

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205917Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 205917

SUPPL #

HFD # 510

Trade Name n/a

Generic Name paricalcitol injection

Applicant Name Hikma Pharmaceuticals Co. Ltd.
C/o Exela Pharma Sciences, LLC

Approval Date, If Known November 18, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

No clinical, bioavailability, or bioequivalence data was submitted to this original application. The applicant is claiming they are therapeutically equivalent to the reference listed drug, NDA 020819, Zemplar (paricalcitol injection). Nonclinical and CMC data were submitted to this application.

FDA granted a waiver of the *in vivo* bioequivalence study requirement per review dated 3/6/14.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

Pediatric exclusivity has been granted for NDA 020819, Zemplar (paricalcitol injection), the listed drug for this application, NDA 205917.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than

deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 020819 Zemplar (paricalcitol injection)

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application

and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # YES ! NO
! Explain:

Investigation #2 !
IND # YES ! NO

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Meghna M. Jairath, Pharm.D.
Title: Regulatory Project Manager
Date: November 17, 2014

Name of Office/Division Director signing form: Jean-Marc Guettier, M.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

MEGHNA M JAIRATH
11/18/2014

JEAN-MARC P GUETTIER
11/18/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 205917 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: n/a Established/Proper Name: Paricalcitol Injection Dosage Form: Intravenous solution 2mcg/ml (1ml); 5 mcg/mL (1 ml and 2 ml)		Applicant: Hikma Pharmaceuticals Co. Ltd Agent for Applicant (if applicable): Exela Pharma Sciences LLC
RPM: Meghna M. Jairath, Pharm.D.		Division: Division of Metabolism and Endocrinology Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (notify CDER OND IO) Date of check: November 18, 2014</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>November 18, 2014</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input type="checkbox"/> None Incomplete (no user fee)-11/15/13
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H
 Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

BLAs: Subpart E
 Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart I
 Approval based on animal studies

Subpart H
 Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments: Original application 6/7/13 submitted was unacceptable due to user fees not being paid. The sponsor paid user fees on 10/18/13 which restarted the PDUFA clock. The clock was extended by 3 months due to a major CMC amendment on 7/8/14 changing the PDUFA date to 11/18/14.

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • Indicate what types (if any) of information were issued 	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type -- 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes Pediatric exclusivity The sponsor submitted Patent II(5,246,925), III (5,587,497) and IV (5,597,815; 6,361,758; 6,136,799)
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) November 18, 2014
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Labeling

❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input type="checkbox"/> Included Please see final label attached to approval letter dated 11/18/14
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included Please see C/C label attached to approval letter dated 11/18/14
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	n/a
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input type="checkbox"/> None DMEPA: <input type="checkbox"/> None 5/28/14, 11/3/14 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input checked="" type="checkbox"/> None SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input type="checkbox"/> None CDRH 9/10/14

Administrative / Regulatory Documents

<ul style="list-style-type: none"> ❖ RPM Filing Review⁴/Memo of Filing Meeting (<i>indicate date of each review</i>) ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee 	<p>9/9/13</p> <p><input type="checkbox"/> Not a (b)(2) Cleared by Clearance Committee via email dated 7/9/14</p>
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<p><input checked="" type="checkbox"/> Included</p>
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p> <p><input type="checkbox"/> Not an AP action</p>
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: PREA not triggered 	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	<p>6/24/13, 8/24/13, 9/12/13, 11/15/13 (2), and 12/31/13; 3/6/14, 3/17/14, 6/11/14 (2), 7/8/14, 10/29/14 (2) and 11/13/14 (2)</p>
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	
<ul style="list-style-type: none"> ❖ Minutes of Meetings <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<p><input checked="" type="checkbox"/> N/A or no mtg</p> <p><input checked="" type="checkbox"/> No mtg</p> <p><input checked="" type="checkbox"/> No mtg</p> <p><input checked="" type="checkbox"/> N/A</p> <p><input checked="" type="checkbox"/> N/A</p>
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	<p><input checked="" type="checkbox"/> No AC meeting</p>
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) 	<p><input checked="" type="checkbox"/> None</p>
<ul style="list-style-type: none"> Division Director Summary Review (<i>indicate date for each review</i>) 	<p><input checked="" type="checkbox"/> None</p>
<ul style="list-style-type: none"> Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) 	<p><input checked="" type="checkbox"/> None</p>
<ul style="list-style-type: none"> PMR/PMC Development Templates (<i>indicate total number</i>) 	<p><input checked="" type="checkbox"/> None</p>
Clinical	
<ul style="list-style-type: none"> ❖ Clinical Reviews 	

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • Clinical Team Leader Review(s) <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> • Clinical review(s) <i>(indicate date for each review)</i> 	9/17/13 and 10/21/14
<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input checked="" type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i>	No clinical studies were completed by the applicant
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and REMS Supporting Document <i>(indicate date(s) of submission(s))</i> • REMS Memo(s) and letter(s) <i>(indicate date(s))</i> • Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i> 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) <i>(include copies of OSI letters to investigators)</i>	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 9/12/13 and 10/27/14
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 7/31/13 and 3/7/14
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None 7/11/13, 7/26/13, and 12/2/13; 9/29/14
❖ Microbiology Reviews	<input type="checkbox"/> Not needed
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)	6/21/13 and 8/22/14
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review) Biopharmaceutics	<input type="checkbox"/> 7/31/13 and 3/6/14
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	CMC review date 9/29/14 pg. 22
<input type="checkbox"/> Review & FONSI (indicate date of review)	
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites ⁵)	Date completed: See page. of CMC review 9/29/14 pg. 23 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)
--	---

Day of Approval Activities

❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	7 <input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done n/a
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done n/a
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

From: [Jairath, Meghna](#)
To: [Jonathan Sterling \(jsterling@exela.us\)](mailto:jsterling@exela.us)
Subject: IR NDA 205917
Date: Wednesday, November 05, 2014 10:30:28 AM
Importance: High

Hello,

We have the following information request below. Please respond and submit to NDA by November 7, 2014 for review.

We recommend you make the change stated below.

Container label for 10 mcg/2 mL

- **Revise the [REDACTED]^{(b) (4)} concentration statement to '5 mcg/mL' in accordance with USP General Chapter <1>.**

Please submit the updated container label for 10mcg/2ml for review.

Please acknowledge the receipt of this email.

Thanks,
Meghna

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/s/

MEGHNA M JAIRATH
11/13/2014

From: [Jairath, Meghna](#)
To: [Lubas, William \(CDER\)](#); [Roman, Dragos](#)
Cc: [Guettier, Jean-Marc](#); [Lucarelli, Pamela K](#)
Subject: FW: First round label NDA 205917***PDUFA date November 18, 2014***
Date: Wednesday, October 29, 2014 3:39:09 PM
Attachments: [first round to sponsor PI NDA 205917 10 27 14.doc](#)

Hello,
The sponsor has no further edits to the label.
Attaching as reference.

I will start drafting the approval letter.

Thanks,
Meghna

-----Original Message-----

From: Jonathan Sterling [<mailto:jsterling@exela.us>]
Sent: Wednesday, October 29, 2014 2:31 PM
To: Jairath, Meghna
Subject: RE: First round label NDA 205917***please respond by today October 29, 2014***

I am hoping to receive the proofs today from the labeling vendor. I gave them the deadline as today.

I am pushing them vigorously.

As far as the labeling, I have no issues to your edits and comments.

-----Original Message-----

From: Jairath, Meghna [<mailto:Meghna.Jairath@fda.hhs.gov>]
Sent: Monday, October 27, 2014 12:21 PM
To: Jonathan Sterling
Subject: First round label NDA 205917***please respond by today October 29, 2014***
Importance: High

NDA 205917

Product: Paricalcitol injection 2 mcg/mL and 5 mcg/mL

Indication: For the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5.

Sponsor: Hikma Pharmaceuticals Co. Ltd

Authorized US agent: Exela Pharma Sciences, LLC. 505 (b)(2) application

Labeling (package insert) attached

Hello,

I am sending the package insert in track changes for your review. Please place comments with the changes you do not agree when sending the label back.

Please do not submit anything to the NDA until we have agreed on a final label.

If you have no changes then please state that.

Please follow the regulatory format and changes to your package insert.

Please respond by today October 29, 2014.

Please acknowledge the receipt of this email.

Thanks,

Meghna M. Jairath, Pharm.D.

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II (ODEII)/ Office of New Drugs (OND)/ Center of Drug Evaluation and Research (CDER)

Meghna.jairath@fda.hhs.gov <<mailto:Meghna.jairath@fda.hhs.gov>>

301-796-4267

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/s/

MEGHNA M JAIRATH
11/13/2014

From: [Jairath, Meghna](#)
To: [Jonathan Sterling \(jsterling@exela.us\)](mailto:jsterling@exela.us)
Subject: First round label NDA 205917***please respond by today October 29, 2014***
Date: Monday, October 27, 2014 12:20:37 PM
Attachments: [first round to sponsor PI NDA 205917 10_27_14.doc](#)
Importance: High

NDA 205917

Product: Paricalcitol injection 2 mcg/mL and 5 mcg/mL

Indication: For the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5.

Sponsor: Hikma Pharmaceuticals Co. Ltd

Authorized US agent: Exela Pharma Sciences, LLC. 505 (b)(2) application

Labeling (package insert) attached

Hello,

I am sending the package insert in track changes for your review. Please place comments with the changes you do not agree when sending the label back.

Please do not submit anything to the NDA until we have agreed on a final label.

If you have no changes then please state that.

Please follow the regulatory format and changes to your package insert.

Please respond by today October 29, 2014.

Please acknowledge the receipt of this email.

Thanks,

Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II (ODEII)/ Office of New Drugs (OND)/ Center of Drug Evaluation and Research (CDER)
Meghna.jairath@fda.hhs.gov
301-796-4267

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/s/

MEGHNA M JAIRATH
10/29/2014

From: Jairath, Meghna
To: [Jonathan Sterling \(jsterling@exela.us\)](mailto:jsterling@exela.us)
Bcc: [Jairath, Meghna](#)
Subject: IR NDA 205917
Date: Wednesday, October 22, 2014 2:58:00 PM
Importance: High

Hello,

We have the following information request below. Please respond and submit to NDA by October 29, 2014 for review.

We acknowledge your submission dated October 8, 2014. However you have only submitted changes to the container labels for the 10 mcg/2mL strength. We recommend you make the change stated below to all the container labels (all 3 strengths):

Move the statement “Rx ONLY” away from the middle of the principal display panel as this information competes for prominence with the established name and strength on the principal display panel.

Please submit the updated container labels for 2 mcg/mL and 5 mcg/mL for review. Please acknowledge the receipt of this email.

Thanks,
Meghna

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/s/

MEGHNA M JAIRATH
10/29/2014



NDA 205917

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Hikma Pharmaceuticals Co. Ltd.
C/o Exela Pharma Sciences, LLC.
Attention: Jonathan Sterling
Vice President of Quality, Regulatory and Product Development
1325 William White Place NE
P.O. Box 818
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your New Drug Application (NDA) dated June 7, 2013, received June 10, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for paricalcitol injection.

On July 3, 2014, we received your July 2, 2014, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is November 18, 2014.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 22, 2014.

If you have any questions, call me at (301) 796-3961.

Sincerely,

{See appended electronic signature page}

Pamela Lucarelli
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

PAMELA LUCARELLI
07/08/2014



NDA 205917

NDA ACKNOWLEDGMENT

Exela Pharma Sciences, LLC.
US Agent for Hikma Pharmaceuticals Co. Ltd.
Attention: Jonathan E. Sterling
Vice President Quality, Regulatory, and Product Development
P.O. Box 818, 1325 William White Place NE
Lenoir, NC 28645

Dear Mr. Sterling:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Paricalcitol Injection, 2 mcg/ml and 5 mcg/ml

Date of Application: June 7, 2013

Date of Receipt: June 10, 2013

Our Reference Number: NDA 205917

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 9, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Meghna M. Jairath, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MEGHNA M JAIRATH
06/24/2013

From: [Jonathan Sterling](#)
To: [Lucarelli, Pamela K](#)
Subject: RE: NDA 205917 (paricalcitol) Information Request
Date: Wednesday, June 11, 2014 2:39:29 PM

Pam,

As discussed, here is my response to the received IR.

Agency Comment # 1:

We are concerned that your product has a higher concentration of (b) (4) than the reference listed product Zemplar (35% vs. 20%).

Exela Response:

The table below provides a comparison between Exela's Paricalcitol Injection Drug Product with Zemplar® (paricalcitol) Injection. As noted, Exela's formulation contains 35% v/v (b) (4) which is 15% v/v higher than Zemplar®; however, when the total (b) (4) concentrations are compared, Exela's formulation is about (b) (4) less than that of Zemplar® (paricalcitol) Injection. Most noted is that Exela's formulation does not contain any propylene glycol and contains only sorbitol in combination with the alcohol (b) (4). Based on the formulation differences, the total (b) (4) concentration is less in Exela's formulation compared to Zemplar® (paricalcitol) Injection.

Ingredients	Exela's Formulation	Zemplar® Formulation ¹
Paricalcitol	2 µg/mL or 5 µg/mL	2 µg/mL or 5 µg/mL
Alcohol, (b) (4), 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 Zemplar® (paricalcitol) Injection formulation was obtained from the current package insert, vial label, and carton.

Agency Comment # 2:

We are concerned that chronic infusions with 35% (b) (4) directly into an AV fistula, could adversely affect the lifespan of the fistula.

Exela Response:

As presented above, the total (b) (4) concentration is less in Exela's formulation compared to Zemplar® (paricalcitol) Injection. Exela's formulation

was evaluated in a 28 day non-clinical study provided in the original NDA submission per the recommendations and requirements communicated in IND (b)(4). The pathology summary of the report concluded that intravenous administration (b)(4) of Zemplar® or Paricalcitol to male and female Sprague-Dawley rats at dose levels of 1 or 3 µg/kg had no effect on morbidity or moribundity. There were no macroscopic observations attributed to intravenous administration of Zemplar® or Paricalcitol in male and female Sprague-Dawley rats at dose levels of 1 or 3 µg/kg. Based on the results of the 28-day study, it is demonstrated that the differences between Exela's formulation and Zemplar®, including the increased alcohol concentration, did not negatively affect the injection site; therefore, Exela's formulation should not impact the fistula or the lifespan of the fistula greater than that of the RLD.

Thanks

JES

-----Original Message-----

From: Lucarelli, Pamela K [<mailto:Pamela.Lucarelli@fda.hhs.gov>]

Sent: Wednesday, June 11, 2014 7:47 AM

To: Jonathan Sterling

Subject: NDA 205917 (paracalcitol) Information Request

Hi Jonathan,

Please see the clinical information request below:

We are concerned that your product has a higher concentration of (b)(4) than the reference listed product Zemplar (35% vs. 20%).

We are concerned that chronic infusions with 35% (b)(4) directly into an AV fistula, could adversely affect the lifespan of the fistula.

Injection of the 35% solution via a port in the dialysis machine might provide an alternative but we would still need data to support that this higher concentration of (b)(4) will not damage the dialysis tubing or membranes and that adequate dilution would occur prior to the solution reaching the AV fistula.

Please provide data to support the safety of (b) (4) solutions of 35% or greater on AV fistulas or alternatively supply data to support the safety of the use of 35% solutions injected via the different ports in standard dialysis machines. List the manufacturers of the dialysis machines and catheter tubing that you have reviewed.

Acknowledge receipt of this email and provide us a timeline as to when you could provide this data.

Thanks,
Pam

Pamela Lucarelli
Chief, Project Management Staff

FDA/Center for Drug Evaluation and Research Division of Metabolism and
Endocrinology Products
W022 - Room 3364
10903 New Hampshire Avenue
Silver Spring, MD 20903

Phone 301.796.3961
Fax 301.796.9712
pamela.lucarelli@fda.hhs.gov

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/s/

PAMELA LUCARELLI
06/11/2014

From: [Jonathan Sterling](mailto:Jonathan.Sterling@exela.us)
To: [Lucarelli, Pamela K](mailto:Lucarelli.Pamela.K@fda.hhs.gov)
Subject: RE: IR1 Paricalcitol NDA 205917 - DMEPA IR Request
Date: Tuesday, June 10, 2014 4:01:15 PM

Received and forwarded for immediate correction and prompt response by amendment.

-----Original Message-----

From: Lucarelli, Pamela K [<mailto:Pamela.Lucarelli@fda.hhs.gov>]
Sent: Tuesday, June 10, 2014 3:59 PM
To: Jonathan Sterling
Subject: RE: IR1 Paricalcitol NDA 205917 - DMEPA IR Request

Hi Jonathan,

Based on your previous email, we request you make the following changes to your container label:

- a. Move the statement "Rx ONLY" away from the middle of the principal display panel as this information competes for prominence with the established name and strength on the principal display panel.
- b. As currently presented, the strength presentation for the 10 mcg/2 mL vial only lists the total quantity per total volume. Add the concentration per milliliter (5 mcg/mL) below the strength "10 mcg/2 mL" as demonstrated by the example below:
10 mcg/2 mL
(5 mcg/mL)

We recommend this to ensure that the labels and labeling conform with the United States Pharmacopeia (USP) General Chapter <1> Injections. Revise the statement of strength to increase the prominence of the statement of total drug content in terms of total strength per total amount of milliliters on the principal display panel followed in close proximity by strength per milliliter enclosed by parentheses.

Acknowledge receipt of this request.

Thank you,
Pam

Pamela Lucarelli
Chief, Project Management Staff
FDA/Center for Drug Evaluation and Research Division of Metabolism and Endocrinology Products
WO22 - Room 3364
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 301.796.3961
Fax 301.796.9712
pamela.lucarelli@fda.hhs.gov

-----Original Message-----

From: Jonathan Sterling [<mailto:jsterling@exela.us>]
Sent: Thursday, May 15, 2014 10:13 AM
To: Lucarelli, Pamela K
Subject: RE: IR1 Paricalcitol NDA 205917 - DMEPA IR Request

Please see attached

-----Original Message-----

From: Lucarelli, Pamela K [<mailto:Pamela.Lucarelli@fda.hhs.gov>]
Sent: Tuesday, May 13, 2014 11:12 AM
To: Jonathan Sterling
Subject: RE: IR1 Paricalcitol NDA 205917 - DMEPA IR Request

Hi Jonathan,

It is important that we receive this labeling, please let me know when it will be submitted.

Thanks,
Pam

Pamela Lucarelli
Chief, Project Management Staff
FDA/Center for Drug Evaluation and Research Division of Metabolism and Endocrinology Products
WO22 - Room 3364
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 301.796.3961
Fax 301.796.9712
pamela.lucarelli@fda.hhs.gov

-----Original Message-----

From: Lucarelli, Pamela K
Sent: Wednesday, May 07, 2014 8:18 AM
To: 'Jonathan Sterling'
Subject: RE: IR1 Paricalcitol NDA 205917 - DMEPA IR Request

Hi Jonathan,

Please provide an update on this request.

Thanks,
Pam

Pamela Lucarelli
Chief, Project Management Staff
FDA/Center for Drug Evaluation and Research Division of Metabolism and Endocrinology Products
WO22 - Room 3364
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 301.796.3961
Fax 301.796.9712
pamela.lucarelli@fda.hhs.gov

-----Original Message-----

From: Lucarelli, Pamela K
Sent: Monday, April 07, 2014 10:13 AM
To: 'Jonathan Sterling'
Subject: RE: IR1 Paricalcitol NDA 205917 - DMEPA IR Request

Hi Jonathan,

Please send the vial labels for the 5mcg/mL (2 mL) vial for our review as well.

Acknowledge confirmation of this request.

Thanks,
Pam

Pamela Lucarelli
Chief, Project Management Staff
FDA/Center for Drug Evaluation and Research Division of Metabolism and Endocrinology Products
WQ22 - Room 3364
10903 New Hampshire Avenue
Silver Spring, MD 20903
Phone 301.796.3961
Fax 301.796.9712
pamela.lucarelli@fda.hhs.gov

-----Original Message-----

From: Jonathan Sterling [<mailto:jsterling@exela.us>]
Sent: Monday, April 07, 2014 9:25 AM
To: Jairath, Meghna
Cc: Lucarelli, Pamela K
Subject: FW: IR1 Paricalcitol NDA 205917 - DMEPA IR Request

-----Original Message-----

From: Jairath, Meghna [<mailto:Meghna.Jairath@fda.hhs.gov>]
Sent: Wednesday, March 05, 2014 3:20 PM
To: Jonathan Sterling
Subject: IR1 Paricalcitol NDA 205917 - DMEPA IR Request
Importance: High

NDA 205917

Information Request

Hello,

I have the following information request below.

In your submission dated June 7, 2013, there is a Word Document containing a copy of the vial labels for Paricalcitol Injection. The vial labels appear to be made in Microsoft Word using the Table function.

As a result, we are unable to evaluate the vial labels because we are unable to visualize the labels on a vial since these labels do not appear to be scaled to the actual size. Therefore, please submit a copy of the actual mock-up version of the vial labels that is scaled to the actual vial size.

Please acknowledge the receipt of this email.

Respond by: 3/7/14

Thx

Meghna

"This message and any attachments are solely for the intended recipient and may contain confidential or privileged information. If you are not the intended recipient, any disclosure, copying, use, or distribution of the information included in this message and any attachments is prohibited. If you have received this communication in error, please notify us by reply e-mail and immediately and permanently delete this message and any attachments. Thank you."

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"This message and any attachments are solely for the intended recipient and may contain confidential or privileged information. If you are not the intended recipient, any disclosure, copying, use, or distribution of the information included in this message and any attachments is prohibited. If you have received this communication in error, please notify us by reply e-mail and immediately and permanently delete this message and any attachments. Thank you."

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/s/

PAMELA LUCARELLI
06/11/2014

From: [Jairath, Meghna](#)
To: [Jonathan Sterling \(jsterling@galexe.us\)](mailto:jsterling@galexe.us)
Subject: IR1 Paricalcitol NDA 205917 - DMEPA IR Request
Date: Wednesday, March 05, 2014 3:20:20 PM
Importance: High

NDA 205917
Information Request

Hello,
I have the following information request below.

In your submission dated June 7, 2013, there is a Word Document containing a copy of the vial labels for Paricalcitol Injection. The vial labels appear to be made in Microsoft Word using the Table function.

As a result, we are unable to evaluate the vial labels because we are unable to visualize the labels on a vial since these labels do not appear to be scaled to the actual size. Therefore, please submit a copy of the actual mock-up version of the vial labels that is scaled to the actual vial size.

Please acknowledge the receipt of this email.

Respond by: 3/7/14

Thx
Meghna

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/s/

MEGHNA M JAIRATH
03/06/2014

From: [Jairath, Meghna](mailto:Jairath.Meghna)
To: [Jonathan Sterling \(jsterling@exela.us\)](mailto:jsterling@exela.us)
Cc: [Lucarelli, Pamela K](mailto:Lucarelli.Pamela.K)
Subject: FDA response to sponsor clarification questions_NDA 205917 Paricalcitol
Date: Wednesday, March 12, 2014 3:54:06 PM

NDA 205917
Paricalcitol

Hello,
Please see our responses to your clarification questions below.

Drug Substance

Sponsor Q1. There is no requirement in the USP or DMF for the drug substance for either specific (b) (4). Is this requirement mandatory by the Division. The drug substance is in mcg quantities; therefore, far less than any specification level in the USP/ICH.

FDA Response: Submit your justification for not performing a chirality test for identity of the drug substance.

Sponsor Q2. The related substances method was validated by the DMF holder and verified by Exela. Is the Division asking Exela to validate a new method from the API supplier?

FDA Response: In the Method Verification Report#:2011-QCMV-141 submitted in the NDA, we found no supporting data for specificity of the method to resolve paricalcitol from the USP identified impurities. Indicate the section of NDA that contains the data, or provide the data.

Drug Product

Sponsor Q6: There are no impurities identified in the drug product as all impurities were less (b) (4) % which per ICH does not require any ID or qualification.

Sponsor Q8: Please advise on the (b) (4) request in the drug product. (b) (4) is controlled in the incoming raw materials; therefore, what is the need for the drug product specification.

FDA Response to Q6 and 8: Submit your justifications in your responses.

Thanks,
Meghna

-----Original Message-----

From: Jonathan Sterling [<mailto:jsterling@exela.us>]
Sent: Wednesday, March 12, 2014 10:49 AM
To: Jairath, Meghna
Cc: Lucarelli, Pamela K
Subject: RE: update: future regulatory contact NDA 205917 Paricalcitol

Meghna

There are a few items I needed clarity on from the deficiency received.
The numbers below correspond to the items on the IR.

Drug Substance

1. There is no requirement in the USP or DMF for the drug substance for either specific (b) (4). Is this requirement mandatory

by the Division. The drug substance is in mcg quantities; therefore, far less than any specification level in the USP/ICH.

2. The related substances method was validated by the DMF holder and verified by Exela. Is the Division asking Exela to validate a new method from the API supplier?

Drug Product

6. There are no impurities identified in the drug product as all impurities were less $(b)(4)$ % which per ICH does not require any ID or qualification.

8. Please advise on the $(b)(4)$ request in the drug product. $(b)(4)$ is controlled in the incoming raw materials; therefore, what is the need for the drug product specification.

Thanks

JES

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/s/

MEGHNA M JAIRATH
03/17/2014



NDA 205917

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Exela Pharma Sciences, LLC.
US Agent for Hikma Pharmaceuticals Co. Ltd.
Attention: Jonathan E. Sterling
Vice President Quality, Regulatory, and Product Development
P.O. Box 818, 1325 William White Place NE
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your New Drug Application (NDA) dated June 7, 2013, received June 10, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for paricalcitol injection, 2 mcg/ml and 5 mcg/ml.

We also refer to your amendments below:

- July 31, 2013, containing a final approved study report 030508, titled, "Paricalcitol versus Zemplar: 4-Week, 3-Times Weekly, Intravenous Toxicity and Toxicokinetic Study in Rats with a 14-Day Recovery Period Study Number," as requested in our phone conversation dated July 29, 2013;
- August 23, 2013, containing a Certification of Patent Holder Notification and a copy of the FedEx return receipts as required per 21 CFR 314.95.patent & exclusivity certification;
- September 25, 2013, containing a response to our correspondence dated August 24, 2013 request and SPL labeling.

We also refer to our acknowledgement letter dated November 15, 2013, which replaced our letter dated June 24, 2013, acknowledging your submission dated June 7, 2013. Your June 7, 2013, submission was considered incomplete under section 736(e) of the Federal Food, Drug, and Cosmetic Act because the appropriate user fee was not received at the time of the submission. Since we received the appropriate user fee for this application on October 18, 2013, therefore, the receipt date for this application is October 18, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**.

Therefore, the user fee goal date is **August 18, 2014**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by **July 22, 2014**.

During our filing review of your application, we identified the following potential review issues:

Chemistry, Manufacturing, and Controls

Drug Substance

1. Include the following tests to your drug substance specification:
 - a. Specific rotation as an identity test;
 - b. [REDACTED] (b) (4)
2. Provide method verification data to demonstrate the specificity of the method for the detection of [REDACTED] (b) (4)
3. Your proposal to release the drug substance based on [REDACTED] (b) (4) Certificate of analysis (CoA) is not acceptable. We recommend that you test drug substance batches prior to use in drug product manufacturing.
4. Describe the packaging configuration (container closure system description, unit size, and quantity etc., Part # etc.) of the drug substance received at your facility.
5. The concentration information provided in Table 2 of the Analytical Method Verification Study Report (Protocol No. [REDACTED] (b) (4)) appears to be incorrect. Clarify whether the concentrations reported for the linearity samples are correct.

Drug Product

6. Provide a side by side comparison of the product related and process related impurities present in your proposed product and the innovator product.

7. What is the maximum solubility of your drug in the proposed alcohol/sorbitol solution mixture and propose a limit for alcohol in the drug product?
8. Including a test for (b) (4) content to your drug product specification. Provide information on the levels of (b) (4) in the drug product and propose a control strategy for limiting the presence of (b) (4) in the finished product.
9. Include a specification for the following:
 - a. Monitor the levels of USP specified related substances (b) (4) in the drug product with appropriate limits;
 - b. Using (b) (4) methods, identify potential process related impurities such as leachables that may migrate from product contact surfaces such as bioprocess containers and container closure system into product. Provide quantitative information on potential leachables (b) (4) or by products present in your product during storage;
 - c. Complete a risk assessment for not monitoring the levels of trace organic compounds in the product;
 - d. Include test for (b) (4) content to your stability specification. Provide (b) (4) content data for stability batches.
10. Demonstrate the specificity of your test method for detecting potential degradants generated from paricalcitol injection stored under acidic, alkaline, and oxidation conditions. Provide validation data to support the method's ability to quantitate potential impurities in the product (e.g., USP specified product related substances).
11. Propose an inspectional plan and a component specification for accepting the container closure components at your manufacturing facility. Your plan should include physical and chemical tests to verify the dimensional specifications and conformity of the components to meet USP (b) (4) monograph requirements (b) (4)
(b) (4)
12. Provide hold time data for the storage of the (b) (4) solution in intermediate storage containers.
13. Revise the product label description to appear as the total drug content per total volume followed in close proximity by the strength per milliliter enclosed in parenthesis.
14. Provide information on the amount of drug released to the environment including the calculation used in the environmental assessment.

Regulatory

15. Submit Form 3397 (User Fee Cover Sheet) included with authorized signature by agent.
16. Submit correctly worded Debarment Certification included with authorized signature from both agent and Applicant.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Meghna M. Jairath, Pharm.D., Regulatory Project Manager, at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JEAN-MARC P GUETTIER
12/31/2013



NDA 205917

**REVISED NDA ACKNOWLEDGMENT
USER FEES RECEIVED**

Exela Pharma Sciences, LLC.
US Agent for Hikma Pharmaceuticals Co. Ltd.
Attention: Jonathan E. Sterling
Vice President Quality, Regulatory, and Product Development
P.O. Box 818, 1325 William White Place NE
Lenoir, NC 28645

Dear Mr. Sterling:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: paricalcitol injection, 2 mcg/ml and 5 mcg/ml

Date of Application: June 7, 2013

Date of Receipt: October 18, 2013

Our Reference Number: NDA 205917

This letter replaces the Agency's letter dated June 24, 2013, acknowledging your submission dated June 7, 2013. Your June 7, 2013, submission was considered incomplete under section 736(e) of the Federal Food, Drug, and Cosmetic Act because the appropriate user fee was not received at the time of the submission. Consequently, the receipt date for this submission will be the date the review division is notified that payment has been received by the bank. We have received the appropriate user fee for this application on October 18, 2013, therefore, the receipt date for this application is October 18, 2013.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **December 17, 2013**, in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications

If you have any questions regarding this application, contact me, at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Meghna Jairath, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

MEGHNA M JAIRATH
11/15/2013



NDA 205917

**REVISED NDA ACKNOWLEDGMENT
USER FEES RECEIVED**

Exela Pharma Sciences, LLC.
US Agent for Hikma Pharmaceuticals Co. Ltd.
Attention: Jonathan E. Sterling
Vice President Quality, Regulatory, and Product Development
P.O. Box 818, 1325 William White Place NE
Lenoir, NC 28645

Dear Mr. Sterling:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: paricalcitol injection, 2 mcg/ml and 5 mcg/ml

Date of Application: June 7, 2013

Date of Receipt: October 18, 2013

Our Reference Number: NDA 205917

This letter replaces the Agency's letter dated June 24, 2013, acknowledging your submission dated June 7, 2013. Your June 7, 2013, submission was considered incomplete under section 736(e) of the Federal Food, Drug, and Cosmetic Act because the appropriate user fee was not received at the time of the submission. Consequently, the receipt date for this submission will be the date the review division is notified that payment has been received by the bank. We have received the appropriate user fee for this application on October 18, 2013, therefore, the receipt date for this application is October 18, 2013.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **December 17, 2013**, in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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Division of Metabolism and Endocrinology Products
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If you have any questions regarding this application, contact me, at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Meghna Jairath, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MEGHNA M JAIRATH
11/15/2013

From: [Jairath, Meghna](#)
To: [Jonathan Sterling](#)
Subject: IR Paricalcitol NDA 205917
Date: Thursday, September 12, 2013 4:35:46 PM
Importance: High

Hello,

Please submit the following requests below ASAP to the NDA.

1. Submit Form 3397 (User Fee Cover Sheet) included with authorized signature by agent.
2. Submit correctly worded Debarment Certification included with authorized signature from both agent and Applicant.

Please acknowledge receipt of email.

Thanks,
Meghna

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/s/

MEGHNA M JAIRATH
09/12/2013

November 15, 2013

Exela Pharma submitted this NDA on June 7, 2013 but it was discovered that the user fees for the fiscal year 2013 were not paid with the NDA submission. The applicant was informed via phone conversation dated October 7, 2013 that the review process will now stop since the user fees were not paid. The applicant understood that the review process will only restart the PDUFA clock once the user fees for the fiscal year 2014 were paid. The sponsor submitted the appropriate user fees for fiscal year 2014 on October 18, 2013.

The communication function of this COR-NDAFILE-04 (Filing Review Issues Identified) has been changed to COR-NDAIR-10 (General Advice Letter). The division will issue a new filing letter.



NDA 205917

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Exela Pharma Sciences, LLC.
US Agent for Hikma Pharmaceuticals Co. Ltd.
Attention: Jonathan E. Sterling
Vice President Quality, Regulatory, and Product Development
P.O. Box 818, 1325 William White Place NE
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your New Drug Application (NDA) dated June 7, 2013, received June 10, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for paricalcitol Injection, 2 mcg/ml and 5 mcg/ml.

We also refer to your amendment dated July 31, 2013, containing a final approved study report 030508, titled, *Paricalcitol versus Zemplar: 4-Week, 3-Times Weekly, Intravenous Toxicity and Toxicokinetic Study in Rats with a 14-Day Recovery Period Study Number* as requested in our phone conversation dated July 29, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**.

Therefore, the user fee goal date is **April 10, 2014**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by **March 14, 2014**.

During our filing review of your application, we identified the following potential review issues:

Biopharmaceutics

1. 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 listed drug do not have any impact on the stability, pharmacokinetics (e.g. renal clearance), efficacy, and safety of the Exela's product, as compared to those of the listed drug.

Chemistry, Manufacturing, and Controls

2. 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.
3. Provide information on the extractables/leachables testing of the primary container closure system of the drug product, or provide its location in the NDA.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

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For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Meghna M. Jairath, Pharm.D., Regulatory Project Manager, at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Division Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
08/24/2013