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RESEARCH**

APPLICATION NUMBER:

204016Orig1s000

MEDICAL REVIEW(S)

Cross-Discipline Team Leader Review #1

DATE	15-NOV-2012
From	Nallaperumal Chidambaram, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	204016
Applicant	Hospira Inc.
Date of Submission	31-JAN-2012
PDUFA Goal Date	30-NOV-2012
Proprietary Name/ Established (USAN) names	Zoledronic Acid Injection
Dosage forms / Strength	4 mg/100 mL
Proposed Indication(s)	Multiple treatment of: <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
Intended Population	<ul style="list-style-type: none"> • (b) (4)
Recommendation:	<p>Complete response</p> <p>(1) Deficiencies related to manufacturing facility.</p> <p>(2) Resolution of minor labeling issues.</p>

1. Introduction

NDA 204016 was submitted in accordance with section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act to the Agency on 31-JAN-2012. This CDTL memo serves to summarize the critical issues noted in all review disciplines and recommends a “**complete response**” action for this application. All individual discipline reviews may be found in DARRTS.

2. Background

The Reference Listed Drug for this submission is Zometa® (zoledronic acid) Injection (NDA 21-233), single-use ready-to-use bottle and is currently marketed by Novartis. The proposed drug product is a sterile, single (b) (4) (b) (4) solution of zoledronic acid (b) (4) in a 100 mL single (b) (4).

The inactive ingredients in the proposed 100 mL (b)(4) bag contains 4.264 mg zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis, 900 mg of sodium chloride, USP, 220 mg of mannitol, USP, water for injection and 24 mg of sodium citrate, USP.

Dosing Regimen and Administration

The recommended dose of Zoledronic acid Injection is as follows:

Hypercalcemia of malignancy

- 4 mg as a single (b)(4) intravenous infusion over no less than 20 minutes
- 4 mg as retreatment after a minimum of 7 days

Multiple myeloma and bone metastasis from solid tumors

- 4 mg as a single (b)(4) intravenous infusion over no less than 20 minutes every 3 to 4 weeks for patients with creatinine clearance of greater than 60 mL/min.
- Reduce the dose for patients with renal impairment.
- Co-administer oral calcium supplements of 500 mg and a multiple vitamin containing 400 IU of Vitamin D daily.

3. CMC

NDA 204016 was submitted on 31-JAN-2012 as a 505(b)(2) application.

General product quality considerations

The CMC reviewer (Dr. Li Shan Hsieh) recommended approval pending overall acceptable recommendation from the Office of Compliance in her review #1 of this NDA dated 11-OCT-2012. In her Memo to file dated 15-NOV-2012, the reviewer noted that the Office of Compliance provided a **Withhold recommendation** to Hospira Boulder facility on 14-NOV-2012, and therefore she continues to recommend approval of this application pending overall acceptable recommendation from the Office of Compliance.

The drug substance is a (b)(4)

(b)(4)

(b)(4) a mutagen, therefore Pharmacology/Toxicology reviewer was consulted to evaluate safe limits for this mutagen. The Pharmacology reviewer (Dr. Wei Chen) opined that if no (b)(4) is observed, then the proposed limit of (b)(4) % is acceptable. Batch analysis data provided indicated either this residual solvent was either not detected or below limit of quantitation. However, this was detected at (b)(4) % in one batch.

Twenty four months of real-time long-term stability data was provided. Based on provided data, a (b) (4) month retest period is granted as proposed for the drug substance.

Zoledronic Acid Injection (4 mg/100 mL) is a sterile aqueous solution for intravenous (I.V.) administration. The drug product is a clear, colorless solution, free from visible particulates, available in 100 ml (b) (4) infusion bags. The bags are closed with a (b) (4) twist-off closure (b) (4). The composition of each 100 mL drug solution consists of the active ingredient Zoledronic Acid 4 mg (on an anhydrous basis), Mannitol 220 mg, Sodium Citrate 24 mg (b) (4) Sodium Chloride 900 mg in Water for Injection. The pH range is (b) (4). This is a (b) (4) product containing no antimicrobial preservatives.

Twelve months of real-time long-term and intermediate stability data, and six months of accelerated stability data were provided. Based on provided data, 24-month of shelf-life is granted as proposed for the drug product.

The proposed container system is a (b) (4) with a single port. However, in order to treat renally impaired patients, dose reduction is needed. The Agency recommended a (b) (4) can be used for infusion.

The applicant proposed a (b) (4) transfer device that is commonly available. The Agency requested that compatibility and in-use stability data be provided for the duration the drug product will be in contact with the sample transfer device(s) that are commonly available. In addition, the Agency also requested information that the applicant can gather about materials of construction for the transfer devices. The applicant provided requested data in an amendment dated 24-OCT-2012. This data was reviewed and found acceptable by the CMC lead (Dr. Haripada Sarker), refer to his review dated 02-NOV-2012.

ONDQA Biopharm review

The Biopharm reviewer (Dr. Kareen Riviere) noted in her review dated 10-SEP-2012 that the reference listed drug (RLD) for this submission is NDA 21-223, Zometa® (zoledronic acid) Injection. The RLD is a concentrate with 4 mg of zoledronic acid in a sterile, single-use 5 mL vial that is intended for use upon dilution with 100 mL of 0.9% Sodium Chloride, USP or 5% Dextrose, USP. The proposed drug product, Zoledronic Acid Injection, is a (b) (4) aqueous solution containing 4 mg of zoledronic acid in a sterile single (b) (4) inactive ingredients and in similar concentration to the reference listed drug.

The applicant requested a waiver of the *in vivo* BA/BE study requirements under 21 CFR §320.22 (b)(1)(i). The focus of this Biopharmaceutics review is on the evaluation and acceptability of the waiver request.

The reviewer noted that the proposed product meets the criteria as described under 21 CFR §320.22 (b)(1)(i) in that the drug product is a parenteral solution intended solely for administration by infusion. The active

ingredient of the proposed drug product is the same as that of the RLD. The proposed product (b) (4) inactive ingredients as that of the diluted RLD. The final concentration after dilution of the RLD with 100 mL of 0.9% sodium chloride, USP, is 0.04 mg/mL, which is similar to proposed concentration. Based on the above, a BA/BE waiver is granted for the proposed product.

Facilities review/inspection

The Office of Compliance issued a pending recommendation for this application but a **withhold** recommendation to Hospira Boulder facility on 14-NOV-2012.

Microbiology

The microbiology reviewer (Dr. R. Mello) identified no deficiencies based on the information provided in the application and had recommended approval of this NDA in his review dated 04-OCT-2012.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer (Dr. W. Chen) in her review dated 17-OCT-2012 noted that no nonclinical studies were submitted and none are needed to support the approval of zoledronic acid injection. In addition, no changes to RLD's package insert were proposed and none recommended.

5. Clinical Pharmacology

The Clinical Pharmacology reviewer (Dr. Pengfei Song) noted a no action is indicated (NAI) recommendation for this application (refer to his NAI dated 17-OCT-2012). The reviewer further noted 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. Consequently, no clinical pharmacology issues were identified.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The clinical reviewer (Dr. Genevieve Schechter) in her review dated 01-NOV-2012 indicated that no new clinical data were submitted in support of this application and that this application relies on the clinical studies of safety and efficacy used in support of the reference listed product Zometa (N21-223 & N21-386). NDA 021386 was a Type 6 NDA submitted for the use of Zometa in multiple myeloma and in patients with document bone metastases in solid tumors in conjunction with standard antineoplastic therapy. After Type 6 NDAs were abolished, the

approved indication was merged into NDA 021223. Based on the above, the medical reviewer recommends tentative approval for the indications noted above.

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

The DMEPA reviewer (Dr. Jibril Abdus-Samad) in his review dated 31-OCT-2012 recommended changes to container and carton labeling. The applicant provided their responses on 14-NOV-2012. The DMEPA reviewer in his review dated 15-NOV-2012 found the responses to carton and container labeling acceptable but labeling negotiations for the insert labeling are ongoing.

Any other outstanding regulatory issues: None

12. Labeling

All issues were satisfactorily resolved except for package insert. Please refer to DEMPAs review (Dr. Jibril Abdus Samad) dated 15-NOV-2012.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

This reviewer recommends **complete response** for this NDA

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 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.

Recommendation for Postmarketing Risk Management Activities

This does not apply to this NDA.

Recommendation for other Postmarketing Study Commitments

None

Recommended Comments to Applicant

Based on provided stability data, a 24-month expiration dating period can be granted when an approval action is taken for Zoledronic acid injection 4 mg/100 mL in the proposed container closure system and when stored (b) (4) 30°C (b) (4) 36°F).

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/s/

NALLAPERUM CHIDAMBARAM
11/15/2012

CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Submission Number	204016
Submission Code	000
Letter Date	01/31/2012
Stamp Date	01/31/2012
PDUFA Goal Date	11/30/2012
Reviewer Name	Genevieve A. Schechter, MD
Clinical Team Leader	Amy McKee, MD
Review Completion Date	10/31/2012
Established Name	zoledronic acid
Trade Name	Zoledronic Acid Injection
Reference NDA	021223
Therapeutic Class	Bisphosphonate
Applicant	Hospira, INC
Priority Designation	S
Formulation	IV
Dosing Regimen	4 mg single (b) (4) IV infusion
Indications	Hypercalcemia of malignancy For 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
Intended Population	(b) (4)

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1.0 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This NDA for zoledronic acid injection, in accordance with section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, was submitted to request approval of therapeutic equivalence of the proposed product to Zometa as defined in the FDA orange book. The sponsor of NDA 021223 for Zometa is Novartis. Zometa is indicated for:

- 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 (1.2)

Important limitation of use: The safety and efficacy of zoledronic acid has not been established for use in hyperparathyroidism or nontumor-related hypercalcemia (1.3)

The patent exclusivity for the indication for use in management of the hypercalcemia of malignancy has expired. No patent existed for the use in multiple myeloma or hypercalcemia of malignancy.

No new clinical data was submitted for this NDA. The Zometa NDAs 021223 and NDA 021386 have been previously reviewed for efficacy and safety. NDA 021386 was a Type 6 NDA submitted for the use of Zometa in multiple myeloma and in patients with documented bone metastases in solid tumors in conjunction with standard antineoplastic therapy. After Type 6 NDAs were abolished, the approved indication was merged into NDA 021223, the original NDA for Zometa®. From the clinical perspective, tentative approval is recommended due to the patent exclusivity for Zometa 4 mg/100 ml.

1.2 Risk Benefit Assessment

Please refer to clinical reviews from NDA 021223 and NDA 021386.

2.0 Introduction and Regulatory Background

2.1 Product Information

Established Name: Zoledronic acid

Proprietary Name: Zoledronic Acid Injection

Applicant: Hospira Inc.
275 N. Field Drive
Dept. 0389 Bldg H2/2

Lake Forest, IL 60045-5046

Drug Class: Bisphosphonate

Proposed Indications:

- 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

Important limitation of use: The safety and efficacy of zoledronic acid has not been established for use in hyperparathyroidism or nontumor-related hypercalcemia.

Proposed Dosage and Administration

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

Multiple myeloma and bone metastasis from solid tumors

- 4 mg as a single (b) (4) intravenous infusion over no less than 15 minutes every 3-4 weeks for patients with creatinine clearance of greater than 60 mL/min
- Reduce the dose for patients with renal impairment
- Coadminister oral calcium supplements of 500 mg and a multiple vitamin containing 400 IU of Vitamin D daily.

Administer through a separate infusion line and do not allow to come in contact with any calcium or divalent cation-containing solutions

Dosage Forms and Strengths

- 4 mg/100 ml single (b) (4)

Contraindications

- Hypersensitivity to any component of Zoledronic Acid Injection

Warnings and Precautions

- Patients being treated with Zoledronic Acid Injection should not be treated with Reclast®
- Adequately rehydrate patients with hypercalcemia of malignancy prior to administration of Zoledronic Acid Injection and monitor electrolytes during treatment
- Renal toxicity may be greater in patients with renal impairment. Do not use doses greater than 4 mg. Treatment in patients with severe renal impairment is not recommended. Monitor serum creatinine before each dose
- Osteonecrosis of the jaw has been reported. Preventive dental exams should be performed before starting Zoledronic Acid Injection. Avoid invasive dental procedures

- Severe incapacitating bone, joint, muscle pain may occur. Discontinue Zoledronic Acid Injection if severe symptoms occur
- Zoledronic Acid Injection can cause fetal harm. Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant

Adverse Reactions

The most common adverse events (greater than 25%) were nausea, fatigue, anemia, bone pain, constipation, fever, vomiting, and dyspnea

2.2 Availability of Proposed Active Ingredient in the United States

Zometa (Zoledronic acid) is available for marketed in the US.

2.3 Summary of Presubmission Regulatory Activity Related to Submission

NDA 021223 was approved on 08/20/2001.

NDA 021386 (Type 6) was approved on 02/22/2002.

NDA 204016 was submitted on 01/31/2012.

2.4 Pediatric Studies

Hospira has requested and been granted a waiver for pediatric studies as this application does not introduce a new ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. Pediatric data is not warranted per 21CFR 314.55.

2.5 Other Relevant Background Information

For this submission Hospira is relying on the patent information for the Zometa 4 mg/ 5 ml preparation. The Orange Book provides the following information regarding patent exclusivity for the 4 mg/5 ml formulation (identified as Product 002 in the Orange Book) as shown in Table 1.

Table 1: Patent Information for Zometa 4mg/5 ml Formulation

NDA	Product	Patent No.	Patent Expiration	Drug Substance Claim	Drug Product Claim	21 CFR Reference
N021223	002	4939130	09/02/2012	Y	Y	314.54(a)(1)(vi)
N021223	002	4939130*Pen	03/02/2013			

NDA 021223/S-020 for Zometa 4mg/100mL formulation (Product 003) was approved on 06/17/2011. The Orange Book provides the following information regarding patent exclusivity for Zometa 4mg/100ml (identified as Product 003) as shown in Table 2. Hospira has not referenced information for this formulation in their original submission. In response to an FDA

information request on 10/24/2012, Hospira responded on 10/31/2012 that they would also rely also on the patent certification for Zometa 4mg/100 mL preparation.

Table 2: Patent Information for Zometa 4mg/100ml Formulation

NDA	Product	Patent No.	Patent Expiration	Drug Substance Claim	Drug Product Claim	21 CFR Reference
N021223	003	4939130	09/02/2012	Y	Y	314.54(a)(1)(vi)
N021223	003	4939130*Pen	03/02/2013			
N021223	003	7932241	02/05/2028	Y	Y	-

The Orange Book also lists as discontinued the Zometa 4 mg base/vial formulation (identified as Product 001 in the Orange Book). This was the original formulation approved on 08/20/2001. Sale of this formulation was discontinued by Novartis after a Federal Register Notice on 04/14/2009 noted that the product was not withdrawn from sale for reasons of safety or efficacy. No unexpired patent exclusivity was identified for the Zometa 4 mg base/vial formulation.

3.0 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Please refer to NDA 021223 CMC, Pharmacology/Toxicology, and Clinical Pharmacology reviews.

During the review, OSE/DMEPA raised concern about the safety of the use of an infusion bag containing 4 mg/100 mL in patients with reduced creatinine clearance. The infusion bag proposed for use has only one port designed to allow only one puncture. As noted in the Dosage and Administration section of Zometa's label, patients with creatinine clearance less than 60 mL/min should receive a reduced dose. No volume could be removed to prevent overdose with this product in patients with reduced creatinine clearance, which presents a problem since (b) (4) could potentially result in overdose in patients with reduced creatinine clearance. Hospira proposed use of a transfer device to remove excess volume in the bag and demonstrated chemical compatibility and in-use stability data for the drug product with three different transfer devices.

To ensure patient safety during administration the following information regarding the transfer device was added to the label:

To prepare reduced doses for patients with baseline CrCl less than or equal to 60 mL/min, withdraw the specified volume of zoledronic acid injection from the (b) (4) (see Table 2) using an intravenous bag transfer device. (b) (4)

Follow the transfer device manufacturer's instructions (b) (4)

4.0 Sources of Clinical Data

Refer to NDA 021233 and NDA 021386.

5.0 Review of Efficacy

Refer to NDA 021223 and NDA 021386

6.0 Review of Safety

Refer to NDA 021223 and NDA021386. See labeling change in Section 3.0

7.0 Appendices

7.1 Literature Review/References

Refer to NDA 021223.

7.2 Labeling Recommendations

See final label.

7.3 Advisory Committee Meeting

None

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/s/

GENEVIEVE A SCHECHTER
11/01/2012

AMY E MCKEE
11/02/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

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

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

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Requests waiver
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? NA

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

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

Reviewing Medical Officer Date

Clinical Team Leader Date

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/s/

GENEVIEVE A SCHECHTER
03/05/2012

YANGMIN NING
03/05/2012