

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201657Orig1s000**

**MEDICAL REVIEW(S)**

## Cross-Discipline Team Leader Review

<b>Date</b>	February 6, 2012
<b>From</b>	Dragos Roman MD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	201-657
<b>Supplement#</b>	
<b>Applicant</b>	Hospira Inc.
<b>Date of Submission</b>	April 7, 2011
<b>PDUFA Goal Date</b>	February 7, 2012
<b>Proprietary Name / Established (USAN) names</b>	None/ Paricalcitol
<b>Dosage forms / Strength</b>	Multiple-dose vials that contain 2 mcg (2 mcg/ml), 5 mcg (5 mcg/ml) and 10 mcg (5 mcg/2ml).
<b>Proposed Indication(s)</b>	Prevention and treatment of secondary hyperparathyroidism
<b>Recommended:</b>	Complete Response

## 1. Introduction

On April 7, 2011 Hospira Inc. submitted a New Drug Application (NDA) for Paricalcitol Injection under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. This NDA lists Abbott's paricalcitol (NDA 20-819; proprietary name: Zemplar) as the listed drug. Zemplar is approved as single-use<sup>1</sup> and multiple-use vials<sup>2</sup>, and is used as an intravenous injection following hemodialysis sessions. Hospira's Paricalcitol for Injection is a multi-dose vial presentation also intended for intravenous injection<sup>3</sup>. As such the active ingredient (paricalcitol), the route of administration (intravenous), the dosage form (vial for injection) are the same for Hospira's paricalcitol as for the listed drug Zemplar. The inactive ingredients, (b)(4) are quantitatively different. Specifically, Hospira's paricalcitol has a higher concentration of alcohol (40% vs. 20% in Zemplar) and a lower concentration of propylene glycol (10% vs. % 30% in Zemplar), with the rest of the vial content (b)(4) being water for injection.

Hospira's plan to submit a 505(b)(2) application was discussed between representatives of Hospira Inc. and FDA in a teleconference that took place on July 29, 2010. The meeting was requested by Hospira who sought advice regarding standard CMC issues (stability data requirements, impurities characterization and acceptance criteria) and regulatory questions

<sup>1</sup> Single dose vials that contain 2 mcg (2 mcg/ml), 5 mcg (5 mcg/ml) and 10 mcg (5 mcg/ml) of paricalcitol.

<sup>2</sup> Multiple-dose vial that contains 10 mcg (5 mcg/ml) of paricalcitol.

<sup>3</sup> Multiple-dose vials that contain 2 mcg (2 mcg/ml), 5 mcg (5 mcg/ml) and 10 mcg (5 mcg/2ml).

related to the sponsor's intent to submit an NDA via the 505(b)(2) pathway. Specifically, the sponsor indicated that they were planning to rely on the findings of safety and efficacy of Abbot's Zemplar, and that they did not intend to submit any clinical information obtained with their paricalcitol product. The sponsor was advised that they need to establish a "bridge" between the proposed product and Zemplar, that bridging to Zemplar via analytical means alone, as intended, was not sufficient, and that comparative animal toxicology data will be needed for qualifying any differences in impurities or degradants with the listed drug. The sponsor was also advised that clinical pharmacology bridging via a bioequivalence (BE) study was not mandatory, and that granting a biowaiver request will be a review issue (the sponsor claimed that bioequivalence is self-evident because both their paricalcitol and Zemplar are intended for intravenous administration).

This submission does not contain any clinical pharmacology data, or safety and efficacy clinical data. It includes a comparative 4-week intravenous rat toxicity study between Hospira's paricalcitol and Zemplar with a 2-week recovery period. The sponsor requested a biowaiver under 21 CFR 320.22 on the basis that the product is a parenteral solution intended solely for administration by intravenous injection. Hospira is also requesting an "AP" rating on the basis of the fact that the "proposed drug product is of the same pharmacological and therapeutic class as that of the RLD [sic] and can be expected to have the same therapeutic effect as the RLD [sic].

## 2. Background

Paricalcitol is a Vitamin D<sub>2</sub> analogue. Similar to natural Vitamin D sterols, hydroxylated Vitamin D products and synthetic Vitamin D<sub>3</sub> analogues, the action of paricalcitol is mediated via the Vitamin D receptors to which it binds in a variety of tissues, including the parathyroid gland where it inhibits the synthesis and secretion of parathyroid hormone (PTH), and subsequently reduces circulating PTH. This constitutes the rationale for Vitamin D analogues use, paricalcitol included, in the treatment of chronic kidney disease (CKD).

Central to this application is whether Hospira has demonstrated that their product is paricalcitol, that it meets current GMP standards, and that differences in impurity profile relative to Zemplar are of no clinical relevance based on side-by-side comparison with Zemplar in animal studies.

## 3. CMC/Device

The CMC review recommends issuing a Complete Response. This recommendation is not based on CMC deficiencies, since none was identified, but rather on a "withhold" recommendation made by the Office of Compliance on April 27, 2011 due to cGMP violations at Hospira's manufacturing and testing facilities in Rocky Mount, North Carolina. The chemistry reviewer assessed that the data submitted in the NDA was satisfactory for the drug

substance, the drug product, the manufacturing processes, and the container closure system. The CMC reviewer recommends an expiry period of 12 months instead of that of that of (b) (4) months requested by the applicant. The CMC review does not include any recommendations for Phase 4 studies.

## 4. Nonclinical Pharmacology/Toxicology

This supplement contains the results of a 4-week intravenous rat toxicity study with a 2-week recovery period that compares Hospira's and Abbott's paricalcitol products. This study was intended to be a "bridge" between the two products and is in fact the only direct comparison provided because, as indicated in Section 5 of this memorandum, the applicant was granted a waiver for bioequivalence studies. The design and assessments of the rat toxicity study are consistent with the recommendations made by the FDA during the July 29, 2010 teleconference. The specific goal of the study was to characterize any biological effects resulting from dissimilarities in impurities and degradants, or due to quantitative differences in inactive ingredients (alcohol and propylene glycol). Several differences were observed between mice treated with Zemplar and Hospira's paricalcitol. They consisted in a delay in the time-course of appearance of soft tissue mineralization and an increase in severity scores for mineralization that was observed with Hospira's paricalcitol. In addition, there were several differences, albeit inconsistent, related to the injection site histopathology. These findings are extensively discussed in both the primary and supervisory pharmacology/toxicology review and memorandum, as well as in the clinical review. The differences observed at the injection site in animals following direct intraaortic administration of the test drug were generally inconsistent, and could not be viewed as proof of difference between the two products. Equally important, any theoretical adverse effect that the higher concentration of alcohol (40%) may have on vascular endothelium is not of clinical relevance in patients with CKD because the drug is not administered directly in the vascular bed, but rather in a side-port wherein it is immediately diluted by the high flow of blood coming from the hemodialysis apparatus<sup>4</sup>. Similarly, potential differences seen in mice with respect to serum calcium and tissue mineralization that could not be explained clearly on the basis of differences between the two products, are also of limited clinical relevance since serum calcium levels are routinely monitored in CKD patients undergoing dialysis and, in response, therapeutic adjustments are made routinely as part of the standard of care. Thus, I am in agreement with the conclusions of the supervisory pharmacology/toxicology memorandum and its interpretation of the clinical relevance of the comparative animal observations; that it is unlikely that the differences observed in the comparative rat toxicity study will result in clinically meaningful differences.

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<sup>4</sup> In his clinical review, Dr. Lubas mentions the following: "[...] in their response [the sponsor] mentioned that the drug product is typically administered via dialysis tubing and not directly into a vein. The sponsor estimated that at the typical flow rate of 300mL/min the 40% (b) (4) in the drug product would be rapidly diluted in the hemodialysis machine before it would gain access to a patient's circulation. They estimated that even a relatively high dose such as 15 µg (i.e. 3 mL) would be diluted to 5% (b) (4) within 2.4 seconds and that this should not be long enough of an exposure to contribute any damage to either the infusion tubing in the dialysis machine or the patients AV fistula."

## 5. Clinical Pharmacology/Biopharmaceutics

There are no clinical pharmacology data submitted in this NDA (Hospira is relying on the clinical pharmacology findings of the listed drug, Zemplar).

The biopharmaceutics review waives the requirement for an *in vivo* bioequivalence study and bases this decision on the fact that the bioequivalence of Hospira's paricalcitol and Zemplar is self-evident. Although the concentration of inactive ingredients ( (b)(4) and propylene glycol) is different for Hospira's paricalcitol relative to Zemplar, the biopharmaceutical review argues that this difference is not expected to impact the amount of drug delivered to the site of action because paricalcitol is an injectable dosage form administered as a bolus.

## 6. Clinical Microbiology

The microbiology recommends approval (no deficiencies are identified). There are no recommendations for Phase 4 studies.

## 7. Clinical/Statistical- Efficacy

There were no clinical data in this supplement. Since this NDA it is a 505(b)(2) application, Hospira is relying on the efficacy findings of the listed drug Zemplar. The clinical review recommends approval once clearance is obtained from the Office of Compliance regarding the cGMP status of Hospira's Rocky Mount, NC. manufacturing facility.

## 8. Safety

There were no clinical data in this supplement. Since this NDA it is a 505(b)(2) application Hospira is relying on the safety findings of the listed drug, Zemplar.

## 9. Advisory Committee Meeting

No Advisory Committee Meeting was held for this supplement.

## 10. Pediatrics

This application is not for a new indication, new active ingredient, new route of administration, new dose regimen, or new dosage form. Therefore it does not trigger PREA.

## 11. Other Relevant Regulatory Issues

As previously indicated, the manufacturing site responsible for the making of paricalcitol has been found to have cGMP violations and the Office of Compliance has issued a withhold recommendation for this site until the existing manufacturing deficiencies are remedied.

## 12. Labeling

Several modifications have been made to the proposed label, which replicates to a large extent the Zemplar label. Most of them relate to the PLR format of Hospira's paricalcitol (Zemplar has not been converted to PRL format yet). Since the Zemplar label contains an indication of (b) (4) of secondary hyperparathyroidism in error, this misstatement has been deleted from Hospira's label. The applicant did not apply for a proprietary name and the product, when approved, will be marketed as "Paricalcitol for injection, solution for intravenous use".

A consultation was obtained from the Division of Medication Error and Prevention Analysis (DMEPA). The consult identified several areas in the proposed label that introduce vulnerability to medication errors and makes a series of specific recommendations that have been incorporated in the insert label and the container and carton label.

## 13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Due to the current withhold recommendation made by the Office of Compliance for the manufacturing site at Rocky Mount in North Carolina, a complete response should be issued for this supplement. To be clear, no other deficiencies have been identified by any of the review disciplines. Consequently, when the withhold recommendation is lifted, approval of this product is anticipated.

- Risk Benefit Assessment

A favorable risk-benefit for paricalcitol has already been established with the approval of Abbott's Zemplar. The minor differences in inactive ingredient concentrations in Hospira's paricalcitol do not change the risk vs. benefit evaluation.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None.

- Recommendation for other Postmarketing Requirements and Commitments

None.

- Recommended Comments to Applicant

The applicant should be informed that a Complete Response decision has been made due to the existing cGMP deficiencies at the Rocky Mountain site in North Carolina.

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/s/  
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DRAGOS G ROMAN  
02/06/2012

MARY H PARKS  
02/06/2012

## CLINICAL REVIEW

Application Type NDA 505(b)(2)  
Application Number(s) 201-657  
Priority or Standard Standard

Submit Date(s) April 7, 2011  
Received Date(s) April 7, 2011  
PDUFA Goal Date February 7, 2012  
Division / Office DMEP/ODEII

Reviewer Name(s) William Lubas, M.D., Ph.D.  
Review Completion Date January 6, 2012

Established Name paricalcitol  
(Proposed) Trade Name (Paricalcitol) Injection  
Therapeutic Class Bone-Vitamin D  
Applicant Hospira Inc.

Formulation(s) injection  
Dosing Regimen (b) (4) no  
more frequently than every other  
day

Indication(s) Prevention and Treatment of  
Secondary Hyperparathyroidism

Intended Population(s) Patients on Hemodialysis

Template Version: March 6, 2009

## Table of Contents

<b>1</b>	<b>RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>	<b>5</b>
1.1	Recommendation on Regulatory Action .....	5
1.2	Risk Benefit Assessment.....	5
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	5
1.4	Recommendations for Postmarket Requirements and Commitments .....	5
<b>2</b>	<b>INTRODUCTION AND REGULATORY BACKGROUND .....</b>	<b>5</b>
<b>4</b>	<b>SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES .....</b>	<b>6</b>
4.1	Chemistry Manufacturing and Controls .....	6
4.2	Clinical Microbiology.....	7
4.3	Preclinical Pharmacology/Toxicology .....	7
<b>5</b>	<b>SOURCES OF CLINICAL DATA.....</b>	<b>7</b>
<b>6/7</b>	<b>REVIEW OF EFFICACY AND SAFETY .....</b>	<b>8</b>
<b>9</b>	<b>APPENDICES .....</b>	<b>9</b>
9.2	Labeling Recommendations .....	9

## Table of Tables

Table 1 Paricalcitol Formulations .....	5
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## Table of Figures

Figure 1 Chemical Structure of Paricalcitol .....	6
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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

This application should be approved once

- clearance is obtained from the Office of Compliance regarding the cGMP status of Hospira's Rocky Mount, NC. manufacturing facility,
- the Microbiology Review is completed and found to be acceptable and
- the labeling negotiations have been completed.

### 1.2 Risk Benefit Assessment

The information submitted in this application support the safety and efficacy of this 505(b)(2) product as described in the revised package insert.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

### 1.4 Recommendations for Postmarket Requirements and Commitments

None

## 2 Introduction and Regulatory Background

Paricalcitol, is a synthetically manufactured analog of calcitriol, the metabolically active form of vitamin D indicated for the prevention and treatment of secondary hyperparathyroidism in patients with chronic kidney disease (CKD). Paricalcitol is currently available in the US, as the active ingredient in Zemplar® injectable, in 1 and 2mL single dose Fliptop vials containing 5µg/mL of solution. In this application, Hospira Inc. is submitting a 505(b)(2) application for another paricalcitol injectable with a novel formulation. Hospira, Paricalcitol contains the same active ingredient as Zemplar® (paricalcitol) injection, but has different amounts of (b) (4) propylene glycol.

**Table 1 Paricalcitol Formulations**

	<b>Abbott (Zemplar)</b>	<b>Hospira (Paricalcitol)</b>
% (b) (4)	20	40
%propylene glycol	30	10
% water	(b) (4)	

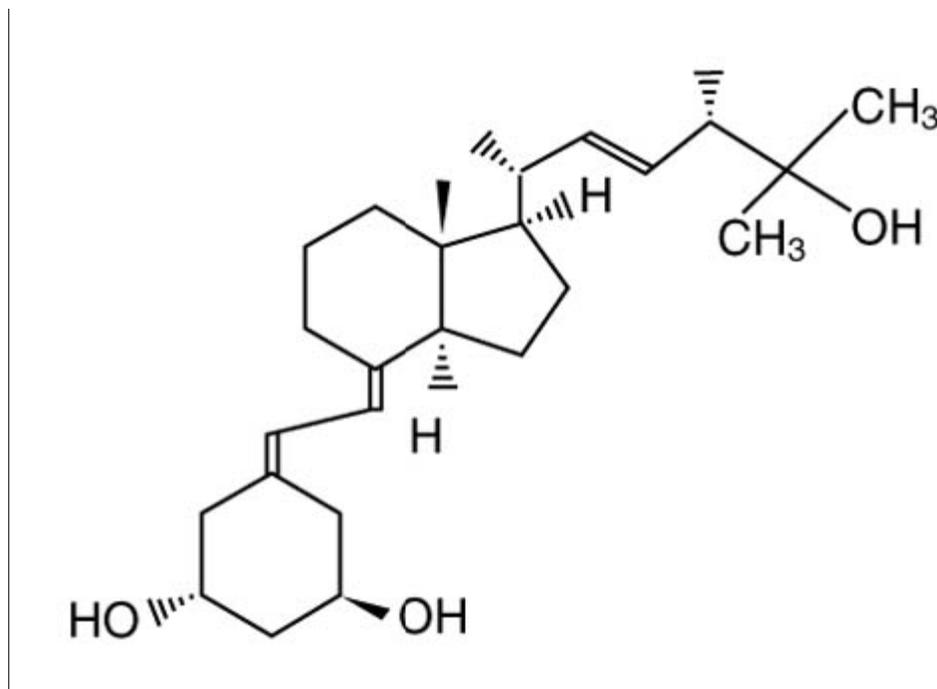
The Hospira formulation will be available in 3 different multi-dose vials containing 2 µg or 5 µg of paricalcitol in 1mL vials and 10 µg of paricalcitol in a 2mL vial.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

Paricalcitol is a synthetic, biologically active vitamin D analog of calcitriol with modifications to the side chain (D2) and the A (19-nor) ring.

**Figure 1 Chemical Structure of Paricalcitol**



The drug product will be packaged in multi-dose glass vials with a rubber stopper and aluminum seal. The Chemistry Review by Dr. Chikhale recommends an expiration period of 12 months (stored at 25°C/40%RH) instead of the (b)(4) months requested by the sponsor and allows for storage at room temperature for up to 28 days after the seal is broken during the initial use of the product. The drug substance, paricalcitol, USP will be manufactured by (b)(4). The drug product will be manufactured at Hospira's Rocky Mount, NC. plant which received a withhold recommendation from the office of compliance on April 27, 2011. Therefore, approval of

this application will depend on the final recommendations of the Office of Compliance with respect to the cGMP status of this facility. There are no other facilities set up to manufacture this drug product at this time.

#### 4.2 Clinical Microbiology

No microbiology issues which could delay approval on this basis had been identified by Dr. Robert Mello as of the last team meeting to discuss this application; however the formal Microbiology review is still pending.

#### 4.3 Preclinical Pharmacology/Toxicology

A 4-week intravenous rat toxicity study with a 2-week recovery period comparing Hospira's and Abbott's paricalcitol products and related vehicle controls, containing (b) (4) without paricalcitol, was performed to comply with pharmtox's request for a bridging study. The study was required even though the active ingredients in the products are (b) (4) different with respect to the amount of (b) (4) propylene glycol which could potentially affect the efficacy and safety of the new product. The pharmtox reviews by Drs. Espandiari and Davis-Bruno indicate that Hospira's formulation with a higher concentration of (b) (4) and less propylene glycol concentration exhibits a delay in the time-course of appearance of soft tissue mineralization as well as increased severity scores for mineralization compared to Zemplar. Injection site histopathology findings differ between the listed paricalcitol and Hospira's product in an inconsistent manner, and a clear effect on the incidence of endothelial hyperplasia, mural thrombus formulation, or chronic vessel wall inflammation could not be established. The sponsor attributed the differences in incidence and severity due to animal variability and the small number of animals (n=5) in the recovery groups. This medical officer agrees with the final pharmtox assessment that "since mineralization is attributed to hypercalcemia and serum calcium is routinely monitored in dialysis patients as part of the standard of care, it is unlikely that these differences observed in the comparative rat toxicity study would achieve a meaningful difference in clinical use or therapeutic outcome." Therefore the observed differences in the bridging animal study do not correspond to differences in the safety or efficacy of this 505(b)(2) product that are likely to be clinically relevant.

## 5 Sources of Clinical Data

No clinical studies were included in this submission. Safety and efficacy were derived from literature relating to the currently approved product Zemplar (paricalcitol) Injection.

## 6/7 Review of Efficacy and Safety

Preclinical and *in vitro* studies from the literature have demonstrated that paricalcitol's biological actions are mediated through binding to the Vitamin D receptor, which results in the selective activation of Vitamin D responsive pathways. Paricalcitol therefore has been shown to reduce PTH levels by inhibiting PTH synthesis and secretion and so should be effective for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease.

The chemistry review showed the active ingredient, paricalcitol, in the Hospira product (b)(4) paricalcitol in the currently approved and marketed Zemlar injectable. The observed differences in the pharmtox bridging animal study between Zemlar and the Hospira product did not correspond to any clinically relevant differences that would affect the safety or efficacy of this 505(b)(2) product. Therefore, no clinical trials were required as part of this submission.

However as it was noted that the new formulation had double the (b)(4) concentration (40%) than the innovator product (20%) and (b)(4) could be potentially toxic to cells, this medical officer was concerned that the high concentration of (b)(4) in the new formulation might be potentially toxic to endothelial cells if the product was directly injected into a vein or artery. Such toxicity could be especially problematic in dialysis patients who require good perfusion through their AV fistulas. The sponsor was asked to address this concern and in their response they mentioned that the drug product is typically administered via dialysis tubing and not directly into a vein. The sponsor estimated that at the typical flow rate of 300mL/min that the 40% (b)(4) in the drug product would be rapidly diluted in the hemodialysis machine before it would gain access to a patient's circulation. They estimated that even a relatively high dose such as 15 µg (i.e. 3 mL) would be diluted to 5% (b)(4) within 2.4 seconds and that this should not be long enough of an exposure to contribute any damage to either the infusion tubing in the dialysis machine or the patients AV fistula. This explanation seems acceptable however, because of the higher (b)(4) concentration in this formulation it will be recommended that the package insert specifically mention that the product is not to be directly injected into a vein but to be administered into the venous medication port of the hemodialysis machine.

As current standards of care do not recommend treating CKD pts with vitamin D analogs to prevent the development of secondary hyperPTH, and no clinical studies were ever performed in the prevention population the original prevention indication was approved as an oversight. It will be recommended that the current indication in this application be revised to support only the treatment and not the prevention of secondary hyperPTH in the CKD dialysis population.

## 9 Appendices

### 9.2 Labeling Recommendations

#### Highlights

##### Indications and Usage

- Revise the indication statement to remove the prevention indication.

##### Dosage and Administration

- Describe that the drug product should not be injected directly into a vein but should be administered into the venous medication port of the hemodialysis machine.
- Add Suggested Dosing Guidelines Table modified to remove the comment that

(b) (4)

##### Dosage Forms and Strengths

- (b) (4)
- (b) (4)
- (b) (4)

##### Warnings and Precautions

- Revise hypercalcemia section to use similar wording to the Zemplar capsule PLR PI
- Add (b) (4) as in the revised Zemplar capsule PLR PI
- Add a new section for adynamic bone disease.

##### Adverse Reactions

- Revise to correlate to most frequent adverse reactions seen in clinical trials (e.g. (b) (4) % and more frequent than placebo).

##### Drug Interactions

- Add section on CYP3A Inhibitors as in the revised Zemplar capsule PLR PI

#### Full Prescribing Information

##### 1 Indications and Usage

- Revise the indication statement to remove the prevention indication.

## 2 Dosage and Administration

- Describe that the drug product should not be injected directly into a vein but should be administered into the venous medication port of the hemodialysis machine.
- Add Suggested Dosing Guidelines Table modified to remove the comment that (b) (4) iPTH is an acceptable level for maintaining the dose.

## 3 Dosage Forms and Strengths

(b) (4)

## 5 Warnings and Precautions

- Hypercalcemia
  - Add additional consequences of hypercalcemia from revised wording in the Zemplar capsule PLR PI (e.g. exacerbate tendencies for cardiac arrhythmias and seizures, potentiate the action of digitalis)
  - Remove (b) (4)
  - Remove adynamic bone disease information and place it in its own section 5.5
  - (b) (4)
- Add section (b) (4) as in the revised Zemplar capsule PLR PI
- Add a new section for adynamic bone disease.

## 6 Adverse Reactions

- Add comment that studies were performed with another paricalcitol product.

## 7 Drug Interactions

- Revise section to include only information on CYP3A Inhibitors as in the revised Zemplar capsule PLR PI

## 8 Use in Specific Populations

- Add comment that studies were performed with another paricalcitol product.

## 10 Overdosage

- Add overdosage can lead to adynamic bone disease
- Remove (b) (4)

- [REDACTED] (b) (4)
- Remove comment on [REDACTED] (b) (4)
  - Remove comment [REDACTED] (b) (4)
- [REDACTED]

12 Clinical Pharmacology

- Update section to be consistent with the revised Zemplar capsule PLR PI

13 Nonclinical Toxicology

- Add comment that studies were performed with another paricalcitol product.

14 Clinical Studies

- Add comment that studies were performed with another paricalcitol product.

16 How Supplied/Storage and Handling

- Update to mention the product is stable for 12 months at room temp if unopened but it is stable for only 28 days after the seal is broken following initial use.

17 Patient Counseling Information

- Update section to be consistent with the revised Zemplar capsule PLR PI

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/s/  
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WILLIAM A LUBAS  
01/10/2012

DRAGOS G ROMAN  
01/10/2012



## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1  Indication:				
	Pivotal Study #2  Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	No clinical data submitted
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	No clinical data submitted
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	No clinical data submitted
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			X	No clinical data submitted
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	No clinical data submitted
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	Relying on Reference Listed Drug Zemplar
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	No clinical data submitted
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	No clinical data submitted
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?			X	No clinical data submitted
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	Due to different concentrations of (b) (4) and propylene

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					glycol in the LD, Zemlar®, and in the new product, Hospira Paricalcitol, a bridging 4-week repeat dose intravenous (bolus) toxicity study with the 2-week recovery period in SD rats was conducted.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	No clinical data submitted
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	This application did not trigger PREA.
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	Drug is unlikely to be abused.
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	No clinical data submitted
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	No clinical data submitted
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	No clinical data submitted
34.	Are all datasets to support the critical safety analyses available and complete?			X	No clinical data submitted
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	No clinical data submitted
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	No clinical data submitted
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	No clinical data submitted
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?			X	No clinical data submitted that requires financial disclosure

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	No clinical data submitted

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_\_Yes\_\_\_X\_\_\_**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1) The sponsor will be asked to 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.

William Lubas MD, PhD 5/31/2011  
 \_\_\_\_\_  
 Reviewing Medical Officer Date

Dragos Roman MD 5/31/2011  
 \_\_\_\_\_  
 Clinical Team Leader Date

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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.**  
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/s/  
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WILLIAM A LUBAS  
06/01/2011

DRAGOS G ROMAN  
06/02/2011

The application is fileable from a clinical perspective.