

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204016Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

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## Clinical Pharmacology Review

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**NDA** 204016  
**Re-submission Date:** 08 January 2013  
**Generic Name:** Zoledronic Acid  
**Formulation:** Zoledronic Acid Injection for IV infusion, 4 mg/100 mL single-use premixed bag  
**Reference Listed Drug:** Zometa<sup>®</sup> 4 mg/5 mL in a single-dose vials, concentrate for intravenous infusion, under NDA21223 (Approved in 2003)  
**OCP Reviewer:** Pengfei Song, Ph.D.  
**OCP Acting Team Leader:** Qi Liu, Ph.D.  
**OCP Division:** Division of Clinical Pharmacology 5  
**ORM Division:** Division of Oncology Products 1  
**Sponsor:** Hospira, Inc.  
**Submission Type; Code:** 505 (b) (2); Resubmission (Type 5- New Formulation or New Manufacturer)  
**Dosing regimen:** Hypercalcemia of malignancy

- 4 mg as a single-dose intravenous infusion over no less than 15 minutes
- 4 mg as retreatment after a minimum of 7 days

Multiple myeloma and bone metastasis from solid tumors

- 4 mg as a single-dose intravenous infusion over no less than 15 minutes every 3-4 weeks for patients with creatinine clearance of > 60 mL/min

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## 1 EXECUTIVE SUMMARY

This New Drug Application (NDA) is for Zoledronic Acid Injection for IV infusion, 4 mg/100 mL, in a single-use premixed bag of zoledronic acid. The applicant seeks the approval of zoledronic acid injection with the same indications, the same route of administration, and the same active ingredient at the same concentration as that of the listed drug (LD) preparation, 100 mL diluted Zometa<sup>®</sup> (zoledronic acid) Injection per Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

There is no bioequivalent study nor clinical study submitted in the original and resubmission of this application. The Applicant is relying on the findings of safety and effectiveness for Zometa<sup>®</sup> to support the approval of the proposed product. The only clinical pharmacology related issue is that the information regarding plasma protein binding and affinity to the cellular components of human blood was updated in the proposed label to keep consistent with the latest labeling language of the LD.

### 1.1 RECOMMENDATIONS

This NDA is approvable from a clinical pharmacology perspective.

#### Signatures:

Pengfei Song, Ph.D. Reviewer Division of Clinical Pharmacology 5		Qi Liu, Ph.D. Team Leader Division of Clinical Pharmacology 5
Cc:	DOP1:	CSO - Modupe Fagbami; MTL - Amy Mckee; MO - Genevieve A. Schechter;
	DCP-5:	DDD - Brian Booth; DD - Nam Atiqur Rahman

## 1.2 DETAILED LABELING INFORMATION

Only relevant clinical pharmacology sections are included. Underlines indicate the content that was added to the proposed label by the Applicant and ~~strike-throughs~~ indicate content taken out from the proposed label by the Agency.

<i>PROPOSED LABELING</i>	<i>AGENCY'S SUGGESTIONS</i>
<b>7. DRUG INTERACTIONS</b>	
<p>(b) (4)</p> <p><u>In-vitro studies indicate that the plasma protein binding of zoledronic acid is low, with the unbound fraction ranging from 60% to 77%.</u> In-vitro studies also indicate that zoledronic acid does not inhibit microsomal CYP450 enzymes. In-vivo studies showed that zoledronic acid is not metabolized, and is excreted into the urine as the intact drug.</p>	<p>The proposed change in the labeling language is acceptable.</p>
<b>12.3 PHARMACOKINETICS</b>	
<p>Pharmacokinetic data in patients with hypercalcemia are not available.</p> <p>Distribution</p> <p>(b) (4)</p> <p><u>In-vitro and ex-vivo studies showed low affinity of zoledronic acid for the cellular components of human blood, with a mean blood to plasma concentration ratio of 0.59 in a concentration range of 30 ng/mL to 5000 ng/mL. In vitro, the plasma protein binding is low, with the unbound fraction ranging from 60% at 2 ng/mL to 77% at 2000 ng/mL of zoledronic acid.</u></p>	<p>The proposed change in the labeling language is acceptable.</p>

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/s/  
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PENGFEI SONG  
06/12/2013

QI LIU  
06/14/2013

REV-CLINPHARM-02 (Review Noted (NAI))  
NDA-204016  
ORIG-1  
Supporting Document 1  
New/NDA  
Form 3674  
Submit Date: 01/30/2012 - FDA Received Date: 01/30/2012

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There is no bioequivalent study nor clinical study submitted in this application. The Applicant is

relying on the findings of safety and effectiveness for Zometa® to support the approval of the

proposed product. No clinical pharmacology issues have been identified.

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/s/  
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PENGFEI SONG  
10/17/2012

**BIOPHARMACEUTICS REVIEW**  
**Office of New Drug Quality Assessment**

<b>Application No.:</b>	NDA 204-016	<b>Reviewer:</b> Kareen Riviere, Ph.D.	
<b>Submission Date:</b>	February 1, 2012		
<b>Division:</b>	Oncology Products	<b>Team Leader:</b> Angelica Dorantes, Ph.D.	
<b>Applicant:</b>	Hospira, Inc.	<b>Acting Supervisor:</b> Richard Lostritto, Ph.D.	
<b>Trade Name:</b>	---	<b>Date Assigned:</b>	February 2, 2012
<b>Generic Name:</b>	Zoledronic Acid Injection	<b>Date of Review:</b>	September 10, 2012
<b>Indication:</b>	Treatment of hypercalcemia of malignancy; Treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors	<b>Type of Submission:</b> 505(b)(2) New Drug Application	
<b>Formulation/strengths:</b>	0.04 mg/mL (4 mg/100 mL)		
<b>Route of Administration:</b>	Intravenous		

**SUMMARY:**

This submission is a 505(b)(2) New Drug Application for 4 mg/100 mL Zoledronic Acid Injection. The proposed indication is for the treatment of hypercalcemia of malignancy; treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors.

The reference listed drug (RLD) for this submission is NDA 21-223, Zometa® (zoledronic acid) Injection, held by Novartis Pharmaceuticals Corporation and approved on March 7, 2003. The RLD is a concentrate with 4 mg of zoledronic acid in a sterile, single-use 5 mL vial that is intended for use upon dilution with 100 mL of 0.9% Sodium Chloride, USP or 5% Dextrose, USP. The proposed drug product, Zoledronic Acid Injection, would be a (b) (4) aqueous solution containing a total drug content of 4 mg of zoledronic acid supplied in a sterile single-use (b) (4) intravenous bag).

This submission includes a BA/BE waiver request for the proposed product. The focus of this Biopharmaceutics review is on the evaluation and acceptability of the waiver request.

**RECOMMENDATION:**

A BA/BE waiver is granted for the proposed product based on the following information/requirements:

1. The proposed product is a parenteral solution as is the RLD.
2. The concentration, strength, quantitative and qualitative composition of the active and inactive ingredients for the proposed drug product (b) (4) for use in the RLD after dilution with 100 mL of 0.9% sodium chloride.

**Kareen Riviere, Ph.D.**  
 Biopharmaceutics Reviewer  
 Office of New Drug Quality Assessment

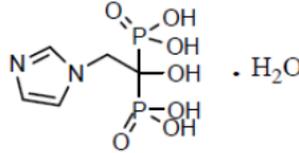
**Angelica Dorantes, Ph.D.**  
 Biopharmaceutics Team Leader  
 Office of New Drug Quality Assessment

cc: Dr. Richard Lostritto

**ASSESSMENT OF BIOPHARMACEUTICS INFORMATION:**

**1. Background**

The structure of zoledronic acid is shown in Figure 1.



**Figure 1.** Chemical structure of zoledronic acid

The composition of the proposed product is shown in Table 1. A quantitative formulation comparison of the proposed drug product and the RLD, Zometa® (zoledronic acid) Injection, is shown in Table 2.

**Table 1.** Quantitative Composition of Zoledronic Acid Injection

Component	Function	Quantity per Milliliter (mL)	Quantity per Liter (L)	Strength: 4 mg/100mL
				Quantity per unit
Zoledronic Acid	Active Ingredient	0.04 mg	0.04 g	4.0 mg
Mannitol	(b) (4)	2.2 mg	2.2 g	220 mg
Sodium Citrate		0.24 mg	0.24 g	24 mg
Sodium Chloride		9.0 mg	9.0 g	900 mg
Water for Injection		q.s. to 1 mL	q.s. to 1.0 L	q.s. to 100 mL
Total Volume		1.00 mL	1 Liter	100 mL

q.s. = Quantity sufficient

**Table 2.** Quantitative Comparison of Hospira’s Formulation and the RLD Formulation

		Reference Listed Drug	Hospira Formulation
Active Ingredient(s)		Zoledronic Acid (4 mg)	Zoledronic Acid (4 mg)
Inactive Ingredient(s)		Mannitol, USP (220 mg) Sodium Citrate, USP (24 mg) Water for Injection, USP	Mannitol, USP (220 mg) Sodium Citrate, USP (24 mg) Sodium Chloride, USP (900 mg) Water for Injection, USP
Strength	Concentrate	4 mg/5 mL (0.8 mg/mL)	Not applicable
	Post Dilution*	4 mg/100mL (0.04 mg/mL)	4 mg/100 mL (0.04 mg/mL)
Diluents		100 mL 5% Dextrose Or 100 mL 0.9% Sodium Chloride	Not applicable

\* Per Dosage and Administration guidance in RLD Label

A comparison of the pH and osmolality of the proposed drug product and the RLD is shown in Table 3.

**Table 3.** Comparison of pH and Osmolality of Hospira’s Formulation and the RLD Formulation

Test Parameter	Hospira Lot # 1023803	Zometa®, USA Lot # S0118 <sup>a</sup>	Zometa®, Canada Lot# S0237 <sup>b</sup>	Zometa®, Australia Lot# S0243 <sup>c</sup>	Zometa®, EMEA Lot# S0250 <sup>d</sup>
pH	(b) (4)				
Osmolality	296	288	288	288	287

**Reviewer's Assessment:**

*The quantitative and qualitative compositions of the active and inactive ingredients in the proposed drug product*

(b) (4)

*Additionally, the pH of both formulations is the same, and the osmolality of both formulations are similar. These data demonstrate that the proposed product should have a similar bioavailability as the reference product.*

**2. Biowaiver Request**

The Applicant is requesting a waiver of the *in vivo* study requirements as allowed under 21 CFR 320.22 (b)(1).

**Reviewer's Assessment:**

*According to 21 CFR 320.22 (b)(1), 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. *It is a parenteral solution intended solely for administration by injection,* (b) (4)
2. *It 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.*

*The proposed product meets the criteria as described in 21 CFR 320.22(b)(1)(i) in that it is a parenteral solution intended solely for administration by injection. Additionally, the proposed product meets the requirement of 21 CFR 320.22(b)(1)(ii) since:*

- a. *The active ingredient of the proposed drug product is the same as that of the RLD;*
- b. *The proposed drug product uses the same active ingredient at the same concentration as that of the diluted RLD, and is intended for administration by intravenous infusion, same as the diluted RLD; and*
- c. *After dilution of the RLD drug product with 100 mL of 0.9% sodium chloride, USP, the dilution yields a zoledronic total concentration of 0.04 mg/mL.*

**Recommendation:**

*A BA/BE waiver is granted for the proposed product based on the above information/requirements.*

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KAREEN RIVIERE  
09/10/2012

ANGELICA DORANTES  
09/10/2012

*Office of Clinical Pharmacology*  
*New Drug Application Filing and Review Form*

**General Information About the Submission**

<b>NDA Number</b>	204016	<b>Brand Name</b>	X
<b>DCP Division (I, II, III, IV, V)</b>	V	<b>Generic Name</b>	Zoledronic Acid Injection, 0.04 mg/mL
<b>Medical Division</b>	Oncology	<b>Drug Class</b>	Bisphosphonate
<b>Submission Type</b>	505 b 2	<b>RLD</b>	Zometa® 4 mg/5 mL in a (b) (4) vials, concentrate for intravenous infusion, under NDA21223 (Approved in 2003)
<b>OCP Reviewer</b>	Pengfei Song, Ph.D.	<b>Indication(s)</b>	<ul style="list-style-type: none"> <li>Hypercalcemia of malignancy</li> <li>Multiple myeloma and bone metastases from solid tumors</li> </ul>
<b>OCP Team Leader</b>	Qi Liu, Ph.D.	<b>Dosage Form / Strengths</b>	4 mg/100 mL in single-use (b) (4)
<b>Sponsor</b>	Hospira, Inc.	<b>Dosing Regimen</b>	<p>Hypercalcemia of malignancy</p> <ul style="list-style-type: none"> <li>4 mg as a single-dose intravenous infusion over no less than 15 minutes</li> <li>4 mg as retreatment after a minimum of 7 days</li> </ul> <p>Multiple myeloma and bone metastasis from solid tumors</p> <ul style="list-style-type: none"> <li>4 mg as a single-dose intravenous infusion over no less than 15 minutes every 3-4 weeks for patients with creatinine clearance of &gt; 60 mL/min</li> </ul>
<b>Date of Resubmission</b>	01/31/2012	<b>Route of Administration</b>	Intravenous injection
<b>PDUFA Due Date</b>	11/30/2012	<b>Priority Classification</b>	Standard review

**Clinical Pharmacology Information**

	<b>“X” if included at filing</b>	<b>Number of studies submitted</b>	<b>Number of studies reviewed</b>	<b>Critical Comments If any</b>
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies				505 b2 NDA submission, no human studies
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods				
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Metabolic profiling				
Isozyme characterization:				
Active Metabolites				
Transporters				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I)				
<i>Healthy volunteers-</i>				
<i>Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
Drug-drug interaction studies				
In-vivo effects on primary drug:				
In-vivo effects of primary drug on other drugs:				
In-vitro:				

<b>Subpopulation studies -</b>				
Body size				
Gender:				
Geriatrics:				
Renal Impairment:				
Race/Ethnicity:				
Hepatic Impairment:				
Pediatrics:				
<b>PD:</b>				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>QT<sub>c</sub> studies</b>				
<b>In-Vitro Release BE</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		<b>0</b>		
<b>Filability and QBR comments</b>				
	X" if yes	Comments		
<b>Application Filable</b>	X			
<b>Comments sent to firm</b>				
<b>QBR questions (key issues to be considered)</b>				
<b>Other comments or information not included above</b>				
<b>Primary reviewer Signature and Date</b>		Pengfei Song, Ph D. 03/07/2012		
<b>Secondary reviewer Signature and Date</b>		Qi Liu, Ph.D. 03/07/2012		

CC:

HFD-150 (CSO –Modupe Fagbami; MTL – Genevieve Schechter; MO – Yangmin (Max) Ning)

HFD-860 (Reviewer – P Song; TL – Q Liu; DDD-B Booth; DD - A Rahman)

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/s/  
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PENGFEI SONG  
03/08/2012

QI LIU  
03/13/2012

**BIOPHARMACEUTICS FILING REVIEW**  
**Office of New Drug Quality Assessment**

<b>Application No.:</b>	NDA 204-016	<b>Reviewer:</b> Kareen Riviere, Ph.D.	
<b>Submission Date:</b>	February 1, 2012		
<b>Division:</b>	Oncology Products	<b>Acting Biopharmaceutics Supervisory Lead:</b> Angelica Dorantes, Ph.D.	
<b>Sponsor:</b>	Hospira, Inc.	<b>Secondary Signature:</b> Sandra Suarez-Sharp, Ph.D.	
<b>Trade Name:</b>		<b>Date Assigned:</b>	February 2, 2012
<b>Generic Name:</b>	Zoledronic Acid Injection	<b>Date of Review:</b>	March 8, 2012
<b>Indication:</b>	Treatment of hypercalcemia of malignancy; Treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors	<b>Type of Submission:</b> 505(b)(2) New Drug Application	
<b>Formulation/strengths:</b>	0.04 mg/mL (4 mg/100 mL)		
<b>Route of Administration:</b>	Intravenous		

**SUBMISSION:**

This is a 505(b)(2) New Drug Application for 4 mg/100 mL Zoledronic Acid Injection. The proposed indication is for the treatment of hypercalcemia of malignancy; treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors.

**BIOPHARMACEUTICS INFORMATION:**

The reference listed drug (RLD) for this submission is NDA 021223, Zometa® (zoledronic acid) Injection 4 mg/5 mL concentrate, held by Novartis Pharmaceuticals Corporation and approved on March 7, 2003.

This submission includes a BA/BE waiver request for the proposed product. A BA/BE waiver may be granted for the proposed product based on the following information/requirements:

1. The proposed product is a parenteral solution as is the RLD.
2. The concentration, strength, quantitative and qualitative composition of the active and inactive ingredients for the proposed drug product [REDACTED] <sup>(b)(4)</sup> for use in the RLD after dilution with 100 mL of 0.9% sodium chloride.

**Quantitative Comparison of Hospira's Formulation and RLD Formulation**

		<b>Reference Listed Drug</b>	<b>Hospira Formulation</b>
<b>Active Ingredient(s)</b>		Zoledronic Acid (4 mg)	Zoledronic Acid (4 mg)
<b>Inactive Ingredient(s)</b>		Mannitol, USP (220 mg) Sodium Citrate, USP (24 mg) Water for Injection, USP	Mannitol, USP (220 mg) Sodium Citrate, USP (24 mg) Sodium Chloride, USP (900 mg) Water for Injection, USP
<b>Strength</b>	Concentrate	4 mg/5 mL (0.8 mg/mL)	Not applicable
	Post Dilution*	4 mg/100mL (0.04 mg/mL)	4 mg/100 mL (0.04 mg/mL)
<b>Diluents</b>		100 mL 5% Dextrose Or 100 mL 0.9% Sodium Chloride	Not applicable

\* Per Dosage and Administration guidance in RLD Label

The acceptability of the waiver request will be a review issue and will be the focus of the Biopharmaceutics review.

**RECOMMENDATION:**

The ONDQA Biopharmaceutics team has reviewed NDA 204-016 for filing purposes. We found this NDA **fileable** from a Biopharmaceutics perspective. The Applicant has submitted a reviewable submission. There are no comments to the Applicant at this time.

**Kareen Riviere, Ph.D.**

Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

**Sandra Suarez-Sharp, Ph.D.**

Senior Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

cc: Angelica Dorantes, Ph.D.

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KAREEN RIVIERE  
03/08/2012

SANDRA SUAREZ  
03/08/2012