CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201657Orig1s000

OTHER REVIEW(S)

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	September 11, 2014
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 201657
Product Name and Strength:	Paricalcitol injection, 2 mcg/ml, 5 mcg/ml, 10 mcg/2 ml (5 mcg/ml)
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Hospira, Inc.
Submission Date:	April 21, 2014
OSE RCM #:	2014-913
DMEPA Primary Reviewer:	Mishale Mistry, PharmD, MPH
DMEPA Team Leader:	Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the carton and container labeling and Prescribing Information for Paricalcitol injection, NDA 201657, submitted on April 21, 2014. The Division of Metabolism and Endocrinology Products (DMEP) requested that DMEPA review the revised labels and labeling for areas of vulnerability that may lead to medication errors. The revisions are in response to recommendations that DMEPA made during a previous label and labeling review.[1]

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	N/A
ISMP Newsletters	D
Other	N/A
Labels and Labeling	E

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA analyzed medication error cases that occurred with the reference listed drug, Zemplar injection. Identified medication error cases reported wrong route of administration, wrong dose (overdose), and wrong drug errors. A review of the currently approved Zemplar Prescribing Information demonstrates that the product contains clear information regarding the dose, but the route of administration is not explicitly stated in the Dosage and Administration section. See Appendix B for additional details regarding medication error cases and our analysis of the cases.

DMEPA also searched the Institute for Safe Medication Practices (ISMP) newsletters and identified one medication error case reporting a wrong drug error between Zemplar and

[1] Baugh D. Label and Labeling Review for Paricalcitol (NDA 201657). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2011 Dec 06. 20 p. OSE RCM No.: 2011-1771.

Fosphenytoin. However, the case is not relevant to this review because the proposed packaging for Paricalcitol does not appear similar to that of Fosphenytoin.

Additionally, DMEPA reviewed the proposed labels and labeling to determine whether there are any significant concerns in terms of safety, related to preventable medication errors. We note that the proposed container and carton labels and labeling and Prescribing Information can be improved to explicitly highlight the unique route of administration and the warning statement to not inject the drug product directly into a vein. Furthermore, we recommend the use of colors on the carton labeling, similar to that of the container labels, to differentiate between the strengths of paricalcitol.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information, to highlight the route of administration, and to better differentiate the strengths in order to promote the safe use of the product and mitigate any confusion.

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA provides the following comments for consideration by the review Division prior to the approval of this NDA:

A. Full Prescribing Information

1. To increase the health care provider's awareness to the proper route of administration for this drug product, include the following statement in bold font immediately after the heading 'Dosage and Administration': "

"For intravenous use through hemodialysis vascular access port only"

4.2 RECOMMENDATIONS FOR HOSPIRA, INC.

Based on this review, DMEPA recommends the following be implemented prior to the approval of this NDA:

A. Vial label

1. To highlight the unique route of administration and the importance of not injecting the drug product directly into a vein, revise the statement, "Intravenous use only" to the following:

"For intravenous use through hemodialysis vascular access port only"

B. Carton labeling

1. To highlight the unique route of administration and the importance of not injecting the drug product directly into a vein, revise the statement, "Intravenous use only", located on the Principal Display Panel and side panel, to the following:

"For intravenous use through hemodialysis vascular access port only"

2. 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).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for P that Hospira, Inc. submitted on April 21, 2014, and the listed drug (LD).

Table 2. Relevant Product Information for Paricalcitol and the Reference Listed Drug		
Product Name	**Paricalcitol**	**Zemplar (RLD)**
Initial Approval Date	N/A	April 17, 1998
Active Ingredient	Paricalcitol	
Indication	Treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5.	Prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5
Route of Administration	Intravenous	
Dosage Form	Solution for injection	
Strength	2 mcg per mL 5 mcg per mL 10 mcg per 2 mL (5 mcg per mL)	
Dose and Frequency	**Initial dose:** 0.04 mcg/kg to 0.1 mcg/kg (2.8 mcg – 7 mcg) administered through a hemodialysis vascular access port as a bolus no more frequently than every other day at any time during dialysis. **Adjust dose:** dose may be increased by 2 mcg to 4 mcg at 2- to 4-week intervals.	**Initial dose:** 0.04 mcg/kg to 0.1 mcg/kg (2.8 mcg – 7 mcg) administered as a bolus dose no more frequently than every other day at any time during dialysis. **Adjust dose:** dose may be increased by 2 mcg to 4 mcg at 2- to 4-week intervals.
How Supplied	**Multi-dose vials:** 2 mcg per mL 5 mcg per mL 10 mcg per 2 mL	**Single-dose vials:** 2 mcg per mL 5 mcg per mL 10 mcg per 2 mL **Multi-dose vials:** 10 mcg per 2 mL
Storage	Store under normal lighting conditions at 20°C - 25°C (68°F -	Store at 25°C (77°F). Excursions permitted between 15°C - 30°C

	77°F) [see USP controlled room temperature]. Do not freeze. After breakage of the seal for first use, the multi-dose vials are stable for up to 28 days when stored between 20°C - 25°C (68°F - 77°F).	(59°F - 86°F).
Container Closure	1-ml and 2-ml fliptop vials	

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

DMEPA previously performed a search of the FDA Adverse Event Reporting System (FAERS), reported in OSE Review #2013-2112 (dated May 28, 2014) to determine medication errors related to the use of this product.[2] Therefore, for this review, we searched FAERS on August 7, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[2]

Table 3: FAERS Search Strategy	
Date Range	**April 10, 2014 to August 1, 2014**
Product	**Paricalcitol** [active ingredient]
Event (MedDRA Terms)	**Medication Errors** [HLGT] **Product Packaging Issues** [HLT] **Product Label Issues** [HLT] **Product Quality Issues** (NEC)[HLT]

B.2 Results

Our search from April 10, 2014 to August 1, 2014 identified three cases, one of which described errors relevant for this review. We excluded one case because it described an error outside of the United States where there may be differences in use and/or labeling of the product. Additionally, we excluded one case because it described an error regarding drug dose omission.

Following exclusions, one case (FAERS Case # 10084015 [v1]) involving wrong route of administration, remained for further analysis. This case reported a patient who received Zemplar subcutaneously, instead of intravenously. No additional details were provided regarding contributing factors or patient outcome as a result of the medication error.

The previous FAERS search was conducted in OSE Review #2013-2112, dated May 28, 2014, and provided a detailed analysis of 10 medication error cases, following exclusions. Duplicates were merged into a single case, and one case described two different types of medication errors, resulting in 11 medication error cases for analysis.

Figure 1 provides a stratification of the number of cases included in the previous review (OSE Review #2013-2112) by type of error.

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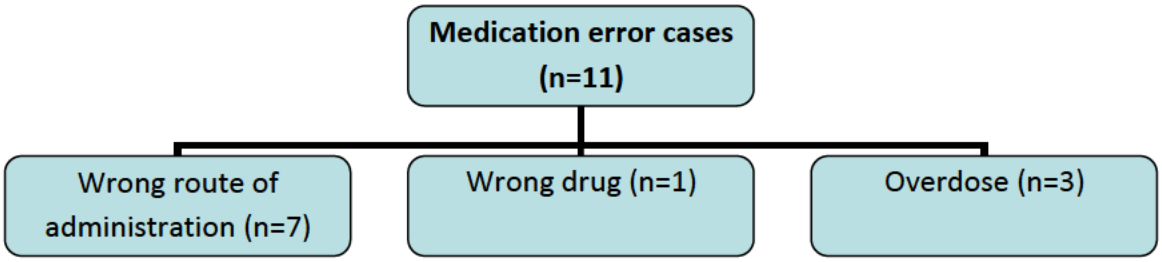
[2] Gao T. Label and Labeling Review for Paricalcitol (NDA 205917). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 May 28. 13 p. OSE RCM No.: 2013-2112.

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

Figure 1. Paricalcitol Medication Errors (n=11), categorized by type of error (OSE Review # 2013-2112)



Wrong route of administration (n=7)

- One case, FAERS Case # 7905193 [v1], reported a patient who received Zemplar 1 ml intramuscularly instead of intravenously. The patient complained that the injection hurt and the pain resolved after the medication was administered. The error may have occurred due to patient getting a hepatitis B vaccine intramuscularly prior to the Zemplar injection, but no additional information was provided regarding contributing factors.
- Six cases reported the administration of Zemplar subcutaneously rather than intravenously. In four of the cases [FAERS Case # 6540808 [v1], 6639997 [v1], 6998766 [v1], 8011161 [v1]), the patients experienced injection site reactions (stinging, redness, tissue necrosis) and hypocalcemia, whereas the outcomes for the other two cases (FAERS Case # 7905181 [v1], 7905187 [v1]) were not provided. In one of the cases (FAERS Case # 7905181 [v1]) where the patient received Zemplar subcutaneously, we attributed the wrong route error to the fact that patient was supposed to receive Epogen subcutaneously but received Zemplar subcutaneously in error. No additional information was provided regarding contributing factors for the other cases.

A review of the currently approved Zemplar® Prescribing Information labeling and identified that the route of administration is not explicitly stated in the Dosage and Administration section. However, we noted that the route of administration is explicitly stated in the Dosage and Administration section of the proposed Prescribing Information labeling for Paricalcitol.

Wrong drug (n=1)

- One case, FAERS Case # 7905181 [v1], reported a patient who received Zemplar (2 mcg/mL, 1 mL vial) instead of Epogen while on dialysis at home. The reporter stated that the patient's mother confused the vial of Zemplar with that of Epogen and intended to inject the patient with Epogen via subcutaneous route. Patient experienced hypocalcemia and Zemplar was discontinued.

A review of the vial labels of Zemplar and Epogen indicate that there are differences between the labels that differentiate the two drug products. Therefore, we not believe revisions to the label are needed at this time.

Overdose (n=3)

- One case, FAERS Case # 6605665 [v1], reported an overdose resulting in hypercalcemia because patient's Zemplar dose was not adjusted despite an increase in calcium and parathyroid hormone (PTH) levels. No additional information was provided regarding contributing factors or patient outcome as a result of the medication error.
- One case, FAERS Case # 7905183 [v1], reported an overdose where the patient received 23 mcg instead of 3 mcg. Patient experienced cramping all over during the patient's dialysis that was resolved when the patient was given saline. This error occurred because the person entering the dose accidently wrote 23 mcg instead of 3 mcg. Therefore, this error does not appear to be associated with the label and labeling of the product.
- One case, FAERS Case # 9236063 [v1], reported an overdose where the patient received 20 mcg/4 mL instead of 4 mcg/0.8 mL. No patient outcome was reported for this error. This error might have occurred due to confusion between 4 mcg and 4 mL. However, this error does not appear to be associated with the label and labeling of the proposed product.

Although we identified three medication errors reporting overdose, a review of the Dosage and Administration section within the currently approved Zemplar® Prescribing Information labeling indicates that the labeling contains clear information regarding dosing of Zemplar. As a result, we do not believe revisions to the labeling are needed at this time.

B.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

Table 4: Identified FAERS Case Numbers and Corresponding Manufacturer Control Numbers Summarized in Review

FAERS Case Number	Version	Manufacturer Control Number
Current Review – OSE Review # 2014-913		
10084015	1	US-ABBVIE-13P-163-1136240-00
OSE Review # 2013-2112		
6540808	1	US-ABBOTT-08P-163-0434913-00
6605665	1	SE-ABBOTT-08P-150-0444481-00
6639997	1	US-ABBOTT-07P-163-0374203-00
6998766	1	US-ABBOTT-09P-163-0561156-00
7905181	1	US-ABBOTT-11P-163-0704486-00

7905183	1	US-ABBOTT-10P-163-0659344-00
7905187	1	US-ABBOTT-11P-163-0704868-00
7905193	1	US-ABBOTT-10P-163-0647838-00
8011161	1	US-ABBOTT-07P-163-0376072-00
9236063	1	US-ABBOTT-12P-163-0928566-00

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive on August 7, 2014 using the term, Paricalcitol to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified two previous reviews[3]. In OSE Review #2011-1771, we confirmed that our previous recommendations were implemented and/or considered.

[3] Gao T. Label and Labeling Review for Paricalcitol (NDA 205917). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 May 28. 13 p. OSE RCM No.: 2013-2112.

Baugh D. Label and Labeling Review for Paricalcitol (NDA 201657). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2011 Dec 06. 20 p. OSE RCM No.: 2011-1771.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on August 7, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newletter(s)	Acute Care, Community
Search Strategy and Terms	Match Exact Word or Phrase: Paricalcitol

D.2 Results

Our search identified one article described an error associated with a mixup of a vial of Zemplar (paricalcitol) 5 mcg/mL and a vial of fosphenytoin 100 mg PE/2 mL due to its look-alike packaging. Both vials have a green flip-top cap with a white label that contains the drug name in green font color.[4]

Although the vial of fosphenytoin that was associated in the mixup was manufactured by Hospira, this case is not relevant to this review because the drug name on the *proposed* vial labels appears prominent in size and bold-faced font and the packaging does not look similar.

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

[4] Institute for Safe Medication Practices. Safety briefs: Look-alike vials. ISMP Med Saf Alert Acute Care. 2008;13(4):1.

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/s/

MISHALE P MISTRY
09/11/2014

YELENA L MASLOV
09/11/2014

505(b)(2) ASSESSMENT

Application Information		
NDA # 201657	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: n/a Established/Proper Name: Paricalcitol Injection Dosage Form: solution for intravenous use Strengths: 2 mcg/1 mL, 5 mcg/1 mL, 10 mcg/2 ml		
Applicant: Hospira, Inc.		
Date of Receipt: April 7, 2011		
PDUFA Goal Date: February 7, 2012 Resubmission: October 21, 2014	Action Goal Date (if different):	
Proposed Indication(s): For the prevention and treatment of secondary hyperparathyrodism associated with chronic kidney disease Stage 5		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Zemplar NDA 20819	FDA's finding of safety & effectiveness

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Hospira requested a waiver of the in vivo study requirements based on the following:
The bioequivalence of Hospira Paricalcitol Injection and Zemplar (listed product) is self-evident. Intravenous administration of the two products will result in an identical amount of drug delivered directly to the systemic circulation, and equivalent paricalcitol plasma concentration profiles can be expected for the two products. They relied on 21 CFR 320.22 repeated below.

> "(b) For certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:
>
> (1) The drug product:
> (i) Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and
> (ii) Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application."

FDA granted waiver of *in vivo* study request.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☐ NO ☒

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☐

*If "**NO**", proceed to question #5.*
*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Zemplar	NDA 20819	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*

*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This product provides for the same active ingredient, indications, route of administration and dosage form as the listed drug (LD), Zemplar®. The inactive ingredients in the proposed product are (b) (4) LD, but the ratio of (b) (4), Alcohol and Propylene Glycol have been modified to ensure complete solubilization of the active drug.

The following statement was provided by the CMC reviewer in regards why this product could not be a 505(j): Per 21 CFR 314.94(a)(9)(iii), an (b) (4) parenteral drug must have the same inactive ingredients as the RLD, with the exception of ingredients for buffer, preservative, or antioxidant (which can be different). Since the difference between this product and the RLD is the amounts of propylene glycol and alcohol, which are not ingredients for buffer, preservative, or antioxidant, this application cannot be a 505(j).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical*

compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☒ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s): **ANDA 091108 for Paricalcitol inject 0.002mg/ml and 0.005mg/ml by Sandoz Canada Inc.**

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s): NDA 21606 Zemplar capsules and generics may be listed as pharmaceutical alternatives.

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

U.S. Patent Number	Patent Expiration
5,246,925	April 17, 2012
5,246,925*PED	October 17, 2012
5,587,497	December 24, 2013
5,587,497*PED	June 24, 2014
6,136,799	April 8, 2018
6,136,799*PED	October 8, 2018
6,361,758	April 8, 2018
6,361,758*PED	October 8, 2018
5,597,815	July 13, 2015
5,597,815*PED	Jan. 13, 2016

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ×

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s): **5597815 and 5597815*PED.** These patents were submitted to NDA 20819 on Nov. 30, 2011.

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): **5,246,925 expires on April 17, 2012 and is subject to period of pediatric exclusivity which expires on October 17, 2012.**

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
In the original April 8, 2011 submission, Paragraph IV certifications were made for the following US patents: 6,136,799 and 6,361,758. In their July 26, 2011 submission, the sponsor changed US patent. No. 5,587,497 from a Paragraph III to a Paragraph IV certification.

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): 6,136,799; 6,361,758; 5,587,497

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): **June 16, 2011 for NDA holder and patent owner received for US patent NOs 6,136,799 and 6,361,758.**

August 3, 2011 for NDA holder and patent owner received for US patent 5,587,497.

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☒ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

"Summons and Complaint" documents were submitted on July 28, 2011 and September 22, 2011 to the administrative file. The 30 month stay associated with the Paragraph IV certifications expired on December 8, 2013.

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

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Review

Date	December 6, 2011
Reviewer	Denise V. Baugh, PharmD, BCPS Division of Medication Error Prevention and Analysis
Team Leader	Lubna Merchant, PharmD, M.S. Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, R.Ph. Division of Medication Error Prevention and Analysis
Drug Name and Strength	Paricalcitol Injection 2 mcg/mL multi-dose vial, 1 mL 5 mcg/mL multi-dose vial, 1 mL (b) (4)
Application Type/Number	NDA 201657
Applicant	Hospira, Inc.
OSE RCM	2011-1771

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Paricalcitol Injection, (NDA 201657) for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

The container labels, carton and insert labeling were submitted by the Applicant on April 8, 2011. This is a 505(b)(2) application which provides for multi-dose vials in the following concentrations and volume sizes: 2 mcg/mL (1 mL vial), 5 mcg/mL (1 mL vial), and (b) (4). The reference listed drug is Zemplar Injection (NDA 020819).

1.2 PRODUCT INFORMATION

The following product information is provided in the April 8, 2011 label and labeling submission:

- Established Name: Paricalcitol Injection
- Indication of Use: prevention and treatment of secondary yperparathyroidism associated with stage 5 chronic kidney disease
- Route of administration: intravenous
- Dosage form: vial
- Dose: Doses are individualized based upon the calcium and phosphorous levels. The recommended initial dose is 0.04 mcg/kg to 0.1 mcg/kg (2.8 mcg to 7 mcg) administered intravenously as a bolus dose no more frequently than every other day at any time during dialysis. If a satisfactory response is not observed, the dose may be increased by 2 to 4 mcg at 2 to 4 week intervals.
- How Supplied: Paricalcitol will be supplied as multi-dose vials in the following strengths and vial sizes: 2 mcg/mL (1 mL vial), 5 mcg/mL (1 mL vial), and (b) (4). Each strength will be supplied in trays of 25 vials.
- Storage: After initial use, the contents of the multi-dose vial remain stable up to 28 days when stored between 20°C to 25°C (68°F to 77°F). Unopened vials should be stored under normal lighting conditions at 20°C to 25°C (68°F to 77°F).
- Container and Closure systems: (b) (4) The container closure system consists of a 2 mL glass vial, with a rubber stopper, and aluminum seal with a (b) (4) button on top.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis[1] and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted April 8, 2011 - see Appendix A for images
- Carton Labeling submitted April 8, 2011 - see Appendix B for images
- Insert Labeling submitted April 8, 2011 (no image)
- Container Label, Carton and Insert Labeling for Zemplar (NDA 020819) – see Appendices C and D for images
- Container Label, Carton and Insert Labeling for Paricalcitol Injection (ANDA 091108 approved July 27, 2011) provided by the Office of Generic Drugs (OGD) via correspondence November 14, 2011 – see Appendices E and F for images

We also looked at our previous reviews (OSE Review # 2010-1039 dated July 21, 2010 and OSE Review # 2007-802, 2007-2178 and 2007-2192 dated December 3, 2007) for information relevant to this proposed drug product.

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

Additionally, since Zemplar and Paricalcitol are currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Zemplar or Paricalcitol that may be applicable to this review. The November 13, 2011 AERS search used the following search terms: active ingredient "Paracalcitol", trade name "Zemplar", and verbatim terms "Paric%" and "Zempl%". The reaction terms used were the MedDRA High Level Group Terms (HLGT) "Medication Errors" and "Product Quality Issues". As our last AERS search was completed May 25, 2010 (OSE 2010-1039 dated July 21, 2010), the search was limited to May 26, 2010 to November 13, 2011.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include those that did not describe a medication error, involved concomitant medications, described a medication error related to another dosage form (capsule), an accidental overdose related to a transcription error, and dose omission likely related to a process-related or human error.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 RESULTS

The following sections describe DMEPA's evaluation of the AERS cases and the proposed labels and labeling.

3.1 MEDICATION ERROR CASES

Our search of the AERS database retrieved a total of 13 cases. Following exclusions, as stated in section 2,we evaluated a total of four cases relevant to this review. One case was counted twice as it concerned wrong drug and wrong route of administration and, therefore, was assessed as two separate medication error cases. The cases are categorized as follows:

Wrong Route of Administration (n = 3)

Three cases involved the administration of Zemplar by the wrong route. Two patients received Zemplar subcutaneously and one patient received the drug intramuscularly. The patient who received the drug intramuscularly complained that the injection hurt whereas no outcome was provided for the other patients. No contributing factors were provided for either case.

Wrong Drug (n = 1)

This case describes a patient who received Zemplar (2 mcg/mL, 1 mL vial) instead of Epogen while on dialysis at home. The reporter stated that the patient's mother confused the vial of Zemplar with that of Epogen and intended to inject the patient with Epogen via subcutaneous route.

3.2 LABEL AND LABELING RISK ASSESSMENT

Since it is possible that these products will be stored adjacent to each other on the pharmacy shelf, we compared the proposed container labels, carton labeling submitted on April 8, 2011, with the labels and labeling for the recently approved Paricalcitol Injection, and for Zemplar (Paricalcitol) Injection to assess their vulnerability to confusion and medication errors. (See Appendices A through F for images).

3.2.1 Container Label and Carton Labeling (Appendices A and B)

The presentation of the established name on the container label is similar for the 2 mcg/mL (1 mL vial) and the 5 mcg/mL (1 mL vial). Specifically, the established name for the 2 mcg/mL (1 mL vial) is presented in pastel orange on a white background and it is pastel pink on a white background for the 5 mcg/mL (1 mL vial).

For the container labels, the dosage form, 'injection' is presented in pale orange/pink, thin font on a white background decreasing the visibility of this information.

The vial is described as "Multi-use Fliptop" which does not reflect current terminology for similar packaging configurations.

The statement "Multi-use" is stated on the carton labeling in small, closely spaced font making it difficult to read.

The net quantity is located beside the NDC number on the carton labeling and may be overlooked.

3.2.2 Insert Labeling (no image)

The route of administration is not explicitly stated in the dosage and administration section of the insert labeling.

The vial is described as 'multi-use' which does not reflect the proper terminology for this packaging configuration.

The statement of strength is presented as "2 mcg/1 mL" and " 5mcg/1 mL".

The statement (b) (4) in the 'Dosage and Administration' subsection under the "Full Prescribing Information" (b) (4)

The handling and storage statement in subsection 16 ("How Supplied/Storage and Handling") under the Full Prescribing Information heading includes redundant information. For example, (b) (4) (italicized words are not useful and are redundant)"

3.3 SIMULTANEOUS AVAILABILITY OF SINGLE-DOSE AND MULTI-DOSE VIALS

The following table summarizes the packaging configurations for the proposed and approved Paricalcitol Injection and Zemplar (Paricalcitol) Injection:

Table 1. Packaging Configurations for Paricalcitol Injection Products

Drug Product, Concentration and Vial Size	Proposed Paricalcitol Injection (NDA 201657)	Zemplar (Paricalcitol) Injection (RLD) (NDA 020819)	Paricalcitol Injection (ANDA 091108)
2 mcg/mL, 1 mL	Multi-dose vial	Single-dose vial	Single-dose vial
5 mcg/mL, 1 mL	Multi-dose vial	Single-dose vial	Single-dose vial
(b) (4)			

With the addition of the proposed multi-dose vials of Paricalcitol Injection, all strengths of this drug product will be available in single-dose and multi-dose packaging configurations. We outline our concerns with this issue in Section 4.

4 DISCUSSION

Our evaluation finds that the proposal to provide all available strengths of Paricalcitol Injection in multi-dose vials introduces vulnerability that can lead to medication errors.

As proposed, Paricalcitol Injection will be provided in multi-dose vials while its RLD (Zemplar [Paricalcitol] Injection) has traditionally been provided in single-dose vials. Based upon previous post-marketing reports involving other drug products (Epogen/Procrit), the simultaneous availability of Paricalcitol Injection in single-dose and multi-dose vials may lead to medication errors. Over time, practitioners may begin to treat both vial configurations as multi-dose and compromise the integrity of the single-

dose products. Therefore, efforts must be made to adequately differentiate between these two configurations to minimize the risk of confusion.

The proposed container label is adequately differentiated from the approved Paricalcitol Injection and Zemplar Injection. However, the proposed carton labeling has the same color scheme as the reference listed drug (RLD), Zemplar (black font on a white background), but is adequately differentiated from the approved Paricalcitol injection. Prominently displaying the accessibility criteria ('multi-dose') on the proposed container label and carton labeling may help ensure that the vials are used properly and minimize selection errors.

As noted in section 3.1, we identified three medication error cases involving the wrong route of administration. Two of the cases involved administration of Zemplar subcutaneously and one case involved intramuscular administration. Although the root cause for these wrong route cases was not stated, ensuring the prominence of the route of administration on the container, carton and insert labeling may minimize the opportunity for overlooking it. Although the route is prominently displayed on the container label and carton labeling, it is not explicitly stated in the insert labeling. We provide recommendations in section 5 to increase the reader's awareness of the proper route of administration for this drug product

5 CONCLUSIONS AND RECOMMENDATIONS

The proposed label and labeling introduce vulnerability that can lead to medication errors. We advise the following recommendations be implemented prior to approval of this NDA:

A. INSERT LABELING

1. In the 'Dosage and Administration' subsection under the headings "Highlights of Prescribing Information" and "Full Prescribing Information", the route of administration is not explicitly stated. Although we recognize the Applicant is following the innovator's insert labeling, we recommend revising (b) (4) [redacted] to read "The recommended initial dose of Paricalcitol is 0.04 mcg/kg to 0.1 mcg/kg (2.8 - 7 mcg) administered *intravenously* as a bolus dose no more frequently . . ." Additionally, we recommend the inclusion of the statement, 'For Intravenous Use Only' after the heading 'DOSAGE AND ADMINISTRATION' to further increase the reader's awareness of the proper route of administration for this drug product.
2. Wherever the statement '(b) (4)' appears, revise to read 'multi-dose' to reflect the proper terminology for this packaging configuration.
3. In the "Dosage Forms and Strengths" subsection under the headings "Highlights of Prescribing Information" and "Full Prescribing (b) (4) [redacted]

4. In the 'Dosage and Administration' subsection under the heading "Full Prescribing Information", delete the statement [redacted] n accordance with the "How Supplied/Storage and Handling" Section (16), add the statement "After first use, Paricalcitol multi-dose vials are stable for up to 28 days when stored between 20° – 25°C (68° – 77°F)".

5. In the "How Supplied/Storage and Handling" subsection (16) under the Full Prescribing Information heading, delete the statement, "storage" that appears below the table of packaging configurations (and before the detailed storage criteria) as this is redundant.

6. In the "How Supplied/Storage and Handling" subsection (16) under the Full Prescribing Information heading, revise the statement [redacted] to read "After first use, following multiple needle entries and product withdrawals Paricalcitol multi-*dose* vials are stable for up to 28 days when stored between 20° – 25°C (68° – 77°F)".

B. Container Label (All Strengths)

1. As currently proposed, the established name, finished dosage form, and statement of strength for the 2 mcg/mL (1 mL vial) and the 5 mcg/mL (1 mL vial) is presented in a pastel orange (2 mcg/mL, 1 mL) or pastel pink (5 mcg/mL) on a white background and are not well differentiated from each other. To prevent selection errors, revise the color scheme for the 2 mcg/mL (1 mL vial) and the 5 mcg/mL (1 mL vial) so that they utilize unique colors for each strength that are well differentiated.
2. Improve the prominence of the dosage form, 'injection' so that it is more visible. Currently, it is presented in a thin font on a white background.
3. Delete the statement [redacted] from the label as it causes clutter and does not provide useful information to the user.
4. Wherever the statement [redacted] appears, revise it to read "Multi-dose" to reflect this packaging configuration.
5. Ensure that space is allotted for the lot number and expiration date.
6. Remove one of the two references to the manufacturer to minimize redundancy and cluttering the label.

C. Carton Labeling (All Strengths)

1. See comments B3 and B4.
2. Increase the prominence of the access criteria ('multi-dose') for this packaging configuration by increasing the font size and boxing it or by utilizing other means.
3. Relocate the net quantity to appear below the route of administration statement so that it is more visible and is not confused with the NDC number.

If you have further questions or need clarifications, please contact OSE Project Manager, Margarita Tossa, at 301-796-4053.

PRIOR OSE REVIEWS

- OSE Review # 2010-1039 dated July 21, 2010. DMEPA Label and Labeling Review for Zemplar (Paricalcitol) Injection, 5 mcg/mL (2 mL multi-dose vial), 5 mcg/mL (2 mL single dose vial), 5 mcg/mL (1 mL single dose vial), and 2 mcg/mL (1 mL single dose vial), Denise V. Baugh, PharmD, BCPS.
- OSE Review # 2007-802, 2007-2178 and 2007-2192. DMEPA Label and Labeling Review for Aranesp (Darbepoetin Alfa) Injection, 25 mcg/0.42 mL, 25 mcg/mL, 40 mcg/0.4 mL, 40 mcg/mL, 60 mcg/0.3 mL, 60 mcg/mL, 100 mcg/0.5 mL, 100 mcg/mL, 150 mcg/0.3 mL, 150 mcg/0.75 mL, 200 mcg/0.4 mL, 200 mcg/mL, 300 mcg/0.6 mL, 300 mcg/mL, 500 mcg/mL and Epogen/Procrit (Epoetin Alfa) Injection 2000 units/mL, 3000 units/mL, 4000 units/mL, 10000 units/mL, 20000 units/mL, 40000 units/mL. Judy Park, PharmD.

ISR Numbers for Cases Cited in this Review:

ISR # 7316338-4	ISR # 7624867-9	ISR # 7051343-7	ISR # 6742670-9
ISR # 6742690-4	ISR # 6742739-9	ISR # 6742743-0	ISR # 7506337-1
ISR # 7424423-1	ISR # 7424433-4	ISR # 7424421-8	ISR # 7424427-9
ISR # 7424434-6			

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

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

/s/

DENISE V BAUGH
12/06/2011

LUBNA A MERCHANT
12/08/2011

CAROL A HOLQUIST
12/08/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 201657 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: None Established/Proper Name: Paricalcitol injection Dosage Form: solution Strengths: 2 mcg/1 mL, 5 mcg/1 mL, 10 mcg/2 mL		
Applicant: Hospira Inc. Agent for Applicant (if applicable):		
Date of Application: April 7, 2011 Date of Receipt: April 7, 2011 Date clock started after UN: n/a		
PDUFA Goal Date: February 7, 2012	Action Goal Date (if different):	
Filing Date: June 6, 2011	Date of Filing Meeting: May 31, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 5 new manufacturer		
Proposed indication(s)/Proposed change(s): for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) × 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	× Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): None, PreNDA mtg (June 29, 2010) under the NDA	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	×			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	×			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	×			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		×		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	×			$771, 000.00 PD3011219

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: × Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: × Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		×		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**			×	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***			×	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:		×		No unexpired exclusivity
If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.				

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		×		Consulted orange book on 6/7/11

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			×	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		×		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?			×	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) × All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	×			
Index: Does the submission contain an accurate comprehensive index?	×			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	×			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

×☐ legible ×☐ English (or translated into English) ☐ pagination ×☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	×			
Are all establishments and their registration numbers listed on the form/attached to the form?	×			From the cover letter: The drug product is manufactured at Hospira's Rocky Mount, NC, facility. This site operates in accordance with cGMP and is ready for FDA inspection. The site received a "withhold" recommendation from compliance on 4/27/11.
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?		×		Need to ask sponsor to submit the proper forms in filing letter.
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*			×	There were no clinical studies conducted for the subject drug product in support of this application.
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	×			Sponsor did not

If yes, ensure that the application is also coded with the supporting document category, "Form 3674." ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***				submit it with the original application but submitted as the first amendment dated 5/2/11.
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	×			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			×	Sponsor has a statement saying this is an electronic submission and they will not send a copy of the technical section.

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:			×	

Pediatrics	**YES**	**NO**	**NA**	**Comment**

PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		×		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?				
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]				
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***		×		
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***		×		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	×☐ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ×☐ Carton labels			

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	×☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	×			In response to the telephone conversation with sponsor on April 14, 2011, in SD 2 on May 3, 2011 the sponsor submitted revised labeling which aligns with the Listed Drug, Zemplar, labeling approved on April 6, 2011. (annotated, word and SPL)
Is the PI submitted in PLR format?[4]	×			

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	×			Consult pending
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			×	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	×			DMEPA reviewers were assigned for C/C labeling review. RCM #2011-1771
OTC Labeling	×☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		×		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		×		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** PreNDA 8/26/10 ***If yes, distribute minutes before filing meeting***	×			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		×		

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 31, 2011

BLA/NDA/Supp #: NDA 201657

PROPRIETARY NAME: Paricalcitol injection

ESTABLISHED/PROPER NAME: None submitted

DOSAGE FORM/STRENGTH: solution/ 2 mcg/1 mL, 5 mcg/1 mL, 10 mcg/2 mL

APPLICANT: Hospira Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): indicated for the prevention and treatment of secondary hyperparathyrodism associated with chronic kidney disease Stage 5.

BACKGROUND: Hospira submitted this new 505(b)(2) application for Paricalcitol injection, 2 mcg/1 mL, 5 mcg/1 mL, 10 mcg/2 mL, as a sterile, clear, colorless, aqueous solution for intravenous injection. Each mL contains paricalcitol, 2 mcg or 5 mcg; and the following inactive ingredients: alcohol 40% (v/v) and propylene glycol, 10% (v/v). Paricalcitol injection is a synthetic, biologically active vitamin D analog of calcitriol with modifications to the side chain (D2) and the A (19-nor) ring.

Hospira listed Zemplar®, NDA 20819 by Abbott as the listed drug. The active ingredient, indications, route of administration and dosage form are the same as those of the listed drug. The proposed drug product contains the same active ingredient at the same concentration as the listed drug but the ratio of the inactive ingredients, alcohol and propylene glycol, in the proposed drug product are different than in the listed drug.

This application does not qualify for submission under 505(j). Per 21 CFR 314.94(a)(9)(iii), an ANDA parenteral drug must have the same inactive ingredients as the RLD, with the exception of ingredients for buffer, preservative, or antioxidant (which can be different). Since the difference between this product and the listed drug is in the amounts of propylene glycol and alcohol, which are neither buffers, preservatives, nor antioxidants, this application cannot be a 505(j).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Meghna M. Jairath	**Y**
	CPMS/TL:	Enid Galliers	**Y**
Cross-Discipline Team Leader (CDTL)	Mary Parks		**Y**
Clinical	Reviewer:	Bill Lubas	**Y**

	TL:	Dragos Roman	**Y**
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	S.W. Johnny Lau	**Y**
	TL:	Jaya Vadiyanathan	**N**
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Parvaneh Espandiari	**Y**
	TL:	Karen Davis-Bruno	**N**
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC) and Biopharmaceutics	Reviewer:	Elsbeth Chikhale	**Y**
	TL:	Su Tran	**Y**
Quality Microbiology *(for sterile products)*	Reviewer:	Robert Mello	**Y**
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection Compliance	Reviewer:	Shawn Gold	**Y**
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI) Nonclinical	Reviewer:	Sripal Mada	**Y**
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	OSE (DMEPA) for C/C Denise Baugh(Reviewer) and Todd Bridges (TL)		**N**
Other attendees	Margarita Tossa (OSE RPM) Amy Egan (Safety Deputy Director) Kushboo Sharma (OSE RPM)		**Y** **Y** **Y**

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES × NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	×☐ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable × FILE ☐ REFUSE TO FILE × Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES × NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:***	☐ YES Date if known: × NO ☐ To be determined Reason:

○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments**:	× Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	× Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	× Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable × FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES × NO
BIOSTATISTICS **Comments**:	× Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable × FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	× Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable × FILE ☐ REFUSE TO FILE × Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: The categorical exclusion claim will be assessed by CMC Reviewer.	☐ Not Applicable ☒ YES NO YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**: Review of sterility Assurance	☐ Not Applicable × YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**: "Withhold" overall recommendation on April 27, 2011: GMP violations at the drug product manufacturer Hospira, Rocky Mount, NC	☐ Not Applicable × YES ☐ NO × YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	× Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	 ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Mary Parks
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Filing date	6-Jun-11
74-day letter	20-Jun-11
Midcycle meeting	8-Sep-11
Wrap up meeting	1-Jan-12
Complete Primary review	3-Jan-12
Complete Secondary review	10-Jan-12
Complete CDTL review	17-Jan-12
Send proposed labeling/PMC/PMR/REMS to applicant with 1 week response	10-Jan-12
Begin Labeling and /PMC/PMR Discussions	17-Jan-12

REGULATORY CONCLUSIONS/DEFICIENCIES

	The application is unsuitable for filing. Explain why:
×	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. × Review issues have been identified for the 74-day letter. List (optional): Review Classification: × Standard Review ☐ Priority Review

ACTIONS ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
×	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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
06/14/2011