

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204016Orig1s000

OTHER REVIEW(S)

Division of Oncology Products 1

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 204016

Name of Drug: Zoledronic Acid Injection, 0.04 mg/mL

Sponsor: Hospira, Inc.

Material Reviewed

Submission Date: November 2, 2015

Receipt Date: November 2, 2015

Background and Summary Description: Hospira initially submitted NDA 204016 on January 30, 2012, as a 505(b)(2) application using reference listed drug Zometa[®] (NDA 021223).

Hospira proposed to change the drug by creating a [REDACTED]^{(b)(4)} formulation comparable to Zometa[®] which requires dilution with 0.9% sodium chloride to achieve 4 mg/5 mL.

FDA issued a Complete Response (CR) letter on November 29, 2012 to NDA 204016. The CR letter was based on a recommendation from the Office of Compliance. Hospira resubmitted their application on January 8, 2013. The FDA issued a Tentative Approval letter on July 3, 2013. On November 2, 2015, Hospira submitted NDA 204016 as a class 1 re-submission in anticipation of the end of the 30 month stay.

NDA 204016 label was reviewed. No major changes were recommended as the label closely followed the reference listed label. The phrase [REDACTED]^{(b)(4)} was change to “single dose” throughout the label and on the carton/container labels. Additionally, the phrase [REDACTED]^{(b)(4)} was removed and replaced with “not made with natural rubber latex.”

Review

Attached is the proposed package insert with “Review Comments”.

Conclusions: NDA can be approved

Jeannette O’Donnell
Regulatory Project Manager

Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff

Amy McKee, MD
Clinical Team Leader

Genevieve Schechter, MD
Clinical Reviewer

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

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

/s/

JEANNETTE L O'DONNELL
12/21/2015

ALICE KACUBA
12/21/2015

GENEVIEVE A SCHECHTER
12/22/2015

AMY E MCKEE
12/22/2015

505(b)(2) ASSESSMENT

Application Information		
NDA # 204016	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Zoledronic Acid Injection Dosage Form: Injection Strengths: 4 mg/100 mL ; 0.04 mg/mL		
Applicant: Hospira Inc.		
Date of Receipt: January 31, 2012		
PDUFA Goal Date: January 2, 2016		Action Goal Date (if different):
Proposed Indications: <ul style="list-style-type: none">• Hypercalcemia of malignancy• Patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.		

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)
NDA 021223 Zometa 4 mg/100 mL ready to use formulation 4 mg/5 mL concentrate	Safety and Efficacy findings

*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).
BA/BE waiver granted on September 10, 2012.

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?

N/A 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)?

N/A 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 applicant has explicitly referenced the listed drug(s), does 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)
Zometa (zoledronic acid) Injection	NDA 021223	Yes

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 application provides for eliminating the requirement for (b) (4)

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)? YES

(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

Note: The proposed product is pharmaceutically equivalent to the 4 mg/100 mL ready-to-use bottle of the Reference Listed Drug

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):

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.

N/A 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):

Patent number: 7,932,241
Expiry date: February 5, 2028

- 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): 8,324,189 and 7,932,241
- (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 24, 2013

- (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

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

/s/

JEANNETTE L O'DONNELL
12/17/2015

OFFICE OF NEW DRUG PRODUCTS
NDPI/NDPBII

Review of Carton Labeling and PI Labeling

Clinical Review Division: DOP1

<u>NDA#:</u> 204016	<u>REVIEW#:</u> 1	<u>REVIEW DATE:</u>	03-Dec-2015
<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED</u>
Class 1 Resubmission	02-Nov-2015	03-Nov-2015	03-Nov-2015
<u>PDUFA GOAL</u>			
02-Jan-2016			

NAME & ADDRESS OF APPLICANT:

HOSPIRA INC
275 NORTH FIELD DR DEPT 0389 BLDG H2 2N
LAKE FOREST, ILLINOIS 60045
UNITED STATES

AUTHORIZED U.S. AGENT: N/A

DRUG PRODUCT NAME

Proprietary: N/A
Nonproprietary/USAN: Zoledronic Acid Injection

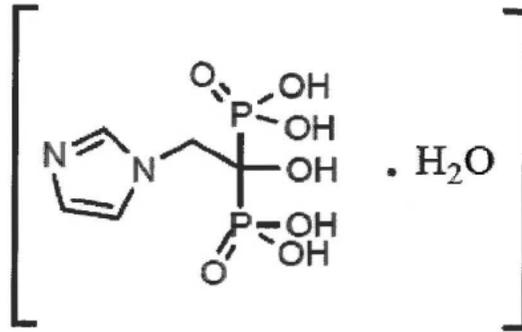
PHARMACOLOGICAL CATEGORY/INDICATION:

DOSAGE FORM: Solution
STRENGTH: 4 mg/100 mL (0.04 mg/mL)

ROUTE OF ADMINISTRATION: Injection (Intravenous)
DISPENSED: Rx OTC
SPECIAL PRODUCTS: Yes No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL. WT:

Chemical Name: [1-hydroxy-2-(1H-imidazol-1-yl)ethane-1,1-diy]bis
Molecular Formula: C₅H₁₀N₂O₇P₂ · H₂O
Molecular Weight: 290.11 g/mol (monohydrate)



REMARKS/COMMENTS:

NDA 204016 for Zoledronic Acid Injection, 4 mg/100 mL, received a FDA tentative approval on July 3, 2013. CMC information in this class 1 resubmission has been previously found adequate and has not changed. Minor updates on proposed carton labeling and Prescribing Information (PI) labeling are reviewed. The only revision needed is to change the term (b) (4) to “single-dose” in labeling.

CONSULT REVIEWS: N/A

COMMENTS/REQUESTS TO BE CONVEYED TO APPLICANT: Yes

Revise term (b) (4) to “single-dose” throughout carton Labeling and PI Labeling in accordance with Draft Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>

CONCLUSIONS & RECOMMENDATIONS:

NDA 204016 class 1 resubmission is recommended for approval from CMC standpoint.

Xing Wang, Ph.D.
Review chemist

Xing Wang -S

Digitally signed by Xing Wang -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
cn=Xing Wang -S, 0.9.2342.19200300.100.1.1=2001221660
Date: 2015.12.03 13:43:04 -05'00'

Olen Stephens, Ph.D.
Branch chief (Acting)

Olen Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Olen Stephens -S,
0.9.2342.19200300.100.1.1=2000558826
Date: 2015.12.03 14:44:36 -05'00'

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: November 13, 2015
Requesting Office or Division: Division of Oncology Products 1 (DOP1)
Application Type and Number: NDA 204016
Product Name and Strength: Zoledronic acid Injection, 4 mg/100 mL
Product Type: Single Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Hospira
Submission Date: November 2, 2015
OSE RCM #: 2015-2424
DMEPA Primary Reviewer: Tingting Gao, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

NDA 204016 for Zoledronic Acid Injection, 4 mg/100 mL, received a FDA tentative approval on July 3, 2013. Since the 30-month stay for Hospira’s NDA 204016 will expire on December 24, 2015, Hospira is submitting a request for final approval for NDA 204016. Additionally, Hospira is proposing minor formatting updates to the carton labeling (e.g. locations of the barcodes, lot number, expiration date, manufacturer information, duplicating the bottom panel to match the top panel, and consequential updates to the commodity number).

The Division of Oncology Products 1 (DOP1) requested that we review the submitted proposed carton labeling and Prescribing Information (PI) labeling for areas of vulnerability that could lead to medication errors.

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.

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

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA previously reviewed Hospira’s Zoledronic Acid container labels and carton labeling and found them acceptable from a medication error perspective.^{1,2} We evaluated the proposed changes to the submitted carton labeling and determined that Hospira’s proposed changes are acceptable from a medication error perspective. However, we noted that the package type is described as “(b) (4) Only – Discard Unused Portion” on the carton labeling. Since the Agency is retiring the term (b) (4) and is recommending “single-dose” to describe a

¹Abdus-Samad, J. Label and Labeling Review for Zoledronic Acid Injection. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 OCT 31. RCM No.: 2012-359.

²Abdus-Samad, J. Label and Labeling Review for Zoledronic Acid Injection. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 NOV 15. RCM No.: 2012-359-1.

container for use with a single patient as a single injection/infusion,³ we recommend revising it to “Single Dose only – Discard Unused Portion”. We recommend the same changes be also made to the previously tentatively approved container label and the submitted PI to ensure consistent terminology throughout label and labeling.

4 CONCLUSION & RECOMMENDATIONS

The previously tentatively approved container label, the proposed carton labeling, and the proposed PI may be improved to further clarify important information. We provide specific recommendations in Sections 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information:

1. Revise the term [REDACTED]^{(b)(4)} to “single-dose” throughout the PI including the Dosage and Administration, Dosage Forms and Strengths, and How Supplied sections in accordance with Draft Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use.³

4.2 RECOMMENDATIONS FOR HOSPIRA

We recommend the following be implemented prior to approval of this NDA:

A. Container label and carton labeling

1. Revise the statement “[REDACTED]^{(b)(4)} only – Discard Unused Portion” to “Single dose only – Discard Unused Portion” in accordance with FDA Draft Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use.

³ Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Zoledronic Acid that Hospira submitted on November 2, 2015, and the listed drug (LD).

Table 2. Relevant Product Information for the Listed Drug and Zoledronic Acid		
Product Name	Zometa (listed drug, NDA 021223)	Zoledronic Acid
Initial Approval Date	August 20, 2001	N/A
Active Ingredient	Zoledronic acid	
Indication	Hypercalcemia of malignancy. Patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.	
Route of Administration	intravenous infusion	
Dosage Form	Injection	
Strength	4 mg/100 mL 4 mg/5 mL	4 mg/100 mL
Dose and Frequency	<p>Hypercalcemia of malignancy 4 mg as a single (b) (4) intravenous infusion over no less than 15 minutes. 4 mg as retreatment after a minimum of 7 days.</p> <p>Multiple myeloma and bone metastasis from solid tumors 4 mg as a single (b) (4) intravenous infusion over no less than 15 minutes every 3 to 4 weeks for patients with creatinine clearance of greater than 60 mL/min.</p>	
How Supplied	4 mg/100 mL single-use ready-to-use bottle 4 mg/5 mL single-use vial of concentrate	4 mg/100 mL single (b) (4) premixed bag (b) (4)
Storage	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)	Temperature not exceeding 30°C (86°F). Do not freeze.
Container Closure	Carton of 1 bottle Carton of 1 vial	(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On November 9, 2015, we searched the L:drive and AIMS using the terms, zoledronic acid, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 3 previous reviews^{4,5,6}, and we confirmed that our previous recommendations were implemented.

⁴ Abdus-Samad, J. Label, Labeling, and Packaging Review for Zoledronic Acid Injection. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 OCT 31. RCM No.: 2012-359.

⁵ Abdus-Samad, J. Label, Labeling, and Packaging Review for Zoledronic Acid Injection. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 NOV 15. RCM No.: 2012-359-1.

⁶ Abdus-Samad, J. Labeling Review for Zoledronic Acid Injection. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 JUL 3. RCM No.: 2012-359-2.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On November 9, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters 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 Newsletter(s)	Acute Care, Community
Search Strategy and Terms	Match Exact Word or Phrase: Zoledronic acid

D.2 Results

The search did not retrieve any relevant articles.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁷ along with postmarket medication error data, we reviewed the following Zoledronic Acid labels and labeling submitted by Hospira.

- Container label – submitted November 15, 2012
- Carton labeling – submitted November 2, 2015

G.2 Label and Labeling Images

Container label – submitted November 15, 2012



⁷ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Carton labeling – submitted November 2, 2015

(b) (4)



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

/s/

TINGTING N GAO
11/13/2015

CHI-MING TU
11/13/2015

**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**

Labeling Review

Date: July 3, 2013

Reviewer: Jibril Abdus-Samad, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Todd Bridges, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Zoledronic Acid Injection
4 mg/100 mL (0.04 mg/mL)

Application Type/Number: NDA 204016

Applicant: Hospira, Inc.

OSE RCM #: 2012-359-2

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

Contents

1	Introduction.....	1
2	Methods and Materials Reviewed.....	1
2.1	Labels and Labeling	1
2.2	Previously Completed Reviews	1
3	Conclusions.....	1
	REFERENCES	2

1 INTRODUCTION

This review evaluates the revised insert labeling for Zoledronic Acid Injection, NDA 204016 submitted in response to the Division of Medication Error Prevention and Analysis' comments in October 31, 2012 OSE Review 2012-359.

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Insert Labeling submitted January 8, 2013
- Insert Labeling (updated) submitted June 28, 2013

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously reviewed Zoledronic Acid Injection in OSE Reviews 2012-359 and 2012-359-1, and we looked at that review to ensure all our recommendations were implemented. All the revisions to the insert labeling were implemented.

3 CONCLUSIONS

DMEPA finds the Applicant's revisions to the insert labeling acceptable.

If you have further questions, please contact Francis Fahnbulleh, OSE project manager, at 301-796-0942.

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

REFERENCES

OSE Reviews

Abdus-Samad, Jibril. OSE Review 2012-359: Label and Labeling Review for Zoledronic Acid, October 31, 2012.

Abdus-Samad, Jibril. OSE Review 2012-359-1: Label and Labeling Review for Zoledronic Acid, November 15, 2012.

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

/s/

JIBRIL ABDUS-SAMAD
07/03/2013

TODD D BRIDGES
07/03/2013

**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 Packaging Review

Date: November 15, 2012

Reviewer: Jibril Abdus-Samad, PharmD
Division of Medication Error and Analysis

Team Leader: Todd Bridges, RPh
Division of Medication Error and Analysis

Drug Name and Strength: Zoledronic Acid Injection
4 mg/100 mL (0.04 mg/mL)

Application Type/Number: NDA 204016

Applicant: Hospira, Inc.

OSE RCM #: 2012-359-1

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

Contents

1	Introduction.....	1
2	Methods and Materials Reviewed.....	1
2.1	Labels and Labeling	1
2.2	Previously Completed Reviews	1
3	Conclusions.....	1
	Appendices.....	2

1 INTRODUCTION

This review evaluates the revised container label, carton, and insert labeling for Zoledronic Acid Injection, NDA 204016 submitted in response to the Division of Medication Error Prevention and Analysis' comments in October 31, 2012 OSE Review 2012-359.

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Label submitted November 12, 2012 (Appendix A)
- Carton Labeling submitted November 12, 2012 (Appendix B)

2.2 PREVIOUSLY COMPLETED REVIEWS

DMEPA previously reviewed Zoledronic Acid Injection in OSE Review 2012-359, and we looked at that review to ensure all our recommendations were implemented. All the revisions to the container label and carton labeling were implemented.

3 CONCLUSIONS

DMEPA finds the Applicant's revisions to the container label and carton labeling acceptable. At this time, labeling negotiations for the insert labeling are ongoing.

If you have further questions, please contact Francis Fahnbulleh, OSE project manager, at 301-796-0942.

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

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

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

/s/

JIBRIL ABDUS-SAMAD
11/15/2012

TODD D BRIDGES
11/15/2012

**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, Labeling, and Packaging Review

Date: October 31, 2012

Reviewer: Jibril Abdus-Samad, PharmD
Division of Medication Error and Analysis

Team Leader: Todd Bridges, RPh
Division of Medication Error and Analysis

Associate Director: Scott Dallas, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Zoledronic Acid Injection
4 mg/100 mL (0.04 mg/mL)

Application Type/Number: NDA 204016

Applicant: Hospira, Inc.

OSE RCM #: 2012-359

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

Contents

1	Introduction.....	1
1.1	Background.....	1
1.2	Regulatory History.....	1
1.3	Product Information.....	1
2	Methods and Materials Reviewed.....	2
2.1	Previously Completed Reviews.....	2
2.2	Literature Search.....	3
2.3	Labels and Labeling.....	3
3	Medication Error Risk Assessment.....	3
3.1	Integrated Summary of Medication Error Risk Assessment.....	4
4	Conclusions.....	7
4.1	Comments to the Division.....	7
4.2	Comments to the Applicant.....	8
	Appendices.....	9

1 INTRODUCTION

This review evaluates the proposed single-port premixed bag, container label, carton, and insert labeling for Zoledronic Acid NDA 204016 for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

The Applicant proposes a single port premixed intravenous bag containing Zoledronic Acid 4 mg/100 mL. The listed drug Zometa is currently available as a 4 mg/5 mL vial that requires dilution and a 4 mg/100 mL bottle ready for infusion. Additionally, the listed drug, Zometa 4 mg/100 mL bottle design allows for preparation of renally-adjusted doses by withdrawing solution utilizing a needle and syringe.

1.2 REGULATORY HISTORY

Zoledronic Acid NDA 204016 is the subject of a 505(b)2 application submitted on January 31, 2012, that notes Zometa (Zoledronic Acid) NDA 021223 as the listed drug.

Previously, in OSE Review 2010-2370, dated January 5, 2011, for Zometa, we recommended the Applicant either provide a Zometa premixed (b) (4) in strengths to accommodate the recommended renal dosages or provide detailed preparation instructions in the insert for healthcare practitioners so that they can safely prepare and administer this product in patients who are renally impaired. Subsequently in OSE Review 2011-408, dated June 3, 2011, we found the Applicant's proposed method of preparation of renally prepared doses error-prone. However, after much discussion, DOP1 and ONDQA decided to label the product based on their recommendations.

Another product Reclast (Zoledronic Acid) (NDA 021817 and NDA 022080) is available in a 5 mg/100 mL ready-to (b) (4). See Appendix B for a comparison of both Zoledronic Acid products.

1.3 PRODUCT INFORMATION

The following product information is provided in the April 30, 2012 submission that provides updated insert labeling.

- Active Ingredient: Zoledronic Acid
- Indication of Use:
 - Treatment of hypercalcemia of malignancy
 - Treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard anti-neoplastic therapy.
- Route of Administration: Intravenous
- Dosage Form: Injection
- Strength: 4 mg/100 mL (0.04 mg/mL)
- Dose and Frequency:

- Hypercalcemia of malignancy : 4 mg intravenously over not less than 15 minutes.
- Multiple Myeloma and Bone Metastases: 4 mg intravenously over not less than 15 minutes every 3 to 4 weeks for patients with creatinine clearance greater than 60 mL/minute.

Co-administer oral calcium supplements of 500 mg and a multiple vitamin containing 400 International Units of vitamin D daily

(b) (4)

Baseline Creatinine Clearance (mL/min)	Zoledronic Acid Injection Recommended Dose* (Volume per mL)
greater than 60	4 mg (b) (4)
50 to 60	3.5 mg (b) (4)
40 to 49	3.3 mg (b) (4)
30 to 39	3 mg (b) (4)
*Doses calculated assuming target AUC of 0.66(mg•hr/L) (CrCl = 75 mL/min)	

- How Supplied: 4 mg/100 mL single (b) (4)
- Storage: Store at temperatures not exceeding 30°C (86°F). (b) (4)
- Container and Closure System: (b) (4)

2 METHODS AND MATERIALS REVIEWED

DMEPA reviewed recently completed Zoledronic Acid labeling reviews and ISMP^{***} literature databases for Zometa and Reclast medication error reports. We also reviewed the Zometa labels and package insert labeling submitted by the Applicant.

2.1 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed the listed drug Zometa (Zoledronic Acid) and we looked at the reviews to ensure the proposed Zoledronic Acid labels and labeling were in concurrence with our previous recommendations. The significant Zometa medication errors documented in OSE Review 2010-2370 included wrong drug, wrong dose, wrong frequency of administration, and wrong rate of administration errors. We concluded the

*** This document contains proprietary data from the Institute for Safe Medication Practices (ISMP), which cannot be shared outside of the FDA. Users wanting this information must contact a designated individual in the Division of Medication Error Prevention who will gain approval from ISMP.

proposed Zometa (b) (4) did not appear to pose a greater risk in causing these types of errors compared to the 4 mg/5 mL vial.

Additionally, DMEPA recently completed a review for Zoledronic Acid Injection, in OSE Review 2012-480, dated October 19, 2012. This review included an updated medication error search of listed drug Zometa. We found the labeling for the proposed Zoledronic Acid adequately address the medication errors (monitoring errors, wrong frequency of administration, wrong route of administration, wrong technique, wrong drug, wrong dose, wrong rate of administration, and prescribing errors) that occurred with the listed drug Zometa. Additionally, we did not find any medication error cases specifically related to preparation of renally-adjusted doses with the currently marketed Zometa premixed bottle. Therefore, the medication errors with Zometa did not note any labeling issues that should be revised for the proposed product labeling.

2.2 LITERATURE SEARCH

We searched PubMed and the ISMP publications on June 29, 2012 for additional cases and actions concerning Zometa (Zoledronic Acid). Two ISMP Newsletters note Zoledronic Acid was listed as one of the primary suspect drugs for reported serious events reported to FDA ((b) (4)).^{1,2} There were no further details provided as to the nature of these serious events and if they were related to medication errors .

2.3 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,³ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Label submitted January 31, 2012 (Appendix C)
- Carton Labeling submitted January 31, 2012 (Appendix D)
- Insert Labeling submitted April 30, 2012
- Replica carton and flexible intravenous bag submitted July 11, 2012

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the risk assessment of the Zoledronic Acid product design as well as the associated label and labeling.

¹ ISMP Medication Safety Alert, Acute Care. October 6, 2011

² ISMP Medication Safety Alert, Acute Care. February 25, 2010

³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3.1 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

3.1.1 Medication Error Case Summary

An updated AERS and ISMP database search for medication error cases was not conducted for this review. See OSE Review 2012-480, dated October 1, 2012, for an AERS and ISMP database results and an assessment of the cases. We find the labeling for the proposed Zoledronic Acid adequately address these previously assessed medication errors. Additionally, we did not find any medication error cases specifically related to preparation of renally-adjusted doses with the currently marketed Zometa premixed (b) (4). Therefore, the medication errors with Zometa did not note any labeling issues that should be revised for the proposed product labeling.

3.1.2 Impact of Physical Design

The proposed single-port pre-mixed bag is designed for administration of Zoledronic Acid 4 mg via connection to an intravenous infusion set. The Applicant proposed a 4 mg strength only and did not propose the other renal dose adjusted strengths of Zoledronic Acid (3.5 mg, 3.3 mg, and 3 mg). Additionally, the proposed product design does not allow for preparation of renally-adjusted doses unlike the currently marketed Zometa (Zoledronic Acid) 4 mg/100 mL bottle design, which allows for adjustment of the dose using a standard syringe and needle. Rather, the Applicant proposes the end-user to infuse the specified reduced volume of Zoledronic Acid Injection from the pre-mixed intravenous bag, which is less than the labeled total volume, using a volumetric infusion pump and then discard any unused portion.

Currently in the marketplace, manufacturers of similarly designed single-port premixed bags provide multiple strengths to accommodate these doses. Examples of these products include Gentamicin (60 mg, 80 mg, 100 mg, 120 mg), Vancomycin (500 mg, 750 mg, 1 g) and Ceftriaxone (1 g and 2 g) premixed bags. In pharmacy practice, if a drug that is available in a premixed formulation is prescribed but there is no premixed formulation available in the strength prescribed, the standard of practice is to compound the prescribed dose using a vial. Currently, there is a Zoledronic Acid 4 mg/5 mL vial currently marketed for pharmacy compounding.

DMEPA is concerned the Applicant's proposal to depend upon a volumetric infusion pump to limit the dose infused introduces an unsafe practice into the medication use system and places patients at risk for being infused with the entire contents of the bag. This type of error administration error has significant clinical consequences because infusion of the entire bag (4 mg) to a patient with impaired renal function may result in increased risk of adverse reactions, in particular renal adverse reactions.

We requested for data to support the proposed administration of renally-adjusted doses (Appendix E). Subsequently, the Applicant provided data supporting the accuracy of volumetric pumps to deliver (b) (4) the various facilities that use Zoledronic Acid actually possess and use these volumetric pumps. Additionally, the Applicant provided one example, Nexterone (Amiodarone Hydrochloride) Injection, of a product whose label instructs the user to administer a volume that is less than the amount in the container.

Despite the fact that volumetric pumps can be programmed and accurately deliver the intended volume, we are still concerned that programming the volumetric pump to administer a volume that is less than the amount in the intravenous bag introduces an unsafe practice. There is potential for the user to program the infusion pump to deliver the total volume instead of the reduced volume. Although, the Applicant provided one example, Amiodarone continuous infusion, of a drug labeled to deliver reduced volume, we are not convinced the nurses are accustomed to programming small intravenous bags intended to deliver a reduced volume. We still find the safest method to deliver renally-adjusted doses is to provide the intended amount of drug in the intravenous bag prior to programming the volumetric pump and administering to patients.

During meeting with DOP1, they requested verification from the Applicant that the single-port on the intravenous bag was not designed for withdrawal or addition of fluid into the intravenous bag, which resulted in ONDQA sending an IR (Appendix F). Subsequently, in preparation for a teleconference, DMEPA sent the Applicant the following three options (Appendix G) for the Applicant to accommodate safe preparation and administration of renally-adjusted doses:

1. (b) (4) Use the currently approved preparation instructions as it appears in the label for Zometa (Zoledronic Acid) 4 mg/100 mL bottle.
2. Develop a (b) (4) bag for the recommended renally adjusted doses (3.5 mg, 3.3 mg, and 3 mg). Additionally, it is imperative the Applicant provide adequate strength differentiation of the carton and container labels to prevent wrong strength selection errors as the doses look similar.
4 mg/100 mL
3.5 mg/ (b) (4)
3.3 mg/ (b) (4)
3 mg/ (b) (4)
3. Revise the container label, carton, and package insert labeling to communicate this product is not intended for use with patients that require renal dose adjustments and therefore, these patients must receive a different Zoledronic Acid product. Additionally, this information should also be noted on a sticker over the tube and twist-off cap portion of the pre-mixed bag so that healthcare practitioners note this warning prior to administration. The length of the statement may require a sticker that has a flap or flange to allow additional space.

Prior to the teleconference, the Applicant responded to our IR by recommending the use of a commercially available transfer device to allow withdraw of the specified amount of Zoledronic Acid solution from the intravenous bag and proposed to adopt similar language from the approved Zometa 4 mg/100 mL (b) (4). Subsequent to the teleconference, DMEPA requested the Applicant provide data that illustrates their recommended transfer device is common in all types of facilities that use Zoledronic Acid, define the type of transfer device, and list any approved drugs that recommend a similar transfer device in the labeling. The Applicants response included data that (b) (4) publications and there is an estimated \$ (b) (4) market for (b) (4). However, this response lacks the granularity of data we need to evaluate their proposal. Furthermore, the package insert labeling revisions did not provide detailed instructions on exactly what type of device to use and how to use it. Thus, DMEPA sent another IR listed as action items from the Teleconference minutes along with joint comments from ONDQA (Appendix M).

On September 28, 2012, the Applicant's response contained examples of intravenous bag transfer devices (Appendix L), described FDA clearance for use with plastic containers for intravenous injections, described their use and accessibility to healthcare institutions, and provided preparation instructions in the insert labeling. However, the Applicant's response lacked in-use stability data of Zoledronic Acid with the materials that compose the transfer devices as requested by the ONDQA.

We are unaware of premixed intravenous bags with labeling that describes use of intravenous transfer device. Healthcare practitioners are familiar premixed bags with a single port that is designed for insertion of intravenous infusion set. This design is common in practice. However, Zometa 4 mg/100 mL (b) (4) is a premixed product with labeling that provides preparation instructions to manipulate the premixed (b) (4) to prepare renally-adjusted doses. Our medication error evaluation did not find errors associated with manipulation of the premixed (b) (4). Since there was no current evidence of medication errors associated with manipulation of a premixed intravenous (b) (4) and intravenous bag transfer devices seem to be widely used, we find the Applicant's proposal to use an intravenous bag transfer device to manipulate the premixed intravenous bag to prepare renally-adjusted doses acceptable.

The manipulation of a premixed product to prepare renally-adjusted doses will represent a change in practice. The steps involved to prepare renally-adjusted doses for the proposed Zoledronic Acid bag differ from the Zometa 4 mg/100 mL (b) (4). Therefore, the insert labeling must contain instructions to alert providers of these differences. However, if a renal dose is required and a healthcare institution does not stock transfer devices, healthcare practitioners can use a different product such as the Zometa 4 mg/100 mL premixed (b) (4) or a 4 mg/5 mL vial to compound the intended renal impairment dose. Thus, a healthcare institution can not only stock the proposed single-port Zoledronic Acid, but stock another packaging configuration to prepare doses for renally impaired patients.

Conversely, if the Applicant does not provide ONDQA with the requested in-use stability data, then DMEPA recommends revising the labels and labeling to alert practitioners that this Zoledronic Acid premixed bag is not for patients with renal impairment. Regardless of whether the Applicant pursues use of transfer devices or limits the product to patients with normal renal function, healthcare practitioners can prepare renally-adjusted doses of Zoledronic Acid by using the proposed method (use transfer devices with the Zoledronic Acid 4 mg/100 mL single-port bag) or the currently practiced method (use Zometa 4 mg/5 mL vial or 4 mg/100 mL (b) (4)).

3.1.3 Container Label and Carton Labeling

The container label and carton labeling required revisions to improve to increase the readability and prominence of important information on the label to promote the safe use of the product. These revisions are detailed in Appendix I. The Applicant's September 7, 2012 revisions were reviewed (Appendices J and K). The remaining revision required is for the Applicant to de-bold the storage information and symbols (b) (4), which are detailed in *Section 4.2 - Comments to the Applicants*. Additionally, the final labeling revisions will be affected by whether the Applicant pursues use of transfer devices or limits the product to patients with normal renal function. We await the Applicant's decision.

4 CONCLUSIONS

We find the Applicant's proposal to use a needless transfer device to with the proposed single-port premixed bag of Zoledronic Acid 4 mg/100 mL for preparation of renal impairment dosages acceptable provided the Applicant submits in-use stability data to ONDQA. If the Applicant fails to submit in-use stability data, then we find it acceptable to mitigate the risk of errors with this packaging configuration by revising the container label, carton and insert labeling to communicate that the product is not intended for use with patients with renal impairment. At the time this review was completed, we await the Applicant's decision.

If you have further questions, please contact Francis Fahnbulleh, project manager, at 301-796-0942.

4.1 COMMENTS TO THE DIVISION

The revisions to the insert labeling section 2.3 – *Dosage and Administration* depends on whether the Applicant submits acceptable in-use stability data or labels the product is not intended for use with patients with renal impairment. Additionally, there are dangerous abbreviations and symbols that require revision.

A. Dosage and Administration, Multiple Myeloma and Metastatic Bone Lesions of Solid Tumors – Section 2.2

1. The Dosage and Administration section contains the abbreviation, *IU*. *IU* has been misinterpreted as IV or 10.⁴ As part of national campaign to eliminate the

⁴ <http://www.ismp.org/Tools/errorproneabbreviations.pdf> Last accessed September 25, 2012

use of dangerous abbreviations and dose designations, FDA agreed to remove such abbreviations from the approved labels and labeling. Therefore, we request the abbreviation, *IU*, be replaced with the words, *International Units*.

2. In Table 1, replace the symbol, -, with the word, to.

4.2 COMMENTS TO THE APPLICANT

A. Container Label

1. De-bold the storage statements. Room temperature storage recommendations do *not* require bolding to alert practitioners
2. Debold the symbols, (b) (4).

B. Carton Labeling

1. De-bold the storage information on the rear panel. Room temperature storage recommendations do *not* require bolding to alert practitioners.
2. Reverse the order of the appearance of the strength and established name to appear in the correct format of established name then strength. Thus, the side panel should appear as:

Zoledronic Acid Injection 4 mg/100 mL (0.04 mg/mL)

APPENDICES

Appendix A: OSE Reviews

1. Abdus-Samad, Jibril. OSE Review 2012-480: Label and Labeling Review for Zoledronic Acid Injection, October 19, 2012
2. Baugh, Denise. OSE Review 2011-408: Label and Labeling Review for Zometa, June 3, 2011
3. Baugh, Denise. OSE Review 2010-2370: Label and Labeling Review for Zometa, January 5, 2011

Appendix B: Zoledronic Acid Product Comparison

Product	Zoledronic Acid Injection (proposed product)	Zometa (Zoledronic Acid) Injection	Reclast (Zoledronic Acid)
NDA	204016	021223, 021386	021817, 022080
Strength	4 mg/100 mL injection	4 mg/5 mL vial 4 mg/100 mL	5 mg/100 mL
Recommended Dose	4 mg	4 mg	5 mg
Renal Adjustment	*3.5 mg for CrCl 50 mL/min to 60 mL/min, 3.3 mg for CrCl 40 mL/min to 49 mL/min, 3 mg for CrCl 30 mL/min to 39 mL/min	*3.5 mg for CrCl 50 mL/min to 60 mL/min, 3.3 mg for CrCl 40 mL/min to 49 mL/min, 3 mg for CrCl 30 mL/min to 39 mL/min	Contraindicated in CrCl < 35 mL/min

* Renal adjustment is only for the indications of Multiple Myeloma and Bone metastasis from solid tumors

Appendix C: Container Label for Zoledronic Acid



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

Appendix E: IR for data to support the proposed administration of renally-adjusted doses

DMEPA is concerned that your proposal for administration of renally-adjusted doses introduces a new practice into the medication use system and places patients at risk for having the entire contents of the bag infused. Specifically, you recommend the user to infuse the specified volume, which is less than the labeled total volume, from the intravenous bag using a volumetric infusion pump. Therefore, we request the following to address our concerns:

1. Discuss whether your proposal to infuse a specific volume, which is less than the labeled total volume, introduces a new practice into the medication use system considering the various medication use processes, facilities, and end-users (physicians, pharmacists, nurses) that will interact with Zoledronic Acid Injection.
2. Are the pumps capable of delivering the exact volume [REDACTED] (b) (4) [REDACTED] of the Zoledronic Acid solution? Provide data about the accuracy of drug solution delivery using volumetric pumps that would be used to deliver Zoledronic Acid Injection. What is the error rate (incorrect volume infused) reported with any infusion pump which may be used to infuse this product?
3. Provide data to support the various types of facilities (for example, community hospital, tertiary care center, outpatient oncology practice, comprehensive cancer center) that will likely use Zoledronic Acid Injection actually possess infusion pumps capable of safely administering the specific volume indicated for renally adjusted doses.

Appendix F: ONDQA IR

In section 2.2 of the proposed draft labeling, you have included dose reductions for renal impairment but you have not provided instructions on how to perform the dose reductions using the single port on the (b) (4) bag. Please respond to the following information request by noon EST on 8/24:

1. Container-closure: (b) (4)
[Redacted]
2. The drug product is sterile and does not contain a preservative. Since any external penetration of the container/closure system of a sterile drug product provides an opportunity for microbial contamination of that drug product, please provide labeling text stating that the drug product (b) (4)
[Redacted]

Please provide labeling text regarding the preparation of educed doses for patients with renal impairment in line with section 2.3 of the ZOMETA label.

Appendix G: DMEPA response to Applicant's submission and subsequent 9/5/2012 IR

The package insert labeling instructs the user to infuse the specified volume via an infusion pump based on the renally-adjusted doses in section 2.3 of the package insert labeling. However, labeling the product to instruct healthcare practitioners to program the infusion pump to delivery partial volumes for a 15 minute infusion is not safe. FDA finds the safest method of administration of renally-adjusted doses is to provide the correct amount of drug in the intravenous bag *prior* to programming the pump and administering to the patient. Thus, we have three options available for you to consider.

1. [REDACTED] (b) (4)
Use the currently approved preparation instructions as it appears in the label for listed drug Zometa (Zoledronic Acid) 4 mg/100 mL bottle.
2. Develop [REDACTED] (b) (4) bags for the recommended renally adjusted doses (3.5 mg, 3.3 mg, and 3 mg). Additionally, it is imperative the Applicant provide adequate strength differentiation of the carton and container labels to prevent wrong strength selection errors as the doses look similar.
4 mg/100 mL
3.5 mg/[REDACTED] (b) (4)
3.3 mg/[REDACTED] (b) (4)
3 mg/[REDACTED] (b) (4)
3. Revise the container label, carton, and package insert labeling to communicate this product is not intended for use with patients that require renal dose adjustments and therefore, these patients must receive a different Zoledronic Acid product. Additionally, this information should also be noted on a sticker over the tube and twist-off cap, so that healthcare practitioners note this warning prior to administration. The length of the statement may require a sticker that has a flap or flange to allow additional space.

Appendix H: Teleconference Minutes

Discussion Points:

- FDA began the discussion asking the Applicant to describe specifically what device they were recommending for use with their product. The Applicant provided a description of the device.
- Considering there are various transfer devices, FDA mentioned the Applicant consider packaging their recommended device with their Zoledronic Acid product.
- FDA noted 8 practicing inpatient pharmacist area were not familiar with these transfer devices but rather transfer devices used in preparation of large volume parenteral or total parenteral nutrition.
- The Applicant provided more background information claiming their recommended transfer device (b) (4)
[REDACTED]
- FDA noted this Zoledronic Acid pre-mix IV bag is designed to be infused as is. One important advantage with using pre-mixed bags is elimination of preparation errors. Once healthcare providers begin to introduce manipulations of a (b) (4) bag, opportunities for preparation errors arise.
- FDA noted their evaluation of the Applicant's proposal is on-going. Any data to support their recommended device is commonly used in all the facilities that are likely to use Zoledronic Acid would be beneficial.

Action Items:

- FDA will send the most up-to-date package insert labeling revisions to the Applicant today.
- The Applicant will update the package insert labeling to include instructions on preparation of renally-adjusted doses with their recommended transfer device. The Applicant agrees to submit the revised package insert labeling edits back to FDA by Friday September 14, 2012.

The Applicant agrees to provide data that illustrates their recommended transfer device is common in all types of facilities that use Zoledronic Acid, such as hospitals and outpatient infusion centers. Additionally, the Applicant will better define the type of transfer device and also list any approved drugs that recommend a similar transfer device in the labeling. The Applicant agrees to submit this data by September 17, 2012.

Appendix I: Container Label and Carton Labeling Comments

A. Container Label

1. Revise the font size and weight of the word *Injection* to match *Zoledronic Acid*.
2. Move the infusion time statement, *Infusion time must not be less than 15 minutes*, to appear directly below the statement, *Do not mix with calcium-containing solutions*.
3. To remove clutter and improve readability by creating space for increased prominence of important information, revise the label as follows:

- a. Revise the statement, (b) (4) to read as follows:

See insert for dosage and administration.

Note deletion of the word (b) (4) and use of lowercase letters for *dosage and administration* to remove clutter, create space, and improve readability of more important information.

- b. Delete the statement, (b) (4)
- c. Delete the statement, (b) (4)
4. Revise the statement, *Discard unused portion*, to read as follows:
5. Add a bar code to be in compliance with 21 CFR 201.25.
6. Revise the storage information to read as follows:

Store (b) (4)
Do not freeze.

B. Carton Labeling

1. Revise the font size and weight of the word *Injection* to match *Zoledronic Acid*.
2. Add the infusion time statement, *Infusion time must not be less than 15 minutes*, to the principal display panel to appear directly below the statement, *Do not mix with calcium-containing solutions*.
3. Add the statement, (b) (4) Only – Discard Unused Portion, to the principal display panel
4. Revise the storage information to read as follows:

Store (b) (4)
Do not freeze.

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

Appendix M: DMEPA and ONDQA IR for additional granular data and in-use stability data on the transfer device

Your response to our 9/10/2012 IR does not provide the granularity we need to evaluate your proposal to recommend a transfer device to prepare renally-adjusted doses. Although closed-transfer devices (b) (4) this does not assure us these devices are used by the healthcare practitioners at all types of facilities that use Zoledronic Acid. Furthermore, the package insert labeling does not provide detailed instructions on exactly what type of device to use and how to use it.

To better evaluate you proposal, we request the following:

1. Improve the description of the transfer device. The term (b) (4) that is used in section 2.3 of the package insert labeling is ambiguous and does not clearly define the intend device. Specify the transfer device, commercial availability, material of construction (e.g. (b) (4)), and in-use stability data for the duration the drug product will be in contact with the transfer device.
2. Include step-by-step instructions on how to prepare the adjusted doses using the transfer device(s).
3. Provide granular data to illustrate the recommended transfer device(s) is common in all types of facilities that use Zoledronic Acid, such as hospitals, outpatient infusion centers, and private physician office practices.
4. Provide data to show the recommended transfer device(s) are mechanically compatible with the Zoledronic Acid (b) (4) bag for withdrawal of solution during preparation and administration to the patient.

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

/s/

JIBRIL ABDUS-SAMAD
10/31/2012

TODD D BRIDGES
10/31/2012

SCOTT M DALLAS
10/31/2012

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 # 204016	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: Zoledronic Acid Injection Dosage Form: Injection Strengths: 4 mg/100 mL; 0.04mg/mL		
Applicant: Hospira Inc. Agent for Applicant (if applicable): N/A		
Date of Application: January 30, 2012 Date of Receipt: January 31, 2012 Date clock started after UN: N/A		
PDUFA Goal Date: November 30, 2012	Action Goal Date (if different): November 15, 2012	
Filing Date: March 31, 2012	Date of Filing Meeting: March 8, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): <ul style="list-style-type: none"> Hypercalcemia of malignancy Patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy 		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	
<i>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.</i>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate	

		products <input type="checkbox"/> Other (drug/device/biological product)			
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:		<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):					
List referenced IND Number: IND 113475; NDA 021223					
Goal Dates/Product Names/Classification Properties		YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>		X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>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.</i>		X			
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)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm <i>If no, ask the document room staff to make the appropriate entries.</i>		X			
Application Integrity Policy		YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm <i>If yes, explain in comment column.</i>			X		
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>					
User Fees		YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?		X			

<p><u>User Fee Status</u></p> <p><i>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.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>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.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>x</p>																		
<p>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)].</p>		<p>x</p>																		
<p>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)]?</p> <p><i>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</i></p>		<p>x</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td>N021223</td> <td>Zometa (zoledronic acid) Injection</td> <td>PED</td> <td>March 2, 2013</td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	N021223	Zometa (zoledronic acid) Injection	PED	March 2, 2013									<p>x</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
N021223	Zometa (zoledronic acid) Injection	PED	March 2, 2013																	
<p><i>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.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>		<p>x</p>																		

<p>Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>				
<p>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)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		x		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		x		
<p>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)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

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

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			x	
If yes, BLA #				
Forms and Certifications				
<i>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.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	x			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	x			Included in the revised submission of 2/1/12
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)?	x			Included in the revised 356h submission of 3/8/12
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)?		x		No clinical or bioequivalence studies
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	x			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with	x			

authorized signature? <i>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].</i> <i>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...”</i>				
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? <i>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)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	(not needed since it is electronic submission.)

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

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>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.</i>		X		

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?		x		
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? <i>If no, request in 74-day letter</i>	x			
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)? <i>If no, request in 74-day letter</i>				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		x		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		x		
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		x		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	x			
Is the PI submitted in PLR format? ⁴	x			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.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? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	x			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
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) <i>If yes, specify consult(s) and date(s) sent:</i>		x		
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		x		

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date: Pre-IND113475/Pre-NDA FDA Preliminary Meeting Response of January 12, 2012	X			
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		x		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 8, 2012

NDA #: 204016

PROPRIETARY NAME: N/A

ESTABLISHED/PROPER NAME: Zoledronic Acid Injection

DOSAGE FORM/STRENGTH: 4 mg/100mL; 0.04 mg/mL

APPLICANT: Hospira Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S)

- Hypercalcemia of malignancy
- Patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy

BACKGROUND:

This NDA has been submitted as a 505(b)(2). The RLD for the application is NDA 021223 Zometa® (zoledronic acid) Injection held by Novartis Pharmaceuticals Corporation.

The following Patents: 4939130-Sept. 2, 2012; 4939130*PED- Mar. 2, 2013; 7932241-Feb. 5, 2028 are still current; and there is unexpired exclusivity for the product (PED) attached to the patent.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Modupe Fagbami	Y
	CPMS:	Frank Cross Jr.	N
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Genevieve Schechter	Y
	TL:	Yang-Min Ning (Acting TL)	Y

Social Scientist Review (<i>for OTC products</i>) N/A	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>) N/A	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>) N/A	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Pengfei Song	N
	TL:	Qi Liu	N
Biostatistics	Reviewer:	Lijun Zhang	N
	TL:	Shenghui Tang	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Wei Chen	Y
	TL:	Anne Pilaro	Y
Statistics (carcinogenicity) N/A	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>) N/A	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Li-Shan Hsieh	Y
	TL:	Haripada Sarker	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Robert Mello	Y
	TL:	Bryan Riley	N
CMC Labeling Review	Reviewer:	Li-Shan Hsieh	Y
	TL:	Haripada Sarker	Y
Facility Review/Inspection	Reviewer:	Mahesh Ramanadham	N
	TL:	Haripada Sarker	Y
OSE/DMEPA (proprietary name)	Reviewer:	Jibril Abdus-Samad	N

	TL:	Todd Bridges	N
OSE/DRISK (REMS)	Reviewer:		
N/A	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
N/A	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
N/A	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
N/A	TL:		
BioPharmaceutics	Reviewer:	Kareen Riviere	Y
	TL:	Sandra Suarez	N
Safety	RPM	Susan Jenney	Y
	TL	Katherine Fedenko	Y
Other Attendee	RPM- ONDQA	Debbie Mesmer	Y
	RPM- DMEPA	Frances Fahnbulleh	Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable

<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain: No clinical or bioequivalence studies conducted</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>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</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • 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? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE

<p>Comments:</p>	<input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) 	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

Comments:	
<u>Facility Inspection</u> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility/Microbiology Review (BLAs only)</u> N/A Comments:	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>CMC Labeling Review</u> Comments: No issues so far	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Amna Ibrahim, M.D. 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review

<input type="checkbox"/>	Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	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).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	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.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • 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 OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	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]
<input type="checkbox"/>	Other

Modupe Fagbami

Regulatory Project Manager

August 23, 2012

Date

Frank Cross Jr.

Chief, Project Management Staff

August 23, 2012

Date

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/

MODUPE O FAGBAMI
08/23/2012

FRANK H CROSS
08/23/2012

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: 204016

Name of Drug: Zoledronic Acid Injection, 4mg/100mL

Applicant: Hospira Inc.

Labeling Reviewed

Submission Date: January 30, 2012

Receipt Date: January 31, 2012

Background and Summary Description

Hospira Inc. has submitted a 505(b)(2) New Drug Application (NDA) for Zoledronic Acid Injection; NDA 204016 that provides for the treatment of Hypercalcemia of malignancy, patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy. The application was filed on March 8, 2012 and it received a Standard Review Designation; thereby making the PDUFA Date November 30, 2012.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

In addition, the following labeling issues were identified:

1. There should be no white-space between the ‘HIGHLIGHTS OF PRESCRIBING INFORMATION’ and the Highlights Limitation Statement
2. The drug product title must be bolded and in all upper case letters
3. Only “adverse reactions” should be included in the PI. Avoid using terms, such as “adverse events”. Please ensure this is corrected in the entire label.
4. Format sentence “to report SUSPECTED ADVERSE REACTION” in HL.

5. Avoid using terms, such as “rare” and “very rare”. Remove them and re-word the label as appropriate
6. The subtitle heading for ‘Adverse Reactions’, 6.1, should read, “Clinical Trials Experience”; not “Clinical Studies Experience” as presently stated
7. Applicant should change “postapproval” to “post-approval” in their verbatim statement
8. Applicant should make updates to the proposed PI for NDA 204016 referencing and incorporating (as appropriate) the most recently approved RLD’s PI.
9. Applicant to remove the revision date on the last page since it is already on HL

We request that you resubmit labeling that addresses these issues by April 12, 2012. The resubmitted labeling will be used for further labeling discussions.

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review and identified above will be conveyed to the applicant in the 74-day letter letter. The applicant will be asked to resubmit the SRPI referencing and incorporating (as appropriate) the most recently approved RLD’s PI, and also to address all the above identified labeling deficiencies by April 12, 2012. The resubmitted labeling will be used for further labeling discussions.

Modupe Fagbami	April 4, 2012
Regulatory Project Manager	Date
Frank H. Cross, Jr.	April 4, 2012
Chief, Project Management Staff	Date

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

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

/s/

MODUPE O FAGBAMI
04/09/2012

FRANK H CROSS
04/10/2012