

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201657Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 201657

SUPPL #

HFD # 510

Trade Name N/A

Generic Name paricalcitol injection

Applicant Name Hospira Inc.

Approval Date, If Known October 21, 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, Zemplar (paricalcitol injection). Nonclinical and CMC data was submitted was to this application.

FDA granted a waiver of the *in vivo* bioequivalence study requirement per review dated 12/13/2011.

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 reference listed drug for this application, NDA 201657.

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: October 20, 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
10/21/2014

JEAN-MARC P GUETTIER
10/23/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 201657 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: 2 mcg/1 mL, 5 mcg/1 mL, 10 mcg/2 ml		Applicant: Hospira Inc. Agent for Applicant (if applicable):
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><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></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 <i>(notify CDER OND IO)</i> Date of check:</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>October 21, 2014</u> • Previous actions <i>(specify type and date for each action taken)</i> 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input type="checkbox"/> None CR-February 6, 2012
❖ 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).

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: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): <i>(confirm chemical classification at time of approval)</i>	
<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 <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies	
BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies	
<input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request	
REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required	
Comments: Resubmission	
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
<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 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) October 21, 2014 CR-February 6, 2012
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 10/21/14
<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
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 checked="" type="checkbox"/> None DMEPA: <input type="checkbox"/> None 12/8/11 and 9/11/14 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 checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /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	6/14/11 <input type="checkbox"/> Not a (b)(2) Cleared by Clearance Committee via email dated 9/3/14
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

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

<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<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>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<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>) 	4/26,6/20,9/8, 9/29, and 10/19/11; 1/11/12; 5/24/13; 2/11(3); 5/5; 8/15 and 8/20/14; 10/1, 10/9 (2), 10/20 (3) and 10/21/14;
<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) 	n/a
<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>) 	<input checked="" type="checkbox"/> N/A or no mtg <input type="checkbox"/> No mtg July 29, 2010 <input checked="" type="checkbox"/> No mtg <input checked="" type="checkbox"/> N/A <input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 2/6/12
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	
<ul style="list-style-type: none"> ❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review see CDTL review 6/2/11 and 1/10/12 <input checked="" type="checkbox"/> None
<ul style="list-style-type: 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
<ul style="list-style-type: none"> ❖ 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 7/29/11
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) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 12/12/11
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/9/11 and 10/13/11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review dated 10/13/11
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		<input type="checkbox"/> None 6/1/11, 6/3/11, 10/21/11, 12/13/11, 12/20/11 and 5/16/14
❖ Microbiology Reviews		<input type="checkbox"/> Not needed 4/28/11 and 1/20/12
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i> Biopharmaceutics		<input type="checkbox"/> None 6/3/11 and 12/13/11
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		CMC review date 10/21/11 pg. 44 and 12/20/11 pg. 47
❖ 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) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>		Date completed: See page. 47 of CMC dated 12/20/11 and page 44 CMC review dated 10/21/11 <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) <i>(original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ 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)

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.

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 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: [McIntyre, Kristina](#)
To: [Jairath, Meghna](#)
Subject: RE: Fifth round of labeling_NDA 201657***please respond by today October 21, 2014***
Date: Tuesday, October 21, 2014 3:39:27 PM
Attachments: [Compare.pdf](#)
[WEN-3686 accepted.doc](#)
[WEN-3686 accepted.pdf](#)
[FDA final track changes NDA 201657.pdf](#)

Dear Meghna,

Please see attached for the following documents:

- Clean word doc reflecting the changes per your prior communication and a pdf of that copy (WEN-3686 accepted)
- A pdf of the document you provided w/track changes accepted (FDA final track changes)
- A compare of the WEN document and the FDA document.

Please note that in our last review of the PI, we made a couple of minor revisions as detailed below:

- Section 6/Page 5: The text was repeated in the investigations section.

Infections and Infestations: Nasopharyngitis, upper respiratory tract infection, vaginal infection (b) (4)

Aspartate aminotransferase increased, bleeding time prolonged, heart rate irregular, laboratory test abnormal, (b) (4)

The text provided in the *Laboratory Investigations and Vital Signs:* was added in the first round of changes, so removed the first Investigations piece.

- Section 5.3/Page 3: Corrected the spelling (Initiating)
- Section 12.3/Page 9: Added a period after subjects.

We have accepted all track changes as proposed by FDA and concur that the edits that have been made are minor/editorial in nature.

Regards,

Kristina McIntyre
Hospira, Inc.
Global Regulatory Affairs
T 224-212-4268 | F 224-212-5401
E kristina.mcintyre@hospira.com

From: Jairath, Meghna [mailto:Meghna.Jairath@fda.hhs.gov]
Sent: Tuesday, October 21, 2014 12:36 PM
To: McIntyre, Kristina
Subject: Fifth round of labeling_NDA 201657***please respond by today October 21, 2014***
Importance: High

NDA 201657
Drug Product: Paricalcitol Injection
Sponsor: Hospira

Labeling (package insert) attached

Hello,

I am sending the attached labels clean and 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. The only changes made were to the description of the product, to the dosage adjustment table and minor edits.

If you have no changes then this version will be the final version of PI.

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

Please respond by today **October 21, 2014**.

Please acknowledge the receipt of this email.

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
10/21/2014

From: [Jairath, Meghna](#)
To: [McIntyre, Kristina](#)
Subject: Fifth round of labeling_NDA 201657***please respond by today October 21, 2014***
Date: Tuesday, October 21, 2014 1:35:35 PM
Attachments: [FDA final clean version NDA 201657.doc](#)
[FDA final track changes NDA 201657.doc](#)
Importance: High

NDA 201657
Drug Product: Paricalcitol Injection
Sponsor: Hospira

Labeling (package insert) attached

Hello,

I am sending the attached labels clean and 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. The only changes made were to the description of the product, to the dosage adjustment table and minor edits.

If you have no changes then this version will be the final version of PI.

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

Please respond by today **October 21, 2014**.

Please acknowledge the receipt of this email.

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
10/21/2014

From: [Jairath, Meghna](#)
To: [McIntyre, Kristina \(Kristina.McIntyre@hospira.com\)](mailto:McIntyre.Kristina@hospira.com)
Subject: Fourth round of labeling_NDA 201657***please respond by today October 21, 2014***
Date: Monday, October 20, 2014 5:34:15 PM
Attachments: [NDA_201657_final_fourth_round_to_sponsor_clean_version.doc](#)
[NDA_201657_final_fourth_round_to_sponsor_track_changes.doc](#)
Importance: High

NDA 201657
Drug Product: Paricalcitol Injection
Sponsor: Hospira

Labeling (package insert) attached

Hello,

I am sending the attached labels clean and 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 please state that in your email.

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

Please respond by today **October 21, 2014**.

Please acknowledge the receipt of this email.

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
10/21/2014

From: [Jairath, Meghna](#)
To: [McIntyre, Kristina \(Kristina.McIntyre@hospira.com\)](mailto:McIntyre.Kristina@hospira.com)
Subject: Third round of labeling_NDA 201657***please respond by today October 20, 2014***
Date: Monday, October 20, 2014 10:44:55 AM
Attachments: [Final label to sponsor third round NDA 201657.doc](#)
Importance: High

NDA 201657
Drug Product: Paricalcitol Injection
Sponsor: Hospira

Labeling (package insert) attached

Hello,

I am sending the attached label for your review. Please accept the changes and place comments on the ones you do not agree on when sending label back.
Please do not submit anything to the NDA until we have agreed on a final label.

Please respond by today **October 20, 2014**.

Please acknowledge the receipt of this email.

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
10/20/2014

From: [Jairath, Meghna](#)
To: [McIntyre, Kristina](#)
Subject: Second round for labeling_NDA 201657***please respond by today October 17, 2014***
Date: Friday, October 17, 2014 1:33:41 PM
Attachments: [NDA 201657 second round to spon.doc](#)
Importance: High

NDA 201657
Drug Product: Paricalcitol Injection
Sponsor: Hospira

Labeling (package insert) attached

Hello,

I am sending the attached label for your review. Please accept the changes and place comments on the ones you do not agree on when sending label back.
Please do not submit anything to the NDA until we have agreed on a final label.

Please respond by today **October 17, 2014**.

Please acknowledge the receipt of this email.

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
10/20/2014

From: Jairath, Meghna
To: [McIntyre, Kristina \(Kristina.McIntyre@hospira.com\)](mailto:McIntyre.Kristina@hospira.com)
Bcc: [Jairath, Meghna](mailto:Jairath.Meghna)
Subject: NDA 201657 first round of labeling ***please respond by October 16, 2014***
Date: Wednesday, October 15, 2014 3:25:00 PM
Attachments: [NDA_201657_first_round_10_15_14.doc](#)
Importance: High

NDA 201657
Drug Product: Paricalcitol Injection
Sponsor: Hospira

Labeling (package insert) attached

Hello,

I am sending the attached label for your review. Please accept the changes and place comments on the ones you do not agree on when sending label back.

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

Please respond by **October 16, 2014**.

Please acknowledge the receipt of this email.

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
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/s/

MEGHNA M JAIRATH
10/20/2014

From: [Jairath, Meghna](#)
To: [McIntyre, Kristina](#)
Subject: Carton/Container Label NDA 201657_paricalcitol
Date: Thursday, October 09, 2014 2:41:25 PM
Importance: High

Hello,

Below our comments to carton and container label highlighted in red. Please incorporate these changes. If you have further comments please send them via email. Please do not submit any labeling to the NDA until we have agreed upon the final changes.

1. Vial label

a. To highlight the unique route of administration and the importance of not injecting the drug product directly into a vein, revise the statement, (b) (4) to the following:

“For intravenous use through hemodialysis vascular access port only”

2. Carton labeling

a. To highlight the unique route of administration and the importance of not injecting the drug product directly into a vein, revise the statement, (b) (4) located on the Principal Display Panel and side panel, to the following:

“For intravenous use through hemodialysis vascular access port only”

b. As currently proposed, the established name, finished dosage form, and statement of strength for the 2 mcg/ml, 5 mcg/ml, and 10 mcg/2 ml carton labeling is presented in black font on a white background and are not well differentiated from one another. **To prevent selection errors, revise the color scheme for all strengths so that they utilize the same colors as proposed on the corresponding vial labels (e.g., 2 mcg/ml – orange, 5 mcg/ml – salmon pink, and 10 mcg/2 ml – green).**

Please acknowledge receipt of email.

Thanks,
Meghna

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/s/

MEGHNA M JAIRATH
10/09/2014

From: [Jairath, Meghna](mailto:Jairath.Meghna)
To: Kristina.McIntyre@hospira.com
Subject: IR NDA 201657
Date: Wednesday, October 01, 2014 4:26:00 PM

Information Request

NDA 201657
Applicant Hospira
Drug Product Paricalcitol injection

Respond: October 3, 2014

Hello,

We refer to your submission dated October 26, 2011 which was in response to our email correspondence dated September 27, 2011.

FDA Question (email dated September 27, 2011): Discuss the safety of using a 40% alcohol formulation and the potential impact of this formulation on infusion tubing and related materials and on AV fistula itself.

Sponsor Response (submission dated October 26, 2011): The dose would be administered into the injection site of the venous line that connects the dialysis machine to the venous flow of the AV fistula. The injection site on the venous line that connects the dialysis machine to the AV fistula is routinely 4-6 feet from the AV fistula. The distance varies with manufacturer. The injected volume will be diluted as the blood into which it is injected travels approximately 5 feet at 300 mL/minute before it enters the AV fistula.

FDA Comment: We have the following concerns. As the venous line tubing is of a small diameter and is subject to laminar flow it is not apparent that there would be sufficient mixing to dilute a bolus injected directly into the venous port despite the 300mL/min flow rate at a distance of only 4 to 6 feet. That said we agree that injection into the arterial port, which will result in mixing in the larger volume of the dialysis machine, should adequately dilute the bolus before the drug product enters the AV fistula.

We suggest that the labeling should stipulate injection

(b) (4)

Please acknowledge receipt of this email. You can respond to me via email then submit this communication to the NDA officially.

Thanks,
Meghna

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/s/

MEGHNA M JAIRATH
10/09/2014

From: Johnson, Jennifer
To: [McIntyre, Kristina \(Kristina.McIntyre@hospira.com\)](mailto:McIntyre.Kristina@hospira.com)
Bcc: [Johnson, Jennifer](mailto:Johnson.Jennifer)
Subject: NDA 201657 (paracalcitol): Request for patent certification proof of notification
Date: Wednesday, August 20, 2014 6:20:00 PM
Attachments: [cover-2012-05-29.pdf](#)
[patent-certification.pdf](#)

Dear Kristina,

Regarding NDA 201657 (paracalcitol injection):

We note that you provided the attached patent IV certification but did not submit proof of notification for patent number 5,597,815.

Although you stated in the cover letter of your resubmission on April 21, 2014, that patent 5,597,815 was listed in the Orange Book after you submitted your application, we still need for you to provide the proof of notification.

Please submit the proof of notification as an amendment to NDA 201657.

Let me know if you have any questions.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

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/s/

JENNIFER L JOHNSON

08/20/2014

Request from Sara Stradley on behalf of the 505(b)(2) clearance committee on 8/19/14

From: Johnson, Jennifer
To: ["McIntyre, Kristina"](#)
Bcc: [Johnson, Jennifer](#)
Subject: NDA 201657 (paricalcitol injection) Resubmission: Question regarding carton/container labels
Date: Friday, August 15, 2014 5:08:00 PM
Attachments: [carton.pdf](#)
[container.pdf](#)

Dear Kristina,

We are currently reviewing the carton and container labels included in your resubmission to NDA 201657 (paracalcitol injection) on April 21, 2014. Please see attached labels.

Are these the labels you intended for us to review? We note that the strengths are not differentiated by color on the carton labeling, as opposed to the container labels, so we would like to ensure that the correct carton labeling was submitted.

Let me know if you have any questions. Thank you for your help.

Kind Regards,
Jennifer

Jennifer Johnson
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2194
Fax: (301) 796-9712
jennifer.johnson@fda.hhs.gov

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JENNIFER L JOHNSON

08/15/2014

IR from DMEPA reviewer Mishale Mistry



NDA 201657

**ACKNOWLEDGE –
CLASS 2 RESUBMISSION**

Hospira, Inc.
Attention: Kristina McIntyre
Senior Associate Global Regulatory Affairs
Department 0389/Building H2-2
275 North Field Drive
Lake Forest, IL 60045

Dear Ms. McIntyre:

We acknowledge receipt of your April 21, 2014, resubmission to your supplemental new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for paricalcitol injection.

We consider this a complete, class 2 response to our February 6, 2012, action letter. Therefore, the user fee goal date is October 21, 2014.

If you have any questions, call Jennifer Johnson at (301) 796-2194.

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
05/05/2014

From: [Jairath, Meghna](#)
To: [Wojtko, Laurie M. \(Laurie.Wojtko@hospira.com\)](mailto:Laurie.Wojtko@hospira.com)
Subject: NDA 201-657, Paricalcitol Injection
Date: Monday, January 06, 2014 6:42:23 PM

Hello,

Please see our response below to your Q1.

Sponsor Question2:

Status of Hospira Rocky Mount as a Filed Establishment

Ideally, we hope that our current facility returns to a compliant status. Is it possible to maintain the Hospira Rocky Mount site in our filing until an action letter is ready to be issued after review of the resubmission? If, at that time, Hospira Rocky Mount has not returned to compliant status, we would be prepared to withdraw the site to keep the review progressing.

FDA Response: All sites with manufacturing responsibilities with respect to this application should be included in the resubmission, and all sites will be evaluated for CGMP adequacy. Per 505(d)(3), if the Rocky Mount site is determined to be inadequate, it may grounds for not approving the resubmission. If, during the review of the resubmission by the Agency, your firm decides to withdraw the Rocky Mount site, this site will not be considered an approved site for manufacturing this drug product.

Thanks,
Meghna

From: Jairath, Meghna
Sent: Monday, December 23, 2013 6:11 PM
To: Wojtko, Laurie M. (Laurie.Wojtko@hospira.com)
Subject: NDA 201-657, Paricalcitol Injection

Hello,

Please see our response below to your Q1.

Sponsor Question1:

Proposed Stability Data Set:

The McPherson manufacturing process aligns with the currently filed process with minor changes made to accommodate the site. In preparation for transfer, we have successfully executed an engineering batch and are in the process of manufacturing exhibit batches, as described in the table below, to support qualification.

No. of Batches	Paricalcitol Injection Presentation
2	2 mcg/1 mL in a 2 mL vial
1	5 mcg/1 mL in a 2 mL vial
1	10 mcg/2 mL (5 mcg/mL) in a 2 mL vial

We would like to accelerate filing to respond to the Complete Response letter as quickly as possible. Due to the stability of the product, established by the data collected in support of the current manufacturing site, we'd like to propose resubmitting with a stability data set containing results collected through 3 months of storage under accelerated and long-term conditions. Will this be accepted for review?

FDA Response: Yes, we agree with your proposal to submit 3-month long-term and accelerated stability data for the four exhibit batches manufactured at the proposed commercial site in McPherson, KS.

Thanks,
Meghna

From: Wojtko, Laurie M. [<mailto:Laurie.Wojtko@hospira.com>]
Sent: Monday, December 23, 2013 2:43 PM
To: Jairath, Meghna
Subject: RE: NDA 201-657, Paricalcitol Injection

Hi Meghna,

Yes, all 4 exhibit batches will be placed on stability and we will provide results for all 4 lots through 3 months of storage at the time of submission. We would plan on updating as requested during the review cycle to further support the review.

Laurie

From: Jairath, Meghna [<mailto:Meghna.Jairath@fda.hhs.gov>]
Sent: Monday, December 23, 2013 1:31 PM
To: Wojtko, Laurie M.
Subject: RE: NDA 201-657, Paricalcitol Injection

Hello,

We have the following clarification on your Q1 below.

FDA Questions: Will all 4 exhibit batches be included in the proposed “stability data set containing results collected through 3 months of storage under accelerated and long-term conditions”?

Thx
Meghna

From: Wojtko, Laurie M. [<mailto:Laurie.Wojtko@hospira.com>]
Sent: Wednesday, December 18, 2013 5:43 PM
To: Jairath, Meghna
Subject: RE: NDA 201-657, Paricalcitol Injection

In follow up to our phone conversation yesterday, I have summarized Hospira's proposed resubmission strategy to the February 6, 2012 Complete Response letter. As the primary issue listed in the complete response letter is the cGMP status of the drug product manufacturing site (Hospira – Rocky Mount, NC), Hospira has initiated activities to transfer the manufacturing process

to another Hospira site currently in good standing (Hospira – McPherson, KS).

Proposed Stability Data Set:

The McPherson manufacturing process aligns with the currently filed process with minor changes made to accommodate the site. In preparation for transfer, we have successfully executed an engineering batch and are in the process of manufacturing exhibit batches, as described in the table below, to support qualification.

No. of Batches	Paricalcitol Injection Presentation
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1	10 mcg/2 mL (5 mcg/mL) in a 2 mL vial

We would like to accelerate filing to respond to the Complete Response letter as quickly as possible. Due to the stability of the product, established by the data collected in support of the current manufacturing site, we'd like to propose resubmitting with a stability data set containing results collected through 3 months of storage under accelerated and long-term conditions. Will this be accepted for review?

Status of Hospira Rocky Mount as a Filed Establishment:

Ideally, we hope that our current facility returns to a compliant status. Is it possible to maintain the Hospira Rocky Mount site in our filing until an action letter is ready to be issued after review of the resubmission? If, at that time, Hospira Rocky Mount has not returned to compliant status, we would be prepared to withdraw the site to keep the review progressing.

Thank you in advance for your follow up on these questions; any feedback you can provide will better ensure that our proposed resubmission is robust.

Kind regards,
Laurie

From: Wojtko, Laurie M. [<mailto:Laurie.Wojtko@hospira.com>]
Sent: Thursday, December 12, 2013 5:19 PM
To: Jairath, Meghna
Cc: McIntyre, Kristina
Subject: NDA 201-657, Paricalcitol Injection

Hi Meghna,

I wanted to reach out to initiate discussion on Hospira's Paricalcitol Injection, NDA 201-657. This application was submitted on April 7, 2011 and a complete response letter was issued on February 6, 2012. The primary issue documented by this complete response letter is the cGMP status of our current drug product manufacturing facility – Hospira Rocky Mount, NC.

We have transferred the process to an alternate manufacturing facility and have successfully run

engineering batches. Our intention is to run new exhibit batches and provide site information and batch data as a response to our complete response. However, we remain hopeful that Hospira Rocky Mount will come into good standing by the time of market formation.

Would you be willing to have a short call with us to discuss the proposed response data set and the possibility of maintaining the current manufacturing site in our application?

Thank you in advance for your time & consideration.

Kind regards,

Laurie Wojtko
Associate Director
US Generic Development
Global Regulatory Affairs

Hospira, Inc.
275 N. Field Dr., Bldg. H2-2, Dept. 392, Lake Forest, IL 60045
Office: +00 1 224.212.6158 | Mobile: (b) (6)
Fax: +00 1 224.212.5401
E: laurie.wojtko@hospira.com | W: www.hospira.com

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/s/

MEGHNA M JAIRATH
02/11/2014

From: [Jairath, Meghna](#)
To: [Wojtko, Laurie M. \(Laurie.Wojtko@hospira.com\)](mailto:Laurie.Wojtko@hospira.com)
Subject: NDA 201-657, Paricalcitol Injection
Date: Monday, December 23, 2013 6:10:44 PM

Hello,

Please see our response below to your Q1.

Sponsor Question1:

Proposed Stability Data Set:

The McPherson manufacturing process aligns with the currently filed process with minor changes made to accommodate the site. In preparation for transfer, we have successfully executed an engineering batch and are in the process of manufacturing exhibit batches, as described in the table below, to support qualification.

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1	5 mcg/1 mL in a 2 mL vial
1	10 mcg/2 mL (5 mcg/mL) in a 2 mL vial

We would like to accelerate filing to respond to the Complete Response letter as quickly as possible. Due to the stability of the product, established by the data collected in support of the current manufacturing site, we'd like to propose resubmitting with a stability data set containing results collected through 3 months of storage under accelerated and long-term conditions. Will this be accepted for review?

FDA Response: Yes, we agree with your proposal to submit 3-month long-term and accelerated stability data for the four exhibit batches manufactured at the proposed commercial site in McPherson, KS.

Thanks,
Meghna

From: Wojtko, Laurie M. [<mailto:Laurie.Wojtko@hospira.com>]
Sent: Monday, December 23, 2013 2:43 PM
To: Jairath, Meghna
Subject: RE: NDA 201-657, Paricalcitol Injection

Hi Meghna,

Yes, all 4 exhibit batches will be placed on stability and we will provide results for all 4 lots through 3 months of storage at the time of submission. We would plan on updating as requested during the review cycle to further support the review.

Laurie

From: Jairath, Meghna [<mailto:Meghna.Jairath@fda.hhs.gov>]
Sent: Monday, December 23, 2013 1:31 PM
To: Wojtko, Laurie M.
Subject: RE: NDA 201-657, Paricalcitol Injection

Hello,

We have the following clarification on your Q1 below.

FDA Questions: Will all 4 exhibit batches be included in the proposed “stability data set containing results collected through 3 months of storage under accelerated and long-term conditions”?

Thx
Meghna

From: Wojtko, Laurie M. [<mailto:Laurie.Wojtko@hospira.com>]
Sent: Wednesday, December 18, 2013 5:43 PM
To: Jairath, Meghna
Subject: RE: NDA 201-657, Paricalcitol Injection

In follow up to our phone conversation yesterday, I have summarized Hospira’s proposed resubmission strategy to the February 6, 2012 Complete Response letter. As the primary issue listed in the complete response letter is the cGMP status of the drug product manufacturing site (Hospira – Rocky Mount, NC), Hospira has initiated activities to transfer the manufacturing process to another Hospira site currently in good standing (Hospira – McPherson, KS).

Proposed Stability Data Set:

The McPherson manufacturing process aligns with the currently filed process with minor changes made to accommodate the site. In preparation for transfer, we have successfully executed an engineering batch and are in the process of manufacturing exhibit batches, as described in the table below, to support qualification.

No. of Batches	Paricalcitol Injection Presentation
2	2 mcg/1 mL in a 2 mL vial
1	5 mcg/1 mL in a 2 mL vial
1	10 mcg/2 mL (5 mcg/mL) in a 2 mL vial

We would like to accelerate filing to respond to the Complete Response letter as quickly as possible. Due to the stability of the product, established by the data collected in support of the current manufacturing site, we’d like to propose resubmitting with a stability data set containing results collected through 3 months of storage under accelerated and long-term conditions. Will this be accepted for review?

Status of Hospira Rocky Mount as a Filed Establishment:

Ideally, we hope that our current facility returns to a compliant status. Is it possible to maintain

the Hospira Rocky Mount site in our filing until an action letter is ready to be issued after review of the resubmission? If, at that time, Hospira Rocky Mount has not returned to compliant status, we would be prepared to withdraw the site to keep the review progressing.

Thank you in advance for your follow up on these questions; any feedback you can provide will better ensure that our proposed resubmission is robust.

Kind regards,
Laurie

From: Wojtko, Laurie M. [<mailto:Laurie.Wojtko@hospira.com>]
Sent: Thursday, December 12, 2013 5:19 PM
To: Jairath, Meghna
Cc: McIntyre, Kristina
Subject: NDA 201-657, Paricalcitol Injection

Hi Meghna,

I wanted to reach out to initiate discussion on Hospira's Paricalcitol Injection, NDA 201-657. This application was submitted on April 7, 2011 and a complete response letter was issued on February 6, 2012. The primary issue documented by this complete response letter is the cGMP status of our current drug product manufacturing facility – Hospira Rocky Mount, NC.

We have transferred the process to an alternate manufacturing facility and have successfully run engineering batches. Our intention is to run new exhibit batches and provide site information and batch data as a response to our complete response. However, we remain hopeful that Hospira Rocky Mount will come into good standing by the time of market formation.

Would you be willing to have a short call with us to discuss the proposed response data set and the possibility of maintaining the current manufacturing site in our application?

Thank you in advance for your time & consideration.

Kind regards,

Laurie Wojtko
Associate Director
US Generic Development
Global Regulatory Affairs

Hospira, Inc.
275 N. Field Dr., Bldg. H2-2, Dept. 392, Lake Forest, IL 60045
Office: +00 1 224.212.6158 | Mobile: (b) (6)
Fax: +00 1 224.212.5401
E: laurie.wojtko@hospira.com | W: www.hospira.com

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/s/

MEGHNA M JAIRATH
02/11/2014

From: [Jairath, Meghna](#)
To: [Wojtko, Laurie M.](#)
Subject: RE: NDA 201-657, Paricalcitol Injection
Date: Monday, December 23, 2013 2:31:29 PM

Hello,

We have the following clarification on your Q1 below.

FDA Questions: Will all 4 exhibit batches be included in the proposed “stability data set containing results collected through 3 months of storage under accelerated and long-term conditions”?

Thx
Meghna

From: Wojtko, Laurie M. [mailto:Laurie.Wojtko@hospira.com]
Sent: Wednesday, December 18, 2013 5:43 PM
To: Jairath, Meghna
Subject: RE: NDA 201-657, Paricalcitol Injection

In follow up to our phone conversation yesterday, I have summarized Hospira’s proposed resubmission strategy to the February 6, 2012 Complete Response letter. As the primary issue listed in the complete response letter is the cGMP status of the drug product manufacturing site (Hospira – Rocky Mount, NC), Hospira has initiated activities to transfer the manufacturing process to another Hospira site currently in good standing (Hospira – McPherson, KS).

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No. of Batches	Paricalcitol Injection Presentation
2	2 mcg/1 mL in a 2 mL vial
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1	10 mcg/2 mL (b) (4) in a 2 mL vial

We would like to accelerate filing to respond to the Complete Response letter as quickly as possible. Due to the stability of the product, established by the data collected in support of the current manufacturing site, we’d like to propose resubmitting with a stability data set containing results collected through 3 months of storage under accelerated and long-term conditions. Will this be accepted for review?

Status of Hospira Rocky Mount as a Filed Establishment:

Ideally, we hope that our current facility returns to a compliant status. Is it possible to maintain the Hospira Rocky Mount site in our filing until an action letter is ready to be issued after review of

the resubmission? If, at that time, Hospira Rocky Mount has not returned to compliant status, we would be prepared to withdraw the site to keep the review progressing.

Thank you in advance for your follow up on these questions; any feedback you can provide will better ensure that our proposed resubmission is robust.

Kind regards,
Laurie

From: Jairath, Meghna [<mailto:Meghna.Jairath@fda.hhs.gov>]
Sent: Monday, December 16, 2013 9:06 AM
To: Wojtko, Laurie M.
Subject: RE: NDA 201-657, Paricalcitol Injection

Hello,
We can talk tomorrow at 11am. You can call me then.
Thx
Meghna

From: Wojtko, Laurie M. [<mailto:Laurie.Wojtko@hospira.com>]
Sent: Thursday, December 12, 2013 5:19 PM
To: Jairath, Meghna
Cc: McIntyre, Kristina
Subject: NDA 201-657, Paricalcitol Injection

Hi Meghna,

I wanted to reach out to initiate discussion on Hospira's Paricalcitol Injection, NDA 201-657. This application was submitted on April 7, 2011 and a complete response letter was issued on February 6, 2012. The primary issue documented by this complete response letter is the cGMP status of our current drug product manufacturing facility – Hospira Rocky Mount, NC.

We have transferred the process to an alternate manufacturing facility and have successfully run engineering batches. Our intention is to run new exhibit batches and provide site information and batch data as a response to our complete response. However, we remain hopeful that Hospira Rocky Mount will come into good standing by the time of market formation.

Would you be willing to have a short call with us to discuss the proposed response data set and the possibility of maintaining the current manufacturing site in our application?

Thank you in advance for your time & consideration.

Kind regards,

Laurie Wojtko
Associate Director
US Generic Development
Global Regulatory Affairs

Hospira, Inc.
275 N. Field Dr., Bldg. H2-2, Dept. 392, Lake Forest, IL 60045
Office: +00 1 224.212.6158 | Mobile: (b) (6)
Fax: +00 1 224.212.5401
E: laurie.wojtko@hospira.com | W: www.hospira.com

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/s/

MEGHNA M JAIRATH
02/11/2014



NDA 201657

GENERAL ADVICE

Hospira, Inc.
Attention: Laurie Wojtko
Associate Director, Global Regulatory Affairs
275 North Field Drive
Lake Forest, Illinois 60074

Dear Ms. Wojtko:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paricalcitol Injection (2 mcg/1 mL, 5 mcg/1 mL, 10 mcg/2 mL).

We also refer to your submission dated May 10, 2013, containing a request for an extension to resubmit the application, in the form of a response to our complete response letter dated February 6, 2012.

We grant you an extension of one year to resubmit this application. We remind you that per 21 CFR 314.110(c), an applicant's failure to resubmit the application within the extended time period or to request an additional extension may be considered a request by the applicant to withdraw the application.

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

Sincerely,

Mary H. Parks, M.D.

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
05/24/2013

From: [Jairath, Meghna](#)
To: ["Wojtko, Laurie M."](#)
Subject: Labeling First round NDA 201657
Date: Wednesday, January 11, 2012 10:30:34 AM
Attachments: [first round labeling_1-11-12.doc](#)
[c-c labeling.doc](#)
Importance: High

Hello,

Attaching the PI with track changes and C/C comments.
Please do not submit anything to the NDA until we have agreed upon a final version of PI and C/C.

Please acknowledge receipt of email.

Thanks,
Meghna

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/s/

MEGHNA M JAIRATH
01/11/2012



NDA 201657

INFORMATION REQUEST

Hopsira, Inc.
Attention: Laurie Wojtko, Sr. Associate, Global Regulatory Affairs
275 North Field Dr.
Dept. 0389, Bldg H2-2
Lake Forest, IL 60045

Dear Ms. Wojtko:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Paricalcitol Injection.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Change the [REDACTED] (b) (4)
2. Propose and justify acceptance criteria for the extractables/leachables ([REDACTED] (b) (4)) as part of the drug product release specifications. The acceptance criteria for fill volume "NLT labeled volume" should be revised to an acceptable range.
3. Explain what is the "controlled score" on the aluminum seal (See Table 1, Summary of Container Closure System, in section 3.2.P.7).
4. Provide a sample of the container closure system with a mock of the proposed label.
5. Include fill volume testing and extractables/leachables testing in the stability testing of the drug product. Acceptance criteria for extractables/leachables should be proposed and justified accordingly.
6. Revise the proposed post-approval stability protocol to include testing for fill volume and testing for the extractables/leachables.

7. Submit a revised table with drug product specifications to include all above changes.

If you have any questions, call Khushboo Sharma, Regulatory Project Manager, at (301) 796-1270.

Sincerely,

{See appended electronic signature page}

Ali Al-Hakim, Ph.D.
Branch Chief, Branch VII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALI H AL HAKIM
10/19/2011

From: [Jairath, Meghna](#)
To: ["Wojtko, Laurie M.";](#)
Subject: RE: Paricalcitol, NDA 201-657, Telecon Update
Date: Tuesday, September 27, 2011 11:38:48 AM

Hello,

Meeting time set for tcon from 12 to 1 pm on OCT 13. Hope that will work for you guys.

Have the following 3 questions listed below that we are seeking further discussion?

Nonclinical

Findings from the nonclinical study in the Hospira paricalcitol-treated males suggested two safety concerns as following: the delay in soft tissues mineralization and increased inflammation at the infusion site.

1. Can you explain the mechanism of the delay in soft tissues mineralization? We are concerned that a longer recovery time might show an increased in incidence of soft tissue mineralization.
2. Do you have any data available for the 5 mcg/kg/dose treated animals as well as toxicokinetics data at the end of the recovery study?

Clinical

3. Discuss the safety of using a 40% alcohol formulation and the potential impact of this formulation on infusion tubing and related materials and on AV fistula itself.

thanks,
Meghna

From: Wojtko, Laurie M. [mailto:Laurie.Wojtko@hospira.com]
Sent: Tuesday, September 27, 2011 10:43 AM

To: Jairath, Meghna
Subject: RE: Paricalcitol, NDA 201-657, Telecon Update

Thanks, Meghna.

So you're aware, we have some critical stakeholders, including myself, attending the GPhA conference next week Monday – Wednesday. Is there anyway that the meeting can be scheduled later in the week?

From: Jairath, Meghna [mailto:Meghna.Jairath@fda.hhs.gov]
Sent: Tuesday, September 27, 2011 9:23 AM
To: Wojtko, Laurie M.
Subject: RE: Paricalcitol, NDA 201-657, Telecon Update

Will send you a date shortly. I am working on it. I am looking at next week sometime!

From: Wojtko, Laurie M. [mailto:Laurie.Wojtko@hospira.com]
Sent: Monday, September 26, 2011 1:51 PM
To: Jairath, Meghna
Subject: Paricalcitol, NDA 201-657, Telecon Update

Hi Meghna,
I am following-up to ask if you have any updates on the scheduling of a teleconference to discuss the alcohol-related questions we discussed briefly last week. Also, I was hoping you could share the review team's concerns if they've been finalized.

Thanks!

Kind regards,

Laurie Wojtko
Senior Associate
Global Regulatory Affairs
Hospira, Inc.
275 N. Field Dr.
Bldg. H2-2, Dept. 389
Lake Forest, IL 60045
P: 224-212-6158
F: 224-212-5401
www.hospira.com

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/s/

MEGHNA M JAIRATH
09/29/2011



NDA 201657

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Hospira, Inc.
Attention: Laurie Wojtko
Sr. Associate, Global Regulatory Affairs
275 North Field Dr.
Dept. 0389, Bldg. H2-2
Lake Forest, IL 60045

Dear Ms. Wojtko:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Paricalcitol Injection, 2 mcg/1 mL, 5 mcg/1 mL, and 10 mcg/2 mL.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is

¹ These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

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.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JULIE C MARCHICK

09/08/2011

J. Marchick signing for M. Parks



NDA 201657

FILING COMMUNICATION

Hospira, Inc.
Attention: Laurie Wojtko
Sr. Associate, Global Regulatory Affairs
275 North Field Dr.
Dept. 0389, Bldg. H2-2
Lake Forest, IL 60045

Dear Ms. Wojtko:

Please refer to your New Drug Application (NDA) dated April 7, 2011, received April 7, 2011 submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Paricalcitol Injection, 2 mcg/1 mL, 5 mcg/1 mL, and 10 mcg/2 mL.

We also refer to your submissions dated May 2 and 3, 2011 containing the form 3674 and labeling changes, respectively.

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 February 7, 2012.

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, midcycle, 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 January 10, 2012.

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

Clinical

1. Perform a data-mining search of approved injectable products with 40% or more alcohol to identify if there is an increased risk for injection site reactions with that much alcohol that would require dilution of the sample prior to dosing.

Chemistry, Manufacturing, and Controls

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

Regulatory

5. Submit patent information on form FDA 3542a per 21 CFR 314.53(c).

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.

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.

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.
Director
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

06/20/2011

Signing on behalf of Mary Parks



NDA 201657

NDA ACKNOWLEDGMENT

Hospira, Inc.
Attention: Laurie Wojtko
Sr. Associate, Global Regulatory Affairs
275 North Field Dr.
Dept. 0389, Bldg. H2-2
Lake Forest, IL 60045

Dear Ms. Wojtko:

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/1 mL, 5 mcg/1 mL, 10 mcg/2 mL)

Date of Application: April 7, 2011

Date of Receipt: April 7, 2011

Our Reference Number: NDA 201657

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 June 6, 2011, 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 314.1

01(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).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 201657** submitted on April 7, 2011, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

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

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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
04/26/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

8/26/10
Pre-NDA

Food and Drug Administration
Silver Spring MD 20993

Pre-NDA 201657

MEETING MINUTES

Hospira, Inc.
Attention: Laurie Wojtko
Sr. Associate, Global Regulatory Affairs
275 North Field Drive
Dept. 389, Bldg. H2-2
Lake Forest, IL 60064

Dear Ms. Wojtko:

Please refer to your Pre-New Drug Application (Pre-NDA) for paricalcitol injection.

We also refer to the teleconference between representatives of your firm and the FDA on July 29, 2010. The purpose of the meeting was to discuss the drug development of paricalcitol injection.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

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

Enclosure

Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: Thursday, July 29, 2010 2:00 p.m. – 3:00 p.m., EST

Application Number: 201657
Product Name: Paricalcitol injection
Indication:
Sponsor/Applicant Name: Hospira, Inc.

Meeting Chair: Dragos Roman, M.D.
Meeting Recorder: Pooja Dharia, Pharm.D.

FDA ATTENDEES

Office of Drug Evaluation II

Enid Galliers	Chief, Project Management Staff, Division of Metabolism and Endocrinology Products (DMEP)
Pooja Dharia, Pharm.D.	Regulatory Project Manager, DMEP
Dragos Roman, M.D.	Acting Clinical Team Leader, DMEP
William Lubas, M.D.	Clinical Reviewer, DMEP
Karen Davis-Bruno, Ph.D.	Pharmacology/Toxicology Team Leader, DMEP
Parvaneh Espandiari, Ph.D.	Pharmacology/Toxicology Reviewer, DMEP

Office of Clinical Pharmacology

S.W. Johnny Lau, Ph.D.	Clinical Pharmacology Reviewer
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Office of New Drug Quality Assessment

Suong T. Tran, Ph.D.	CMC Lead
Elsbeth Chikhale, Ph.D.	Chemistry Reviewer
Angelica Dorantes, Ph.D.	Biopharmaceutics Team Leader

SPONSOR ATTENDEES

Laurie Wojtko	Sr. Associate, Global Regulatory Affairs
Wendy Tian	Manager, Global Regulatory Affairs
Lisa Zbori	Director, Global Regulatory Affairs
Dennis Stalker	Director, Clinical Research & Development
Rao Tata-Venkata	Sr. Group Leader, Research & Development
Colleen Nichol	Program Manager

1.0 BACKGROUND

A Pre-NDA meeting was requested by Hospira, Inc. on March 8, 2010 to discuss the drug development plan for paricalcitol injection. Hospira plans to submit a 505(b)(2) application that uses Abbott Laboratories' Zemplar (paricalcitol) injection as the listed drug. This meeting focused on the requirements that Hospira needs to meet for a complete future submission of a 505(b)(2) New Drug Application.

2. DISCUSSION

The sponsor's questions appear in regular font, and they are followed by FDA's preliminary responses sent July 27, 2010, in bold font. The discussion that occurred at the meeting is presented in italicized font.

1. Question: Hospira would like to present the data and justification to the agency to support a proposed abbreviated stability data package at submission. Can FDA provide input regarding the acceptability of the proposal after reviewing the data provided in the briefing book?

FDA Response:

- a. **The drug product has to be stored in both upright and inverted positions during the stability study.**
- b. **The number of batches (i.e., 7) is acceptable.**
- c.  (b) (4)
- d. **Drug product specifications (release and stability) must include testing for impurities  and all the stopper/tubing related impurities if these are not part of impurities .**
- e. **Expiry dating is a review issue.**

Discussion: The sponsor asked if it would be acceptable to file the NDA with less than 12 months of stability data. FDA questioned why the sponsor could not provide 12 months of stability data. Sponsor responded that they wanted to submit the NDA as soon as possible; i.e. submit 9 months of data with initial NDA submission and 3 months of additional data 2 months later. The sponsor also proposed to base the expiry on that of the listed drug. FDA responded that the NDA should be complete upon submission. It is the sponsor's risk to submit limited stability data in the initial submission which may result in a short expiry. Proposed additional data may or may not be reviewed, depending on FDA's resources at the time of receipt. In addition, the determination of an expiry is based on "Guidance for Industry: Q1E Evaluation of Stability Data" (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073380.pdf>) and will be based on the sponsor's data for the new product, not on the listed drug's expiry.

2. **Question:** Due to the low concentration of Paricalcitol Injection, 2 µg/mL or 5 µg/mL, the related substances method is extremely sensitive. Hospira has observed trace peaks in the drug product related substances chromatogram. These peaks are unrelated to the drug and have been identified as originating from the stopper or solution contact with manufacturing parts. The same peaks have also been observed in the RLD product, as Hospira is using the same stopper material. Hospira does not intend to include the quantities of these peaks when reporting related substances results. Hospira would like to provide a summary of the stopper extractable qualification studies. Can FDA provide guidance regarding the adequacy of the study conducted?

FDA Response: Refer to responses to 1a and 1d. Please also refer to “Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics”. (<http://inside.fda.gov:9003/downloads/CDER/OfficeofPharmaceuticalScience/OfficeofBiotechnologyProducts/UCM169586.pdf>).

Discussion: No discussion occurred.

3. **Question:** Hospira will request a waiver of *in vivo* Bioavailability or Bioequivalence. Based on the proposed product formulation and justification to be provided in the briefing book, can FDA review and provide confirmation that this strategy is appropriate?

FDA Response: Yes, the proposed biowaiver strategy is adequate.

CFR 320.22(b)(1) allows FDA to waive the requirement for the submission of *in vivo* bioavailability/bioequivalence (BA/BE) data for certain drug products which *in vivo* BA/BE is self-evident. A drug product’s *in vivo* BA/BE may be considered self-evident if (i) the product is a parenteral solution intended solely for administration by injection, and (ii) it contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full NDA or ANDA. Therefore, we may waive the CFR’s BA/BE requirement for the proposed product. You should include the biowaiver request and supporting information in the NDA application.

Discussion: No discussion occurred.

We also have the following comments and recommendations:

4. **You have proposed a 505(b)(2) nonclinical development pathway for injectable paricalcitol using Zemplar (NDA 020819) as the listed drug. There are likely differences in manufacturing between the products which may result in differences in impurity/degradant profiles between the products. These anticipated differences would require nonclinical studies to qualify any differences, assuming that the analytic characterization of your product was considered sufficient from the Chemistry, Manufacturing and Controls (CMC) viewpoint. These nonclinical**

studies might include a subchronic comparative bridging toxicology study comparing your product to the listed product in a single relevant species.

A 505(b)(2) application relies on FDA's finding of safety and effectiveness for the listed drug and you will be required to demonstrate sufficient similarity between your product and Zemplar if you chose to reference it. You must establish that such reliance is scientifically appropriate and submit the data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug. You should establish a bridge between the proposed product and each listed drug upon which you propose to rely.

Discussion: The sponsor stated that they did not have plans to submit any nonclinical data. FDA questioned how they would bridge between the listed drug and their drug. Sponsor responded that they would bridge purely by analytical means. FDA responded that the sponsor would likely need animal data for qualification of any differences in impurities or degradants in their product compared to the listed drug based on manufacturing differences. It is unlikely that an acceptable bridge to the listed drug could be obtained using only CMC information.

- 5. Provide an analytical comparison (quantitative results and impurity/degradation profiles) between the proposed new drug product and the listed drug on which it relies. Any differences will require safety information.**

Discussion: The sponsor explained that HPLC chromatograms show the same impurity peaks in the listed drug and the sponsor's drug. FDA responded that retention times alone may not be adequate to show that both products have the same impurities. A more thorough characterization of the products, including a structural analysis to identify the impurities, may be required.

- 6. Please refer to "Guidance for Industry: Q3A(R) Impurities in New Drug Substances" for impurity thresholds for reporting, identification, and qualification. Please also refer to Guidance for Industry: Q3B(R) Impurities in New Drug Products (Revision 2)". These guidances can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065005.htm>.**

Discussion: No discussion occurred.

- 7. Propose acceptance criteria (as part of the drug product specifications) for impurities (extractables/leachables) from stopper and tubing materials and provide safety information in support of the proposed acceptance criteria.**

Discussion: The sponsor explained that the levels of extractables and leachables are very low and well within safety limits. Therefore, acceptance criteria are not proposed. FDA responded that adequate information should be included in the NDA to justify the safety limits and data (including stability data monitoring leachables) should be included as part of a justification for proposing certain acceptance criteria or for not proposing any acceptance criteria.

8. Identify the extractable/leachable impurities in the proposed drug product and in the listed drug to support your claim that they are the same.

Discussion: The sponsor explained that since the same container closure systems are used for the sponsor's drug and the listed drug, the extractables/leachables are expected to be the same. FDA responded that it is not possible for FDA to confirm whether the same container closure components are used in the listed drug. In addition, the formulations are different. Therefore, information should be submitted in the NDA in support of the claim that the extractables/leachables are the same, including information on the identity of these compounds.

9. If you submit a 505(b)(2) NDA, you should clearly identify the information for the proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by your reliance on published literature. We request that you use the chart format shown below to identify the listed drug and/or literature used to support each section of your application, including the labeling. If literature is used, copies of the articles must be included and any trade names stated in those reports identified. Further, a 505(b)(2) application may not rely on any specific data for the listed drug (e.g., such as that included in a summary basis of approval).

Example:

Source of information (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
1.	
2.	
3.	
4.	

Discussion: The sponsor understood that they should clearly state their sources of information.

10. **Because reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate, you should describe how you bridged the proposed product to the referenced product(s); for example, BA/BE studies. Also, that description should identify the specific name (e.g., brand name) of each listed drug given in any of the published literature on which your application relies to support approval.**

Discussion: No discussion occurred.

11. **We remind you that your labeling must conform to the Physicians Labeling rule (PLR) format and that 505(b)(2) applications are subject to the Prescription Drug User Fee Act.**

Discussion: No discussion occurred.

12. **The Division strongly encourages you to request a pre-NDA meeting to discuss the details regarding submission of this 505(b)(2) application. To be useful, the meeting must be held at least two to three months prior to submission of the NDA.**

Discussion: No discussion occurred.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201657	GI-1	HOSPIRA INC	PARICALCITOL INJECTION

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

/s/

POOJA DHARIA
08/26/2010