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RESEARCH**

APPLICATION NUMBER:

203231Orig1s000

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

Clinical Pharmacology Review

NDA 203231
Submission Date: 09 January 2012
Generic Name: Zoledronic Acid
Formulation: Zoledronic Acid Injection for IV infusion, 4 mg/100 mL
Reference Listed Drug: Zometa[®] 4 mg/5 mL in a single-dose vials, concentrate for intravenous infusion, under NDA21223 (Approved in 2003)
OCP Reviewer: Pengfei Song, Ph.D.
OCP Acting Team Leader: Qi Liu, Ph.D.
OCP Division: Division of Clinical Pharmacology 5
ORM Division: Division of Oncology Products 1
Sponsor: Sagent Pharmaceuticals, Inc.
Submission Type; Code: 505 (b) (2); Original-1 (Type 5- New Formulation or New Manufacturer)
Dosing regimen: 4 mg/15 minutes infusion Q28 days
Indications:

- Hypercalcemia of malignancy
- Multiple myeloma and bone metastases from solid tumors, in conjunction with standard antineoplastic therapy.

1 EXECUTIVE SUMMARY

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

There is no bioequivalent study nor clinical study submitted in this application. The Applicant is relying on the findings of safety and effectiveness for Zometa[®] to support the approval of the proposed product. The only clinical pharmacology related issue is that drug interaction information with thalidomide should be consistent with the latest labeling language of the RLD.

1.1 RECOMMENDATIONS

This NDA is acceptable from a clinical pharmacology perspective, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the labeling language.

Signatures:

Pengfei Song, Ph.D. Reviewer Division of Clinical Pharmacology 5		Qi Liu, Ph.D. Team Leader Division of Clinical Pharmacology 5
Cc:	DOP1:	CSO - Kim Robertson; MTL - Yangmin (Max) Ning; MO - Kim Geoffery;
	DCP-5:	DDD - Brian Booth; DD - Nam Atiqur Rahman

1.2 DETAILED LABELING INFORMATION

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

<i>PROPOSED LABELING</i>	<i>AGENCY'S SUGGESTIONS</i>
HIGHLIGHTS OF PRESCRIBING INFORMATION	
-----DRUG INTERACTIONS-----	
<p>Aminoglycosides: May have an additive effect to lower serum calcium for prolonged periods (7.1)</p> <p>Loop diuretics: Concomitant use with Zoledronic Acid Injection may increase risk of hypocalcemia (7.2)</p> <p>Nephrotoxic drugs: Use with caution (7.3)</p> <p> (b) (4)</p>	<p>Aminoglycosides: May have an additive effect to lower serum calcium for prolonged periods (7.1)</p> <p>Loop diuretics: Concomitant use with Zoledronic Acid Injection may increase risk of hypocalcemia (7.2)</p> <p>Nephrotoxic drugs: Use with caution (7.3)</p>
7.4 THALIDOMIDE	
<p> (b) (4)</p>	<p><u>No dose adjustment for Zoledronic Acid Injection 4 mg is needed when co-administered with thalidomide. In a pharmacokinetic study of 24 patients with multiple myeloma, Zoledronic acid 4 mg given as a 15 minute infusion was administered either alone or with thalidomide (100 mg once daily on days 1-14 and 200 mg once daily on days 15-28). Coadministration of thalidomide with Zometa did not significantly change the pharmacokinetics of zoledronic acid or creatinine clearance.</u></p>

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/s/

PENGFEI SONG
09/17/2012

QI LIU
09/19/2012

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	203-231
Submission Date:	01/06/2012
Brand Name:	N/A
Generic Name:	Zelodronic Acid Injection
Formulation:	Injection
Strength:	4 mg/100 mL
Applicant:	ACS DOBFAR INFO SA
Type of submission:	Original NDA, 505(b)(2), Standard Review
Reviewer:	Zedong Dong, Ph.D.

SUBMISSION:

NDA 203-231 was initially submitted on 08/29/2011 under FDC 505(b)(2) category for zelodronic acid injection (4 mg/100 mL) in reference to Zometa Injection (4 mg/5 mL) as approved in NDA 21-223 on 03/07/2003. Due to CMC issues, an RFT action was taken on this NDA. On 01/06/2012, the NDA was re-submitted with updated stability data. It is noted that before the initial submission of NDA 203-231, Orange Book listed the recently approved Zometa Injection (4 mg/100 mL) as a new RLD, however, the applicant states that they are using the currently approved 4 mg/5 mL strength as the RLD. The applicant requested a waiver of evidence for *in vivo* BA/BE as per 21 CFR §320.22 (b)(1)(i) & (ii).

BIOPHARMACEUTICS REVIEW:

The applicant provided the comparison of the components and compositions of Zometa Injection both concentrate (4 mg/5 mL) and diluted drug product in 100 mL 0.9% Sodium Chloride, USP) and zelodronic acid injection (see Table below).

Name of Ingredients	Zoledronic Acid Injection 4mg/100ml Ready-to-Infuse Solution	Zometa® Injection Concentrate for Intravenous Infusion	Zometa® Injection Diluted for Administration
Active Substance(s)	Content (mg/ml)		
Zoledronic Acid	0.04	(b) (4)	0.04
(as monohydrate form)	0.04264		0.04264
Excipient(s)			
Sodium Chloride (USP)	9.0		(b) (4)
Mannitol (USP)	2.2		2.2
Sodium Citrate (as anhydrous basis) (USP)			(b) (4)
			(b) (4)

As shown in the above table provided by the applicant, it appears that the proposed zelodronic acid injection has the same active and inactive ingredients as well as the same

concentrations as the diluted RLD. In the formulation, sodium chloride and mannitol are used for [REDACTED] (b) (4), and sodium citrate is used for pH adjustment.

All excipients fall below the FDA Inactive Ingredient Guide (IIG) limits for intravenous administration (see table below).

Component	Amount per bag	IIG levels
Sodium Chloride	0.90 %	90.0 %
Mannitol	[REDACTED]	(b) (4)
Sodium Citrate Dihydrate	[REDACTED]	[REDACTED]

The 4 mg/5 mL RLD concentrated solution is diluted in 100 mL of sterile 0.9% Sodium Chloride, USP or 5% Dextrose Injection, USP prior to use. Due to the slightly larger volume of the diluted RLD than the proposed zelodronic acid injection, there is slight but insignificant difference in the concentrations of the active and inactive ingredients. However, this is considered as low risk and it is unlikely to affect the bioavailability and bioequivalence of the proposed zelodronic acid injection in reference to the diluted Zometa Injection Concentrate (4 mg/5 mL). Therefore, a waiver of bioavailability or bioequivalence studies is appropriate for the proposed zelodronic acid injection in this NDA.

RECOMMENDATION

The Applicant's request for a waiver of the CFR requirement to provide in vivo bioequivalence data to support the approval of their proposed product under NDA 203-231 is acceptable and the biowaiver for Zelodronic Acid Injection is granted.

From the Biopharmaceutics viewpoint, NDA 201-231 for Zelodronic Acid Injection is recommended for approval.

Zedong Dong, Ph.D.
Reviewer
ONDQA Biopharmaceutics

Date

Angelica Dorantes, Ph.D.
Supervisory Lead
ONDQA Biopharmaceutics

Date

CC: NDA 203-231/DARRTS
Zedong Dong, Deborah Mesmer

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/s/

ZEDONG DONG
04/02/2012

ANGELICA DORANTES
04/02/2012

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

NDA Number	203231	Brand Name	XXX®
DCP Division (I, II, III, IV, V)	V	Generic Name	Zoledronic Acid Injection for IV infusion, 4mg/100mL
Medical Division	Oncology	Drug Class	Bisphosphonate
Submission Type	505 b 2	RLD	Zometa® 4 mg/5 mL in a single-dose vials, concentrate for intravenous infusion, under NDA21223 (Approved in 2003)
OCP Reviewer	Pengfei Song, Ph.D.	Indication(s)	<ul style="list-style-type: none"> Hypercalcemia of malignancy Multiple myeloma and bone metastases from solid tumors
OCP Team Leader	Qi Liu, Ph.D.	Dosage Form / Strengths	4 mg in a single-use 100 mL bag
Sponsor	Sagent Pharmaceuticals, Inc.	Dosing Regimen	Hypercalcemia of malignancy <ul style="list-style-type: none"> 4 mg as a single-dose intravenous infusion over no less than 15 minutes 4 mg as retreatment after a minimum of 7 days Multiple myeloma and bone metastasis from solid tumors <ul style="list-style-type: none"> 4 mg as a single-dose intravenous infusion over no less than 15 minutes every 3-4 weeks for patients with creatinine clearance of > 60 mL/min
Date of Resubmission	01/09/2012	Route of Administration	Intravenous injection
PDUFA Due Date	11/09/2012	Priority Classification	Standard review

Clinical Pharmacology Information

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

Subpopulation studies -				
Body size				
Gender:				
Geriatrics:				
Renal Impairment:				
Race/Ethnicity:				
Hepatic Impairment:				
Pediatrics:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
QT_c studies				
In-Vitro Release BE				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		0		
Filability and QBR comments				
	X" if yes	Comments		
Application Filable	X			
Comments sent to firm				
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date		Pengfei Song, Ph D. 2/17/2012		
Secondary reviewer Signature and Date		Qi Liu, Ph.D. 2/17/2012		

CC:

HFD-150 (CSO –Kim Robertson; MTL –Patricia Cortazar; MO – Geoffrey Kim)

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

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/s/

PENGFEI SONG
03/08/2012

QI LIU
03/08/2012

ONDQA BIOPHARMACEUTICS FILING REVIEW

NDA#:	203-231
Submission Date:	01/06/2012
Brand Name:	N/A
Generic Name:	Zelodronic Acid Injection
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Strength:	4 mg/100 mL
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Reviewer:	Zedong Dong, Ph.D.

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Mannitol (USP)	2.2		2.2
Sodium Citrate (as anhydrous basis) (USP)			(b) (4)
			(b) (4)

The applicant also submitted information that all excipients fall below the FDA Inactive Ingredient Guide (IIG) limits for intravenous administration (see table below).

Component	Amount per bag	IIG levels
Sodium Chloride	0.90 %	90.0 %
Mannitol	(b) (4)	
Sodium Citrate Dihydrate		

With the above submitted information, the NDA is deemed fileable from Biopharmaceutics perspective.

REVIEWER COMMENT

N/A

RECOMMENDATION

NDA 203-231 for Zelodronic Acid Injection (4 mg/100 mL) is fileable from Biopharmaceutics perspective.

 Zedong Dong, Ph.D.
 Reviewer
 ONDQA Biopharmaceutics

 Date

 Angelica Dorantes, Ph.D.
 Supervisory Lead
 ONDQA Biopharmaceutics

 Date

CC: NDA 203-231
 Zedong Dong, Angelica Dorantes, Deborah Mesmer

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/s/

ZEDONG DONG
02/22/2012

ANGELICA DORANTES
02/22/2012