

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205917Orig1s000

CHEMISTRY REVIEW(S)

NDA 205917

TradenameTM (Paricalcitol) Injection

Hikma Pharmaceuticals Co. Ltd

**Muthukumar Ramaswamy, Ph.D.
Office of New Drug Quality Assessment
Chemistry Review For Division of Metabolism and
Endocrinology Products**

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 205917
2. REVIEW #: 2
3. REVIEW DATE: 9/26/2014
4. REVIEWER: Muthukumar Ramaswamy

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Chemistry Review #1 for NDA205917	12/02/13
Original	06/10/ 2013
Amendment	09/27/2013

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	7/02/14

7. NAME & ADDRESS OF APPLICANT:

Name: Hikma Pharmaceuticals

Address: Bayader Wadi El Seer, Amman, Jordan

Representative: Jonathan Sterling, EXELA Pharma Sciences,
1325 William White Place, Lenoir, NC 28645

Telephone: 828-758-5474 ext. 104

8. DRUG PRODUCT NAME/CODE/TYPE:

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

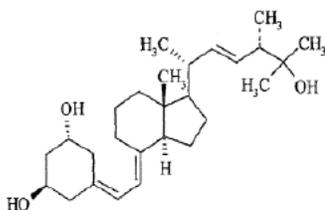
9. LEGAL BASIS FOR SUBMISSION: 505(b)2

10. PHARMACOL. CATEGORY: Prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease stage 5.

Chemistry Review Data Sheet

11. DOSAGE FORM: Injectable solution
12. STRENGTH/POTENCY: 2 mcg/mL (2 mcg per vial) or 5 mcg/mL (5 mcg or 10 mcg per vial)
13. ROUTE OF ADMINISTRATION: Intravenous Administration
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:



COMPENDIAL NAME: Paricalcitol, USP

CHEMICAL NAME: (1 α ,3 β ,7E,22E)-19-Nor-9,10-Secoergosta-5,7,22-triene-1,3,25-triol;
 (7E,22E)-19-Nor-9,10- Secoergosta- 5,7,22- triene-1 α , 3 β , 25-triol

MOLECULAR FORMULA AND WEIGHT: C₂₇H₄₄O₃ and 416.64 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETE	COMMENTS
(b) (4)	II	(b) (4)	Paricalcitol, USP	3	Adequate	NA	Reviewed by P. Selvam, Aug. 13, 2013 & by Dr. Ysem 9/09/14.
	III		(b) (4)	4	Adequate	NA	Reviewed by Don Klein dated 9/5/2012
	III		(b) (4)	3	Adequate	NA	For (b) (4) stopper formulation, refer to DMF (b) (4) review dated 6/06/11 by J. Jee; For (b) (4) Refer to R. Kasliwal review dated 9/03/09; For (b) (4) stopper formulation, Refer to Z. Dong Review dated

Chemistry Review Data Sheet

							7/22/2009 .
(b) (4)	IV		(b) (4)	1	Adequate	9/23/14	M. Ramaswamy

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 revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	9/24/14	
Pharm/Tox.	Acceptable	9/10/14	Dr. Parvaneh Espandiari
Biopharmaceutics	Biowaiver granted		Dr. A. Noory
LNC	N/A		Dr. M Ramaswamy, NDA review
Methods Validation	Not required		Dr. M Ramaswamy.
EA	Adequate	9-23-14	Dr. M Ramaswamy, NDA review (in consultation with Dr. R. Bloom)
Microbiology	Acceptable for (b) (4) processing procedures and microbiological methods	8/22/14	Dr. Robert Mello

Executive Summary Section

The Chemistry Review for 205917**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

From CMC perspective, this NDA is recommended for approval. All CMC related deficiencies are satisfactorily resolved. *Biopharm Reviewer (Dr. A. Noory) has determined that a biowaiver can be granted for this application. At this time, the microbiology reviewer, Dr. R. Mello has recommended approval of this application and an overall acceptable recommendation for facilities associated with the NDA is available from the Office of Compliance.*

A shelf life of 24 months is granted for product packaged in 2 mL Type I glass vials and sealed with (b) (4) closure and aluminum seal for storage at 25± 2°C/60% RH.

Trade name for this drug product is not proposed at this time.

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

None at this time.

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

Paricalcitol Injection, will be available as a sterile, colorless, solution containing 2 or 5 µg of Paricalcitol/mL in 2mL Type I USP glass vial sealed with (b) (4) stopper and will be further packaged in a single unit carton. Each vial contains 2 or 5 or 10 µg per unit dose container. Paricalcitol Injection is intended for intravenous use without further dilution and is meant for single use only.

Drug Substance (DS): Paricalcitol is a potent Vitamin D2 analog (Chemical Name: 19-nor-1,25-(OH)₂-vitamin D2 or 19-nor-1,25-dihydroxyvitamin D2). (b) (4)

The Applicant is using Paricalcitol USP monograph to accept the drug substance used for manufacturing the drug product. The proposed specifications for drug substance include test for appearance, identity, assay (Limit: NLT) (b) (4)

Executive Summary Section

The Applicant will be using a Paricalcitol USP as reference standard for assuring the identity and quality of the proposed drug substance and this is acceptable. The Applicant has provided method verification reports used for the determination of API content and related substance levels in the bulk drug substance.

The drug substance (Paricalcitol USP) will be purchased from (b) (4). The Applicant has referenced DMF (b) (4) for all CMC information pertaining to the drug substance. The status of the DMF is adequate to support the NDA.

Drug Product:

Paricalcitol Injection is proposed for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease stage 5, which is the same as the indication approved for Zemplar® (paricalcitol) Injection marketed by (b) (4). The proposed product contains 35% alcohol and (b) (4)% sorbitol. The innovator product contains 20% alcohol and 30% propylene glycol. The drug product is meant for single use only and does not contain any preservative.

The drug product manufacturing process involves (b) (4)

The excipients used in the manufacture of the drug product are compendial and the proposed levels of inactive ingredients are within the levels present in approved products. The NDA contains drawings, and dimensional specifications for the packaging components and provides adequate reference to their drug master files (DMFs).

The NDA provides adequate description of the name and address of the manufacturing facility, manufacturing process and equipment to be used for the manufacture of the drug product, copies of the executed batch production records, specifications and certificates of analysis for the components and excipients used for the manufacture of the stability batches. A copy of the master batch record to be used for manufacturing commercial scale batch is also provided in the NDA.

The Applicant's proposed manufacturing process ((b) (4) scale) is based on the process used for manufacturing stability batches at (b) (4) scale. The commercial process utilizes (b) (4)

The NDA contains adequate manufacturing and in-process control information to support the proposed NDA. The proposed in-process controls include (b) (4)

The proposed product specification include tests for appearance, identity (b) (4)

Executive Summary Section

The Applicant's proposed methods for testing the purity of the product during release and stability are adequate.

CMC reviewer has performed risk assessment on the adequacy of process controls and the influence of manufacturing process parameters on product quality attributes. Risk assessment concluded that adequate manufacturing controls (process parameters, incoming controls, and specification) are proposed to control the quality of the finished product. Controls proposed for sterility and endotoxin are typical parenteral manufacturing process. No additional risk mitigation necessary.

Executive Summary					
From Initial Risk Assessment			Review Assessment		
Product attribute/CQA	Factors that can impact the CQA	Initial Risk ranking	Final Risk ranking	Risk Evaluation	Comment
Assay	Formulation Analytical methods Container closure Raw materials Process parameters Scale/equipment Site		(b) (4)	Acceptable	
Related Compounds % % Individual and total impurities	Formulation Analytical methods Container closure Raw materials Process parameters Scale/equipment Site		Acceptable		
Limit for (b) (4)	Formulation Container closure Raw materials Process parameters Scale/equipment Site		Acceptable		
Sterility	Formulation Container closure Process parameters		Acceptable		

Executive Summary Section

	Scale/equipment Site	(b) (4)		(b) (4)
Endotoxin (b) (4)	Formulation Container closure Process parameters Scale/equipment Site		Acceptable	
Appearance	Formulation Container closure Process parameters Scale/equipment Site		Acceptable	
Uniformity of dose	Formulation Container closure Process parameters Scale/equipment Site		Acceptable	
Particulate matter	Formulation Container closure Raw materials Process parameters Scale/equipment Site		Acceptable	
Leachables/ /Extractables	Formulation Container closure Process parameters Scale/equipment Site		Acceptable	

Executive Summary Section

					(b) (4)
					(b) (4)
Fill Volume	Container closure			(b) (4)	Acceptable

The Applicant has requested 24 months shelf-life for the proposed product based on data from 6 months accelerated (40°±5°C/75%±5%RH) and 24 months long-term stability data at 25°±2°C/ 60%±5%RH for seven batches of product filled in single dose containers. The information provided in the NDA is adequate to support 24 month shelf-life.

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

Paricalcitol Injection is indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5. Paricalcitol Injection is provided as 2 mcg/mL or 5mcg/mL solution in single-use vial. The product is to be administered by intravenous administration without further dilution. The recommended initial dose of Paricalcitol is 0.04 mcg/kg to 0.1 mcg/kg (2.8 – 7.0 mcg) administered as a bolus dose no more frequently (b) (4) during dialysis. The drug product should not be injected directly into a vein. Per label, the dose may be increased by 2 to 4mcg at 2- to 4- week intervals to reach desired levels. Paricalcitol should not be given to patients with evidence of vitamin D toxicity, hypercalcemia, or hypersensitivity to any ingredient in this product. Store the product at 25°C (77°F).

C. Basis for Approvability or Not-Approval Recommendation

From CMC perspective, this NDA is recommended for approval. All CMC related issues are satisfactorily resolved. The NDA contains adequate CMC information for the manufacturing of Paricalcitol injection.

The microbiology reviewer, Dr. R. Mello has recommended approval of this application based on his review of the process controls provided in the manufacturing process (b) (4)

An overall acceptable recommendation from Office of Compliance for the manufacture’s readiness to make this product is available as of 9/25/14.

The Applicant has requested a biowaiver for the proposed 2 and 5 µg/mL strength Paricalcitol Injection, on the grounds that it has the same active ingredient, dosage form, strength, route of administration, and

Executive Summary Section

conditions of use as listed for ZEMPLAR (Paricalcitol) Injection, approved under NDA 20-819. Biopharm Reviewer (Dr. A. Noory) has determined that a biowaiver can be granted for this application.

III. Administrative**A. Reviewer's Signature**

Chemist Name/Date: Muthukumar Ramaswamy, Ph.D.

B. Endorsement Block

Chemistry Team Leader Name/Date: Danae Christodoulou, Ph.D.

C. CC Block

CMC Lead: Suong Tran Ph.D.

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/s/

MUTHUKUMAR RAMASWAMY
09/26/2014

DANAE D CHRISTODOULOU
09/29/2014

NDA 205917

TradenameTM (Paricalcitol) Injection

Exela Pharma Sciences

Muthukumar Ramaswamy, Ph.D.
Office of New Drug Quality Assessment
Chemistry Review For Division of Metabolism and
Endocrinology Products

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 205917

2. REVIEW #: 1

3. REVIEW DATE: 12/2/2013

4. REVIEWER: Muthukumar Ramaswamy

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
None	

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	06/10/ 2013
Amendment	09/27/2013

7. NAME & ADDRESS OF APPLICANT:

Name: Hikima Pharmaceuticals

Address: Bayader Wadi El Seer, Amman, Jordan

Representative: Jonathan Sterling, EXELA Pharma Sciences,
1325 William White Place, Lenoir, NC 28645

Telephone: 828-758-5474 ext. 104

8. DRUG PRODUCT NAME/CODE/TYPE:

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

9. LEGAL BASIS FOR SUBMISSION: 505(b)2

10. PHARMACOL. CATEGORY: Prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease stage 5.

Chemistry Review Data Sheet

11. DOSAGE FORM: Injectable solution
12. STRENGTH/POTENCY: 2 mcg/mL (2 mcg per vial) or 5 mcg/mL (5 mcg or 10 mcg per vial)
13. ROUTE OF ADMINISTRATION: Intravenous Administration

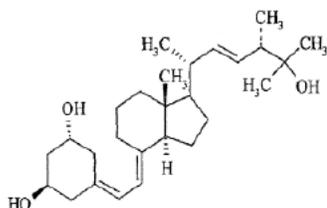
14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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



COMPENDIAL NAME: Paricalcitol, USP

CHEMICAL NAME: (1 α ,3 β ,7E,22E)-19-Nor-9,10-Secoergosta-5,7,22-triene-1,3,25-triol;
(7E,22E)-19-Nor-9,10- Secoergosta- 5,7,22- triene-1 α , 3 β , 25-triol

MOLECULAR FORMULA AND WEIGHT: C₂₇H₄₄O₃ and 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, USP	3	Adequate	NA	Reviewed by P. Selvam, Aug. 13, 2013
	III	(b) (4)	(b) (4)	4	Adequate	NA	Reviewed by Don Klein dated 9/5/2012
	III	(b) (4)	(b) (4)	3	Adequate	NA	For (b) (4) stopper formulation, refer to DMF (b) (4) review dated 6/06/11 by J. Jee; (b) (4) Refer to R. Kasilwal review dated 9/03/09; For (b) (4) stopper formulation, Refer to Z. Dong Review dated 7/22/2009 .

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 revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending		
Pharm/Tox.	NA		
Biopharm	pending		Banu Zolnik
LNC	N/A		M Ramaswamy, NDA review
Methods Validation	May be required		
EA	Adequate	10-04-06	M Ramaswamy, NDA review
Microbiology	pending		Robert Mello

Executive Summary Section

The Chemistry Review for 205917

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

From CMC perspective, this NDA is not recommended for approval until a satisfactory response to CMC deficiencies is available. This CMC recommendation does not incorporate any potential facility inspection issues or biopharmaceutics issues or any potential microbiology review related issues. As of 12/2/13, an acceptable recommendation for facilities associated with the NDA from the Office of Compliance, biowaiver assessment from biopharmaceutics reviewer and adequacy of the (b) (4) processing procedures and microbiological methods from microbiology reviewer is pending.

A shelf-life of 12 months is recommended for product packaged in 2mL Type I glass vials and sealed with (b) (4) closure and aluminum seal for storage at 25± 2°C/60% RH.

Trade name for this drug product is not proposed at this time.

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

None at this time.

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

Paricalcitol Injection, will be available as a sterile, colorless, solution containing 2 or 5 µg of Paricalcitol/mL in 2mL Type I USP glass vial sealed with (b) (4) stopper and will be further packaged in a single unit carton. Each vial contains 2 or 5 or 10 µg per unit dose container. Paricalcitol Injection is intended for intravenous use without further dilution and is meant for single use only.

Paricalcitol Injection is proposed for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease stage 5, which is the same as the indication approved for Zemplar® (paricalcitol) Injection marketed by (b) (4). The proposed product contains 35% alcohol and (b) (4) % sorbitol. The innovator product contains 20% alcohol and 30% propylene glycol. The drug product is meant for single use only and does not contain any preservative.

Paricalcitol is a potent Vitamin D2 analog. (b) (4)

The drug product manufacturing process involves (b) (4)

Executive Summary Section

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

Paricalcitol Injection is indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5. Paricalcitol Injection is provided as 2 mcg/mL or 5mcg/mL solution in single-use vial. The product is to be administered by intravenous administration without further dilution. The recommended initial dose of Paricalcitol is 0.04 mcg/kg to 0.1 mcg/kg (2.8 – 7 mcg) administered as a bolus dose no more frequently (b) (4) during dialysis. Paricalcitol should not be given to patients with evidence of vitamin D toxicity, hypercalcemia, or hypersensitivity to any ingredient in this product. Store the product at 25°C (77°F).

C. Basis for Approvability or Not-Approval Recommendation

An information request will be sent to the Applicant to clarify questions related to potential CMC deficiencies listed at the end of the review. With the exception of these issues listed, the NDA contains *adequate* CMC information for the manufacturing of Paricalcitol injection.

Drug Substance (DS): The drug substance (Paricalcitol USP) will be purchased from (b) (4). The Applicant has referenced DMF (b) (4) for all CMC information pertaining to the drug substance. The current status of the DMF is adequate to support the NDA.

The Applicant is using Paricalcitol USP monograph to accept the drug substance used for manufacturing the drug product. The proposed specifications for drug substance include test for appearance, identity, *Assay (Limit: NLT*

(b) (4)

The Applicant will be using a USP reference standard for assuring the identity and quality of the proposed drug substance and is acceptable. The Applicant has provided method verification reports used for the determination of API content and related substance levels in the bulk drug substance. *The Applicant's method verification study did not verify the ability of the method to detect USP and the DS supplier specified product related substances* (b) (4)

Drug Product:

The NDA provides description and composition of the drug product and contains adequate information on the components used for manufacturing the product. *The excipients used in the manufacture the drug product are compendial and the proposed levels of inactive ingredient are within the levels present in approved products.* The NDA contains drawings, and dimensional specifications for the packaging components and provides adequate reference to their drug master files (DMFs).

The NDA contains a description of the name and address of the manufacturing facility, and equipment to be used for the manufacture of the drug product, copies of the executed batch production records, specifications and certificates of analysis for the components and excipients used for the manufacture of the stability batches. A copy of the master batch record to be used for manufacturing commercial scale batch is also provided in the NDA.

The manufacturing process is comprised (b) (4)

Executive Summary Section

The NDA contains adequate manufacturing and in-process control information to support the proposed NDA. The proposed in-process control include [REDACTED] (b) (4)

The proposed product specification is consistent with USP <1> injections. It includes tests for appearance, identity [REDACTED] (b) (4)

The Firm is proposing to use [REDACTED] (b) (4)

The Applicant's proposed method for testing the purity of the product during release and stability is inadequate, as it did not evaluate the ability of the method to detect potential product related substances and degradation products in the product [REDACTED] (b) (4)

The Applicant has requested 24 months shelf-life for the proposed product based on data from 6 months accelerated (40°±5°C/75%±5%RH) and 12 months long-term stability data at 25°±2°C/ 60%±5%RH for seven batches of product filled in single dose containers. The information provided in the NDA is adequate to support 12 month shelf-life.

The Applicant has claimed a biowaiver for the proposed 2 and 5 µg/mL strength Paricalcitol Injection, on the grounds that it has the same active ingredient, dosage form, strength, route of administration, and conditions of use as listed for ZEMPLAR (Paricalcitol) Injection, approved under NDA 20-819. As of 10/21/13, a recommendation for the waiver request, from Biopharm Reviewer (Dr. Banu Zolnik) is pending.

Manufacturing facilities. An overall recommendation from Office of Compliance for the manufacture's readiness to make this product is pending.

III. Administrative

A. Reviewer's Signature

Chemist Name/Date: Muthukumar Ramaswamy, Ph.D.

B. Endorsement Block

Chemistry Team Leader Name/Date: Danae Christodoulou, Ph.D.

C. CC Block

CMC Lead: Suong Tran Ph.D.

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

/s/

MUTHUKUMAR RAMASWAMY
12/02/2013

DANAE D CHRISTODOULOU
12/02/2013

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	NDA 205-917
Submission Date	June 10, 2013
Product name, generic name of the active	Paricalcitol injection
Dosage form and strength	2 µg/mL and 5 µg/mL
Applicant	Exela Pharma Sciences as a regulatory agent for Hikma Pharmaceutical Co. Ltd.
Clinical Division	Division of Metabolism and Endocrinology Products
Type of Submission	505 (b) (2)
Biopharmaceutics Reviewer	Banu S. Zolnik, Ph.D.
Secondary Signature	Sandra Suarez Sharp, Ph.D.
Acting Supervisor	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					
<u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING					
	Parameter	Yes	No	N/A	Comment
1.	Does the application contain dissolution data?			X	The application contains Paricalcitol for injection and the proposed drug product is in solution, therefore there is no dissolution data.
2.	Is the dissolution test part of the DP specifications?			X	
3.	Does the application contain the dissolution method development report?			X	
4.	Is there a validation package for the analytical method?	X			Bioanalytical Validation of LC/MS/MS is submitted for quantification of paricalcitol in rat plasma.
5.	Does the application contain in vitro alcohol induced dose dumping studies?			X	NA
6.	Does the application include a biowaiver request?	X			The Applicant submitted a request for waiver of in vivo bioavailability/bioequivalence.
7.	Is there information provided to support the biowaiver request?		X		The Applicant did not provide any data (published literature/study data) to demonstrate that the differences in the alcohol concentration and presence of sorbitol between their product and the RLD have no impact on the pharmacokinetics, efficacy and safety of their product.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

8.	Does the application include an IVIVC model?		X		
9.	Is information such as BCS classification mentioned, and supportive data provided?		X		
10.	Is information on mixing the product with foods or liquids included?		X		
11.	Is there any <i>in vivo</i> BA or BE information in the submission?		X		
12.	Are there any manufacturing changes implemented to the clinical trial and bio batch formulations?			X	There is no clinical trial or bio batch formulation
13.	Is there any data to submitted to support the manufacturing changes			X	
14.	Is there any data submitted to support the proposed dissolution specification?			X	

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
15.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	X		
16.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
17.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
18.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	X		Yes, however, IR comments will be sent to the Applicant in the 74-day letter. The comments are outlined in the Attachment.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

BIOPHARMACEUTICS INITIAL ASSESSMENT

SUMMARY

This 505(b)(2) NDA application for paricalcitol, a synthetically manufactured analog of calcitriol, the metabolically active form of vitamin D, is for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5. The approved NDA# 20819 for paricalcitol is Abbvie's Zemplar (paricalcitol) 2 µg/mL and 5 µg/mL.

The Applicant is requesting a waiver of in vivo bioavailability/bioequivalence requirements for their Paricalcitol Injection.

Below is the Comparison Table of the ingredients in Exela's product, with the RLD.

A comparison of the ingredients in Exela's Paricalcitol Injection, 2 µg/mL and 5 µg/mL, with Abbott Laboratories Zemplar® (paricalcitol) Injection is presented in the following tables.

Ingredients	Exela's Formulation	Abbott Laboratories Formulation ¹
Paricalcitol, USP	2 µg/mL or 5 µg/mL	2 µg/mL or 5 µg/mL
Alcohol, 190 proof, USP	35% v/v	20% v/v
Propylene Glycol, USP		30% v/v
Sorbitol Solution, 70%, USP	7% v/v	
Water for Injection, USP	q.s.	q.s.

¹ Information regarding Abbot Laboratories Zemplar ® (paricalcitol) Injection formulation was obtained from the current package insert, vial label, and carton.

The Exela's formulation contains 35% (v/v) alcohol, whereas the approved reference listed drug contains 20% (v/v) alcohol. In addition, Exela's formulation contains sorbitol solution (70%) at a concentration of 7% ((v/v), whereas the RLD contains propylene glycol at a concentration of 30% (v/v).

As per 21 CFR § 320.22 (b)(1), FDA shall waive the requirement for the submission of data demonstrating bioequivalence if the drug product is a parenteral solution for injection and contains the same active and inactive ingredients in the same concentration as a drug product that is the

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

subject of an approved full new drug application. The alcohol concentration of the proposed product is not in the same concentration as those of the Reference Listed Product (RLD) product. In addition, there are might be some differences in pH, tonicity, and osmolarity between the two products. Therefore, a sufficient justification with supporting data (e.g., published literature, study data, etc.) is requested to demonstrate that the differences in alcohol concentration, pH, tonicity, and osmolarity between Exala's product and the RLD do not have any impact on the pharmacokinetics, efficacy, and safety of the Exala's product, as compared to those of the RLD.

The Biopharmaceutics review will be focused on the waiver request of in vivo bioavailability/bioequivalence requirements for Exela's Paricalcitol Injection.

RECOMMENDATION:

From the ONDQA-Biopharmaceutics perspective, NDA 205-917 for Exala's Paricalcitol, 2mcg/mL and 5 mcg/mL is **fileable**. The following comments should be conveyed to the Applicant in the 74-Day Letter.

Biopharmaceutics Comments:

Provide a justification with supporting data (e.g., published literature, study data, etc.) demonstrating that the presence of sorbitol, differences in alcohol concentration, pH, tonicity, and osmolarity between your product and the RLD do not have any impact on the stability, pharmacokinetics (e.g, renal clearance), efficacy, and safety of the Exala's product, as compared to those of the RLD.

{See appended electronic signature page}

Banu S. Zolnik, PhD
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

07/30/13
Date

{See appended electronic signature page}

Sandra Suarez Sharp, Ph.D.
Secondary Signature
Office of New Drug Quality Assessment

07/30/13
Date

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

/s/

BANU S ZOLNIK
07/30/2013

SANDRA SUAREZ
07/31/2013

ONDQA Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications

1. NEW DRUG APPLICATION NUMBER: 205917

2. DATES AND GOALS:

Letter Date: 6/07/2013	Submission Received Date : 6/10/2013
PDUFA Goal Date: 4/10/2014 (NDA is not part of "The Program")	

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	None proposed
Established or Non-Proprietary 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

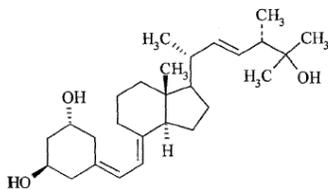
4. INDICATION: Prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease stage 5.

5. DRUG SUBSTANCE STRUCTURAL FORMULA:

Chemical Name(s): (1 α ,3 β ,7E,22E)-19-Nor-9,10-Secoergosta-5,7,22-triene-1,3,25-triol.

Or

(7E,22E)-19-Nor-9,10- Secoergosta- 5,7,22- triene-1 α , 3 β , 25-triol



**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Molecular Formula: C₂₇H₄₄O₃

Molecular Weight: 416.64 g/mol

6. NAME OF APPLICANT (as indicated on Form 356h): Hikma Pharmaceuticals

7. SUBMISSION PROPERTIES:

Review Priority (select one)	Standard
Submission Classification (Chemical Classification Code):	5
(Application Type):	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (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			

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	x		
2.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
3.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	x		<ul style="list-style-type: none"> The fill volume ranges are (b) (4) for the 1 mL vials and (b) (4) for the 2 mL vial. Provide a justification for the excess volumes that exceed the USP recommended volumes for the two fill sizes, with data to demonstrate that the excess is necessary to consistently withdraw (b) (4)% of the labeled volumes. Provide information on the extractables/leachables testing of the primary container closure system of the drug product, or provide its location in the NDA.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

**CMC Summary:
Critical Issues and Complexities**

Summary of Critical CMC Issues Previously Discussed with the Applicant (if any):			
No CMC issue was previously discussed.			
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) – review by Robert Mello Biopharmaceutics (biowaiver request) – review by Banu Zolnick

Summary or Highlights of the Application (not already mentioned in other sections)
<ul style="list-style-type: none"> The NDA is a 505(b)(2) application for Paricalcitol Injection, with the approved Zemplar as referenced product. The two products differ in formulation as follows: (new product vs. Zemplar) Alcohol, (b)(4) USP (35% vs. 20%), Propylene Glycol, USP (none vs. 30%), and Sorbitol Solution, 70%, USP (7% vs. none). The new product cannot be submitted in an ANDA because of the different (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. Sterility assurance will be evaluated by the OPS Microbiology Staff. The established name of the product is “paricalcitol” based on the dosage strength, which is acceptable per current CDER’s policy on nomenclature. The primary stability batches and the commercial product have the same formulation, same container closure system, same manufacturing site and process, and the stability batch size is (b)(4)% commercial batch size.
<p>Drug Substance Paricalcitol is a small synthetic molecule drug substance. Reference is made to the DMF (b)(4) for all CMC information on the drug substance. A copy of the approved drug substance specification is included in Attachment 3 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.</p>
<p>Drug Product <u>Composition.</u> A copy of the product composition is included in Attachment 1 of this review. The product is for direct IV injection (no dilution/reconstitution).</p> <ul style="list-style-type: none"> (b)(4) Excipients are within FDA’s IIG limits for the same dosage form and route of administration. There is no preservative, and the labeling states that all vials are for single-dose use. <p><u>Manufacture.</u> The manufacturing process is typical of this dosage form, consisting of</p>

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

(b) (4)	
Master batch records are included in the NDA for the commercial manufacturing process (complying with 505(b)(2) regulations).	
<p><u>Drug product specification.</u> A copy of the drug product specification is included in Attachment 2 of this review. The attributes are standard for this type of dosage form (injectable solution). The limit on an unknown impurity is (b) (4)%, which meets the ICH identification and qualification thresholds for the maximum daily dose. The limit on Total Impurities is (b) (4)%, which is comparable to the limits in other approved products. Based on the stability report, degradation appears to be very minimal.</p>	
<p><u>Container closure system.</u> 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.</p>	
<p><u>Stability.</u> The NDA includes 9-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 mcL/mL in 1mL vials, three batches of the 5 mcL/mL in 2 mL vials, and one batch of the 5 mcL/mL in 1mL vials. All vials were stored inverted. Stress studies include photostability (b) (4). Information on leachable testing cannot be located (see the 74-day letter comment). The primary reviewer will determine the final expiry based on all available data and per ICH Q1E Evaluation of Stability Data.</p>	
Description of Any Facility Related Risks or Complexities with this Application.	
<i>See EES for complete list of facilities related to this application.</i>	

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
4.	Is the CMC section organized adequately?	x		
5.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
6.	Are all the pages in the CMC section legible?	x		
7.	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.	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

	Parameter	Yes	No	Comment
8.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
9.	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

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

	Parameter	Yes	No	Comment
10.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • 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		
11.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

	Parameter	Yes	No	Comment
12.	<p>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:</p> <ul style="list-style-type: none"> • 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		
13.	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
14.	Has an environmental assessment or claim of categorical exclusion been provided?	x		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

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

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

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

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

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

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

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
34.	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	(b) (4)
	III		(b) (4)	
	III			
	III			

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

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

[See appended electronic signature page](#)

CMC-Lead or CMC Senior Reviewer

Division

Office of New Drug Quality Assessment

[See appended electronic signature page](#)

Branch Chief or Designee

Division

Office of New Drug Quality Assessment

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Appendix 1. Composition of Drug Product (*Optional*)

Component	Quality Standard	Function	Paricalcitol Injection (5 µg / mL and 2 µg / mL)
Paricalcitol	N/A	Drug Substance	5 µg / mL and 2 µg / mL
Alcohol, (b) (4)	USP	(b) (4)	35% v/v
Sorbitol Solution, 70%	USP	(b) (4)	7% v/v
Water for Injection	USP	(b) (4)	q.s. to 1.0 mL

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Appendix 2. Drug Product Specification (Optional)

Paricalcitol Injection (2 µg/mL), 1 mL fill

TEST	SPECIFICATION	
Physical Appearance and Description		
A. Solution Description	A. Clear, colorless, solution	C
B. Container/Closure Appearance	B. No visible leak, precipitate, or other abnormalities	C
C. Visual Particulate Matter	C. Essentially free of visible particulate matter	C
Identification		
A. UV	(b) (4)	C
B. HPLC Retention Time	Conforms to standard	
Assay, % Label Claim	(b) (4)	
Limit of (b) (4)	NMT (b) (4)	
Related Substances, %		
A. Single Individual Unknown	NMT (b) (4)	
B. Total Impurities	NMT (b) (4)	
Fill Volume, mL	NLT (b) (4)	
Sterility	No growth is observed	
Bacterial Endotoxin, EU/µg	NMT (b) (4) Paricalcitol	
Particulate Matter, per Container:		
A. (b) (4)	NMT (b) (4)	
B. (b) (4)	NMT (b) (4)	

APPEARS THIS
WAY ON ORIGINAL

NMT = Not More Than
NLT = Not Less Than

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Paricalcitol Injection (5 µg/mL), 2 mL fill

TEST	SPECIFICATION
Physical Appearance and Description	
A. Solution Description	A. Clear, colorless, solution
B. Container/Closure Appearance	B. No visible leak, precipitate, or other abnormalities
C. Visual Particulate Matter	C. Essentially free of visible particulate matter
Identification	
A. UV	(b) (4)
B. HPLC Retention Time	Conforms to standard
Assay, % Label Claim	(b) (4)
Limit of (b) (4)	NMT (b) (4)
Related Substances, %	
A. Single Individual Unknown	NMT (b) (4)
B. Total Impurities	NMT (b) (4)
Fill Volume, mL	NLT (b) (4)
Sterility	No growth is observed
Bacterial Endotoxin, EU/µg	NMT (b) (4) Paricalcitol
Particulate Matter, per Container:	
A. (b) (4)	NMT (b) (4)
B. (b) (4)	NMT (b) (4)

APPEARS THIS WAY
ON ORIGINAL

NMT = Not More Than
NLT = Not Less Than

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Appendix 3. Drug Substance Specification (Optional)

TEST	SPECIFICATION
Description	White to almost white, powder
Identification IR/ USP<197K> HPLC Retention Time	Conforms to Standard Conforms to Standard
Loss on Drying, USP <891>	NMT (b) (4)
Assay (b) (4)	(b) (4)
Related Compounds Unknown Impurity Total Impurities	(b) (4)
Residual Solvents (b) (4)	(b) (4)
Microbial Limits / USP<61> Total Aerobic Count Yeast and Mold	(b) (4)
Microbial Limits / USP<62> Salmonella Escherichia coli Staphylococcus aureus Pseudomonas aeruginosa	(b) (4)
Bacterial Endotoxin / USP<85>	(b) (4)

NMT: Not More Than

ND: Not Detected

(b) (4)

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ORIGINAL

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/s/

SUONG T TRAN
07/26/2013

DANAE D CHRISTODOULOU
07/26/2013

ONDQA Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications

1. NEW DRUG APPLICATION NUMBER: 205917

2. DATES AND GOALS:

Letter Date: 6/07/2013	Submission Received Date : 6/10/2013
PDUFA Goal Date: 4/10/2014 (NDA is not part of "The Program")	

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	None proposed
Established or Non-Proprietary 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

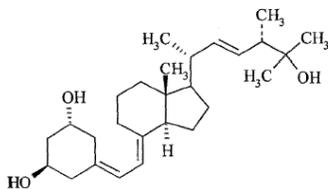
4. INDICATION: Prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease stage 5.

5. DRUG SUBSTANCE STRUCTURAL FORMULA:

Chemical Name(s): (1 α ,3 β ,7E,22E)-19-Nor-9,10-Secoergosta-5,7,22-triene-1,3,25-triol.

Or

(7E,22E)-19-Nor-9,10- Secoergosta- 5,7,22- triene-1 α , 3 β , 25-triol



**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

Molecular Formula: C₂₇H₄₄O₃

Molecular Weight: 416.64 g/mol

6. NAME OF APPLICANT (as indicated on Form 356h): Hikma Pharmaceuticals

7. SUBMISSION PROPERTIES:

Review Priority (select one)	Standard
Submission Classification (Chemical Classification Code):	5
(Application Type):	505(b)(2)
Breakthrough Therapy	No
Responsible Organization (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			

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	x		
2.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
3.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	x		<ul style="list-style-type: none"> The fill volume ranges are (b) (4) for the 1 mL vials and (b) (4) for the 2 mL vial. Provide a justification for the excess volumes that exceed the USP recommended volumes for the two fill sizes, with data to demonstrate that the excess is necessary to consistently withdraw (b) (4)% of the labeled volumes. Provide information on the extractables/leachables testing of the primary container closure system of the drug product, or provide its location in the NDA.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

**CMC Summary:
Critical Issues and Complexities**

Summary of Critical CMC Issues Previously Discussed with the Applicant (if any):			
No CMC issue was previously discussed.			
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) – review by Robert Mello Biopharmaceutics (biowaiver request) – review by Banu Zolnick

Summary or Highlights of the Application (not already mentioned in other sections)
<ul style="list-style-type: none"> The NDA is a 505(b)(2) application for Paricalcitol Injection, with the approved Zemplar as referenced product. The two products differ in formulation as follows: (new product vs. Zemplar) Alcohol, (b)(4), USP (35% vs. 20%), Propylene Glycol, USP (none vs. 30%), and Sorbitol Solution, 70%, USP (7% vs. none). The new product cannot be submitted in an ANDA because of the different solvent system. 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. Sterility assurance will be evaluated by the OPS Microbiology Staff. The established name of the product is “paricalcitol” based on the dosage strength, which is acceptable per current CDER’s policy on nomenclature. The primary stability batches and the commercial product have the same formulation, same container closure system, same manufacturing site and process, and the stability batch size is (b)(4)% commercial batch size.
<p>Drug Substance Paricalcitol is a small synthetic molecule drug substance. Reference is made to the DMF (b)(4) for all CMC information on the drug substance. A copy of the approved drug substance specification is included in Attachment 3 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.</p>
<p>Drug Product <u>Composition.</u> A copy of the product composition is included in Attachment 1 of this review. The product is for direct IV injection (no dilution/reconstitution).</p> <ul style="list-style-type: none"> (b)(4) Excipients are within FDA’s IIG limits for the same dosage form and route of administration. There is no preservative, and the labeling states that all vials are for single-dose use. <p><u>Manufacture.</u> The manufacturing process is typical of this dosage form, consisting of</p>

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications**

(b) (4)	
Master batch records are included in the NDA for the commercial manufacturing process (complying with 505(b)(2) regulations).	
<p><u>Drug product specification.</u> A copy of the drug product specification is included in Attachment 2 of this review. The attributes are standard for this type of dosage form (injectable solution). The limit on an unknown impurity is (b) (4)%, which meets the ICH identification and qualification thresholds for the maximum daily dose. The limit on Total Impurities is (b) (4)%, which is comparable to the limits in other approved products. Based on the stability report, degradation appears to be very minimal.</p>	
<p><u>Container closure system.</u> 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.</p>	
<p><u>Stability.</u> The NDA includes 9-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 mcL/mL in 1mL vials, three batches of the 5 mcL/mL in 2 mL vials, and one batch of the 5 mcL/mL in 1mL vials. All vials were stored inverted. Stress studies include photostability (b) (4). Information on leachable testing cannot be located (see the 74-day letter comment). The primary reviewer will determine the final expiry based on all available data and per ICH Q1E Evaluation of Stability Data.</p>	
Description of Any Facility Related Risks or Complexities with this Application.	
<i>See EES for complete list of facilities related to this application.</i>	

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
4.	Is the CMC section organized adequately?	x		
5.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
6.	Are all the pages in the CMC section legible?	x		
7.	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.	

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	Parameter	Yes	No	Comment
8.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
9.	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

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	Parameter	Yes	No	Comment
10.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • 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		
11.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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		

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	Parameter	Yes	No	Comment
12.	<p>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:</p> <ul style="list-style-type: none"> • 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		
13.	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
14.	Has an environmental assessment or claim of categorical exclusion been provided?	x		

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

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

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

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

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
34.	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	(b) (4)
	III		(b) (4)	
	III			
	III			

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

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This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

[See appended electronic signature page](#)

CMC-Lead or CMC Senior Reviewer

Division

Office of New Drug Quality Assessment

[See appended electronic signature page](#)

Branch Chief or Designee

Division

Office of New Drug Quality Assessment

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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Appendix 1. Composition of Drug Product (*Optional*)

Component	Quality Standard	Function	Paricalcitol Injection (5 µg / mL and 2 µg / mL)
Paricalcitol	N/A	Drug Substance	5 µg / mL and 2 µg / mL
Alcohol, (b) (4)	USP	(b) (4)	35% v/v
Sorbitol Solution, 70%	USP	(b) (4)	7% v/v
Water for Injection	USP	(b) (4)	q.s. to 1.0 mL

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Appendix 2. Drug Product Specification (Optional)

Paricalcitol Injection (2 µg/mL), 1 mL fill

TEST	SPECIFICATION	
Physical Appearance and Description		
A. Solution Description	A. Clear, colorless, solution	C
B. Container/Closure Appearance	B. No visible leak, precipitate, or other abnormalities	C
C. Visual Particulate Matter	C. Essentially free of visible particulate matter	C
Identification		
A. UV	(b) (4)	C
B. HPLC Retention Time	Conforms to standard	
Assay, % Label Claim	(b) (4)	
Limit of (b) (4)	NMT (b) (4)	
Related Substances, %		
A. Single Individual Unknown	NMT (b) (4)	
B. Total Impurities	NMT	
Fill Volume, mL	NLT	
Sterility	No growth is observed	
Bacterial Endotoxin, EU/µg	NMT (b) (4) Paricalcitol	
Particulate Matter, per Container:		
A. (b) (4)	NMT (b) (4)	
B.	NMT	

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NMT = Not More Than
NLT = Not Less Than

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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Paricalcitol Injection (5 µg/mL), 2 mL fill

TEST	SPECIFICATION
Physical Appearance and Description	
A. Solution Description	A. Clear, colorless, solution
B. Container/Closure Appearance	B. No visible leak, precipitate, or other abnormalities
C. Visual Particulate Matter	C. Essentially free of visible particulate matter
Identification	
A. UV	(b) (4)
B. HPLC Retention Time	Conforms to standard
Assay, % Label Claim	(b) (4)
Limit of (b) (4)	NMT (b) (4)
Related Substances, %	
A. Single Individual Unknown	NMT (b) (4)
B. Total Impurities	NMT (b) (4)
Fill Volume, mL	NLT (b) (4)
Sterility	No growth is observed
Bacterial Endotoxin, EU/µg	NMT (b) (4) Paricalcitol
Particulate Matter, per Container:	
A. (b) (4)	NMT (b) (4)
B. (b) (4)	NMT (b) (4)

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NMT = Not More Than
NLT = Not Less Than

**ONDQA Initial Quality Assessment (IQA) and Filing Review
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Appendix 3. Drug Substance Specification (Optional)

TEST	SPECIFICATION
Description	White to almost white, powder
Identification IR/ USP<197K> HPLC Retention Time	Conforms to Standard Conforms to Standard
Loss on Drying, USP <891>	NMT (b) (4)
Assay (b) (4)	(b) (4)
Related Compounds Unknown Impurity Total Impurities	(b) (4)
Residual Solvents (b) (4)	(b) (4)
Microbial Limits / USP<61> Total Aerobic Count Yeast and Mold	(b) (4)
Microbial Limits / USP<62> Salmonella Escherichia coli Staphylococcus aureus Pseudomonas aeruginosa	(b) (4)
Bacterial Endotoxin / USP<85>	(b) (4)
NMT: Not More Than ND: Not Detected (b) (4)	

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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
07/11/2013

DANAE D CHRISTODOULOU
07/11/2013