

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204016Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

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|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Date | (electronic stamp) |
| From | Geoffrey Kim, M.D. |
| Subject | Division Director Summary Review |
| NDA/BLA # | NDA 204016 |
| Supplement # | Class 1 Resubmission |
| Applicant Name | Hospira, Inc. |
| Date of Submission | November 2, 2015 |
| Proprietary Name / Established (USAN) Name | N/A Zoledronic Acid Injection |
| Dosage Forms / Strength | 4 mg/ 100 mL |
| Proposed Indication(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. |
| Action/Recommended Action | Approval |

The regulatory history for this application has been summarized in the CMC review as follows:

“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.”

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

As noted in the combined RPM and clinical review:

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

The review team recommends approval. I concur with the review team. There were no other outstanding issues that would preclude approval that have been identified from the other review disciplines.

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/s/

GEOFFREY S KIM
12/28/2015

Summary Memo for Regulatory Action

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|-------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Date | 7/3/2013 |
| From | Amna Ibrahim MD |
| Subject | Deputy Director Memo |
| NDA/BLA # | 204016 |
| Supplement # | Class 2 resubmission |
| Applicant Name | Hospira Inc. |
| Date of Submission | 1/8/2013 |
| PDUFA Goal Date | 7/8/2013 |
| Proprietary Name / Established (USAN) Name | None Zoledronic acid |
| Dosage Forms / Strength | Intravenous formulation/ 4 mg/100 mL |
| Proposed Indication(s) | 1. Hypercalcemia of malignancy 2. Treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors |
| Action for NME: | Tentative approval |

Zometa[®] (NDA 21223) is approved for hypercalcemia of malignancy and for patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Dosage is reduced for patients with renal impairment.

NDA 204016 for zoledronic acid was submitted using the 505(b)(2) pathway, relying on listed drug Zometa 4 mg/5 mL (NDA 21223). NDA 204016 received a CR letter from the FDA on 11/29/2012. This recommendation was based on a withhold recommendation for a Hospira Boulder facility from the Office of Compliance. There were no other issues noted by other disciplines, except for the patent exclusivity, as per Dr. Schechter (clinical reviewer). The reviewers from the following discipline recommended approval from their disciplines perspective: CMC, microbiology product quality, pharmacology/toxicology, and Clinical Pharmacology. A BA/BE waiver was granted. DSI audits were not conducted due to lack of new clinical studies. The DMEPA reviewer cleared the carton and container labeling. For details see reviews from the original submission.

The applicant responded with this class 2 resubmission on 1/8/2013. CMC reviewer Li-Shan Hsieh Ph.D. in her review dated April 11, 2013 states that Office of Compliance has issued an overall acceptable recommendation for this application dated February 5, 2013. OPDP reviewer, Marybeth Toscano, did not have any comments on the draft labeling. DMEPA reviewer, Jibril Abdus-Samad PharmD, finds the insert labeling acceptable.

However patent certification was not addressed adequately in this resubmission. A memorandum was sent from the FDA to Hospira, dated June 3, 2013. FDA concluded

that that Hospira must identify the 4 mg/5 mL presentation of Zometa as a listed drug and submit a certification with respect to the '241 patent. In this memo, it was stated that Agency "could have been more explicit and perhaps should have identified the need for Hospira to identify the 4 mg/100 mL presentation of Zometa as a listed drug and submit relevant patent certifications, this silence does not relieve Hospira of its obligation to identify the appropriate listed drug(s) upon which it relies and certify to relevant patents, including patents on any pharmaceutically equivalent drug products." The applicant provided an updated patent certification and an adequate proof of notification to the patent holder for the two paragraph IV certifications.

All the issues have been resolved from all disciplines. Also see CDTL Review by Ali Al-Hakim, Ph.D., who recommends a Tentative Approval. Clearance has been obtained from from the 505b2 perspective from OND-IO and from the patent perspective from ORP.

As stated in the action letter to the applicant, "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."

Recommendation:

This application will be granted a Tentative Approval.

Amna Ibrahim MD
Deputy Director
DOP1, OHOP

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/s/

AMNA IBRAHIM
07/03/2013

Summary Review for Regulatory Action

| | |
|-------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Date | 11/30/2012 |
| From | Amna Ibrahim MD |
| Subject | Deputy Director Summary Review |
| NDA/BLA # | 204016 |
| Supplement # | Original NDA |
| Applicant Name | Hospira Inc. |
| Date of Submission | 1/30/2012 |
| PDUFA Goal Date | 11/30/2012 |
| Proprietary Name / Established (USAN) Name | None Zoledronic acid |
| Dosage Forms / Strength | Intravenous formulation/ 4 mg/100 mL |
| Proposed Indication(s) | 1. Hypercalcemia of malignancy 2. Treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors |
| Action for NME: | Complete Response |

| Material Reviewed/Consulted | Names of discipline reviewers |
|------------------------------------|--------------------------------------|
| OND Action Package, including: | |
| Medical Officer Review | Genevieve Schechter |
| Pharmacology Toxicology Review | Wei Chen |
| CMC Review/OBP Review | Li-Shan Hsieh |
| Microbiology Review | Robert Mello |
| Clinical Pharmacology Review | Pengfei Song |
| CDTL Review | Nallaperum Chidambaram |
| OSE/DMEPA | Jibril Abdus-Samad |

OND=Office of New Drugs
DMEPA=Division of Medication Error Prevention and Analysis
CDTL=Cross-Discipline Team Leader

1. Introduction

Zometa[®] (NDA 21223) is approved for hypercalcemia of malignancy and for patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Dosage is reduced for patients with renal impairment. NDA 204016 for zoledronic acid has been submitted using the 505(b)(2) pathway, relying on listed drug Zometa 4 mg/5 mL (NDA 21223).

2. Background

The applicant's stated aim was to develop an alternative to the currently approved Zometa[®] product offering improved convenience by (b) (4).

In this NDA, the applicant submitted a paragraph III certification signed 10/31/2012, stating that Hospira certifies that it will not market the Zoledronic Acid Injection for which this application is submitted until after the expiry of U.S. Patent Nos. 4,939,130 and 7,932,241 including any pediatric extension thereof.

Due to a withhold recommendation for a Hospira Boulder facility from the Office of Compliance, a Complete Response action will be taken for this NDA. Please see review by CDTL Nallaperum Chidambaram PhD for details.

3. CMC/Device

Li-Shan Hsieh, Ph.D. in her review stated that "this New Drug Application for Zoledronic Acid Injection, 0.04 mg/mL (4 mg/100 mL) in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, is recommended for approval from the Chemistry, Manufacturing and Controls perspective, pending overall recommendation from the Office of Compliance and resolution of labeling issues." She also stated that based on the stability data, 24 months expiry has been granted when stored at controlled room temperature.

One review issue was that there was a lack of a safe method for dose modification for renal insufficiency. The applicant identified transfer devices (b) (4) could be used to withdraw the appropriate amount of solution. Per Haripada Sarkar, Ph.D., Zoledronic Acid Injection was shown to be compatible with the transfer devices, and it demonstrated acceptable stability for the in-use period of (b) (4).

Robert J Mello Ph.D. recommended approval from microbiology product quality standpoint. I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

According to a memo by Sarah Pope Miksinski PhD, dated 11/29/2012, an overall withhold recommendation was issued on 16-NOV-2012 from the Office of Compliance, which precludes an approval recommendation from a CMC standpoint. While all CMC deficiencies have been resolved, there is now a final overall withhold recommendation for the application. The application did not receive the required acceptable recommendation, and this needs to be resolved before a recommendation of approval can be made from a CMC standpoint.

4. Nonclinical Pharmacology/Toxicology

Per Wei Chen PhD, no nonclinical study reports were submitted or are needed to support approval at this time. No changes to the Reference Listed Drug's package insert were recommended in sections containing nonclinical data. There are no issues from the Pharmacology/Toxicology discipline that would preclude approval of this zoledronic acid product for the proposed indications.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology reviewer, Pengfei Song PhD noted that 'a no action is indicated' (NAI) recommendation for this application. He stated that no bioequivalent study or clinical study was submitted in this application and that the applicant was relying on the findings of safety and efficacy for Zometa to support the approval of their application. No clinical pharmacology issues were identified.

Karen Riviere PhD stated in her review that a BA/BE waiver was granted.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Dr Genevieve Schechter states in her review that no new clinical data was submitted for this NDA. The Zometa NDAs 021223 and NDA 021386 have been previously reviewed for efficacy and safety. She also states that from the clinical perspective, tentative approval is recommended due to the patent exclusivity for Zometa 4 mg/100 ml.

8. Safety

See above.

9. Advisory Committee Meeting

None

10. Pediatrics

Not applicable.

11. Other Relevant Regulatory Issues

- DSI Audits: not conducted. No new clinical studies were submitted to support this 505B2 NDA.
- Financial Disclosure. Not applicable
- DMEPA: Jibril Abdus-Samad, PharmD, stated in his review that “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.” He also stated that 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.
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12. Labeling

The labeling discussions had not been completed by the time of action on this NDA.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action
A complete Response action will be taken for this NDA.
- Risk Benefit Assessment

Per CDTL, “The review of this NDA is based primarily on chemistry, manufacturing and controls data. All Chemistry, manufacturing and controls deficiencies are resolved but the application has received an overall pending recommendation, and a withhold recommendation for the Hospira Boulder facility from the Office of Compliance. Therefore, this application cannot be recommended for approval until all the deficiencies related to the above manufacturing facility are satisfactorily addressed, and an overall

acceptable recommendation is received from the Office of Compliance.” In addition, there is now an overall recommendation of “withhold” for the NDA.

I concur with the CDTL’s recommendation of a Complete Response action.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
None.

- Recommendation for other Postmarketing Requirements and Commitments

None.

Amna Ibrahim MD
Deputy Division Director
Division of Oncology Products 1

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/s/

AMNA IBRAHIM

11/29/2012