] The discrepancy in statements regarding the photostability of the product should be clarified (see the 74-day letter comment on the first page of this review).

- As mentioned earlier, the container closure system is labeled as [redacted] and the applicant claims that the diluent system is antimicrobial. The primary CMC reviewer will consult with the primary Microbiologist on the appropriate shelf life limits of alcohol and propylene glycol to ensure adequate antimicrobial effectiveness through the proposed shelf life. No in-use stability data can be located in the NDA to support the labeled in-use period of 28 days at room temperature for the "multi-use" product vials (see the 74-day letter comment at the end of this review).

Supporting NDA or IND: none

Supporting DMFs:

The following Drug Master File (DMF) Letters of Authorization are provided herein:

[redacted] Type II DMF [redacted] Paricalcitol

[redacted]

GMP facilities: "Withhold" overall recommendation on 27-APR-2011

Table 2. Site Establishment Information

Production Site Address	Responsibilities	Inspection Status
(b) (4)	Drug Substance Manufacturer Release & Stability Testing	Ready for Inspection
Hospira, Inc. Contact Name: Hector Jimenez Telephone Number: 252-977-5606 Central File Number (CFN) 1021343	Release Testing	Ready for Inspection

Table 1. Site Establishment Information

Company Name and Address	Contact Name	Responsibilities
Hospira, Inc. Highway 301 North Rocky Mount, NC 27801 Registration No. 1021343	Hector Jimenez Manager, Plant Quality Assurance Tel. (252) 977-5606 Fax (252) 977-3786 Email: hector.jimenez@hospira.com	Drug Substance acceptance testing Excipient testing Component testing Manufacture of drug product Release testing of drug product Packaging and labeling of drug product Qualification of reference standard
Hospira, Inc. 10501 80th Ave. Pleasant Prairie, WI 53158 Registration No. 3005564767	Gary Moulton Manager, Quality Tel. (224) 212-4631 Fax (224) 212-5205 Email: gary.moulton@hospira.com	Storage of registration and commercial stability samples
Hospira, Inc. 375 North Field Drive Lake Forest, IL 60045 Registration No. 3004591926	Gary Moulton Manager, Quality Tel. (224) 212-4631 Fax (224) 212-5205 Email: gary.moulton@hospira.com	Stability testing for registration and commercial stability batches

Drug Product Specification

Test	Acceptance Criteria	Regulatory Analytical Procedure	Alternate Analytical Procedure	Justification for Specification
Clarity	Solution must be clear. Solution must not contain one or more particles that are visible upon attentive examination	USP <1> Ph.Eur.2.2.1	N/A	Complies with current USP <1> Injections and Ph. Eur 2.2.1.
Color	Solution must be colorless	P-0613	N/A	Conforms to the color description in innovator's package insert
Volume	NLT labeled volume (b) (4)	USP<1> Ph.Eur2.9.17	N/A	Specification is based upon process capabilities and complies with current USP <1> and Ph. Eur. 2.9.17 of NLT label volume.
Identification (HPLC)	Matches reference standard	USP	N/A	Complies with ICH 6A.
Assay	90.0% to 110.0%	MTS.01007-8A[1,2] MTS.01008-8A[1,2]	N/A	Complies with the Paricalcitol Injection USP monograph.

Test	Acceptance Criteria	Regulatory Analytical Procedure	Alternate Analytical Procedure	Justification for Specification
Degradation Products Specified Related Compound (b) (4) Related Compound Related Compound Related Compound Related Compound Related Compound Related Compound Related Compound Related Compound Unspecified Other Individual Total	 NMT (b) (4) NMT NMT NMT NMT NMT NMT NMT NMT NMT NMT	USP	N/A	Specification is consistent with the Paricalcitol Injection USP monograph and aligns with ICH guideline Q3B, and the maximum daily dose calculated per product insert.
Content of (b) (4) Alcohol	(b) (4)	MTS.01007-8D[1,2] MTS.01008-8D[1,2]	N/A	The specification interval, (b) (4) matches the USP monograph, but has been applied to the 40% target concentration.
Content of Propylene Glycol	(b) (4)	MTS.01007-8D[1,2] MTS.01008-8D[1,2]	N/A	The specification interval, (b) (4) matches the USP monograph, but has been applied to the 10% target concentration.
Particulate Matter	(b) (4)	USP <788> Ph.Eur. 2.9.29	N/A	Complies with current USP and Ph.Eur..
Sterility	Meets USP/EP requirements	USP <71> Ph.Eur. 2.6.1	N/A	Complies with current USP and Ph.Eur..
Limit of (b) (4)	(b) (4)	USP	N/A	Consistent with the Paricalcitol Injection USP monograph

Test	Acceptance Criteria	Regulatory Analytical Procedure	Alternate Analytical Procedure	Justification for Specification
Bacterial Endotoxins	(b) (4)	USP <85> Gel Clot Ph.Eur. 2.6.14	B-0820[3]	Specification is based upon the maximum dose calculated per product insert.
Bacterial Endotoxins		USP <85> Gel Clot Ph.Eur. 2.6.14	B-0822[3]	Specification is based upon the maximum dose calculated per product insert.
(b) (4)				

1 HPLC = High performance liquid chromatography; NLT = Not less than; NMT = Not more than

2 Non-USP analytical procedures are provided in *Section 3.2.P.5.2 Analytical Procedures*.

3 The validation data for the analytical procedures are provided in *Section 3.2.P.5.3 Validation of Analytical Procedures*.

4 We acknowledge that in the event of dispute, only the results obtained by the USP monograph will be considered conclusive.

5 Full Justification for Specification is provided in *Section 3.2.P.5.6 Justification of Specifications*.

PRODUCT QUALITY
FILING REVIEW FOR NDA (ONDQA)

NDA Number: 201657

Established/Proper Name: Paricalcitol

Applicant: Hospira Inc. **Letter Date: 07-APR-2011** **Stamp Date: 07-APR-2011**

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*				
	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.**			
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		
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		

* 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.

C. ENVIRONMENTAL ASSESMENT

	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or 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?			Reference is made to DMF.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Reference is made to DMF.
14.	Does the section contain information regarding the characterization of the DS?			Reference is made to DMF.
15.	Does the section contain controls for the DS?			Reference is made to DMF.
16.	Has stability data and analysis been provided for the drug substance?			Reference is made to DMF.
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		
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		
J. filing conclusion				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		See the first page of this review.

{See appended electronic signature page}

Su (Suong) Tran
CMC Lead
Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

{See appended electronic signature page}

Ali Al Hakim
Branch Chief
Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

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
06/01/2011

ALI H AL HAKIM
06/01/2011