

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204016Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review #2

Date	July 3, 2013
From	Ali Al-Hakim, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	204016
Applicant	Hospira
Date of Submission	January 08, 2013
PDUFA Goal Date	July 08, 2013
Proprietary Name / Established Name	N/A Zoledronic Acid Injection
Dosage forms / Strength	4 mg/100 mL
Proposed Indication(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 <div style="text-align: right; font-size: small;">(b) (4)</div>
Recommended	Tentative Approval

1. Introduction

NDA 204016 (**Zoledronic Acid**) was submitted in accordance with section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act to the Agency on 31-JAN-2012.

The original CTDL recommendation for the NDA was a **Complete Response** action as indicated in CTDL review no. 1 by Dr. Nallaperumal Chidambaram dated 11/15/2012. The Complete response was based on two outstanding issues related to withhold recommendation of manufacturing sites and a labeling issue. The sponsor submitted responses to the above issues on January 08, 2013 (class 2 resubmission). **Therefore, this CTDL(review no. 2) will focus only on addressing the responses to the CR Action issues and will reference any other unchanged information to the original CTDL(review No. 1).**

With respect to the manufacturing sites, Office of Compliance updated the status of the manufacturing site and an Overall Acceptable recommendation for the sites was issued on February 25, 2013 (see CMC memo by Dr. Li Shang Hseih dated 04/12/2013). Regarding the labeling issues, the sponsor submitted labeling

responses/revisions to the draft labeling (Package Insert {PI} for zoledronic acid injection) in response to the CR letter. These labeling responses were reviewed by Dr. Marybeth Toscano and the clinical reviewer Dr, Genevieve Schechter, who concluded that the draft labeling is acceptable.

Patent Issue

The Tentative Approval Action recommendation is based on the following letter addressed to the sponsor.

The listed drug upon which your application relies is subject to a period of patent protection and therefore final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until the period has expired.

Your application contains certifications to patents under section 505(b)(2)(A)(iv) of the Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of, this drug product under this application (“Paragraph IV certifications”).

Section 505(c)(3)(C) of the Act provides that approval of a new drug application submitted pursuant to section 505(b)(2) of the Act shall be made effective immediately, unless an action is brought for infringement of one or more of the patents that were the subject of the paragraph IV certifications. This action must be taken prior to the expiration of 45 days from the date the notice provided under section 505(b)(3) is received by the patent owner/approved application holder. You notified us that you complied with the requirements of section 505(b)(3) of the Act. However, because the 45-day period described in section 505(c)(3)(C) of the Act has not yet expired, final approval cannot be granted

2. Background

The Reference Listed Drug for this submission is Zometa® (zoledronic acid) Injection (NDA 21-223), single-use ready-to-use bottle and is currently marketed by Novartis. See CTDL review no. 1; no new information is provided.

Dosing Regimen and Administration

See CTDL review no. 1; no new information is provided.

3. Chemistry, Manufacturing and Controls (CMC)

General product quality considerations

The CMC reviewer (Dr. Li Shan Hsieh) recommended, in her review dated April 12, 2013, approval of this NDA after Office of Compliance issued an acceptable recommendation dated February 25, 2013.

CMC information for the Drug Substance and Drug Product remained the same as per CTDL review no. 1; no new information is provided.

ONDQA Biopharm review

See CTDL review no. 1; no new information is provided

Facilities review/inspection

Office of Compliance updated the status of the manufacturing sites, and an Overall Acceptable recommendation for the sites was issued on February 25, 2013

Microbiology

See CTDL review no. 1; no new information is provided.

4. Nonclinical Pharmacology/Toxicology

See CTDL review no. 1; no new information is provided.

5. Clinical Pharmacology

See CTDL review no. 1; no new information is provided.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

See CTDL review no. 1; no new information is provided

8. Safety

No new clinical data were provided for this submission.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics, Geriatrics, and Special Populations

Not applicable

11. Other Relevant Regulatory Issues

Application Integrity Policy (AIP): This application is not in the AIP list.

Exclusivity or patent issues of concern: Pediatric exclusivity determination – 2-MAR-2013.

Patent #7932241, expiration date of 5-FEB-2028

Financial disclosures: None submitted or needed

Other GCP issues: None

DSI audits: Not applicable

Other discipline consults: DDMAC/DMEPA/Micro/Biopharm/

Methods Validation: not required

Any other outstanding regulatory issues: None

12. Labeling

The labeling responses/revisions draft labeling (Package Insert {PI} for zoledronic acid injection) submitted by the sponsor were reviewed by Dr. Marybeth Toscano and the clinical reviewer Dr, Genevieve Schechter, who concluded the draft labeling is acceptable.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

This reviewer recommends a Tentative Approval Action for this NDA based on the patent issue discussed above.

Risk Benefit Assessment

The review of this NDA is based primarily on chemistry, manufacturing and controls data. All Chemistry, manufacturing and controls deficiencies are resolved including the status of manufacturing sites.

Recommendation for Postmarketing Risk Management Activities

None

Recommendation for other Postmarketing Study Commitments

None

Recommended Comments to Applicant

None

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/s/

ALI H AL HAKIM
07/03/2013