

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203231Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Summary Review #3

Date	July 31, 2013
From	Ali Al-Hakim, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA #	203231
Applicant	ACS Dobfar Info. S.A.
Date of Submission	January 06, 2013
PDUFA Goal Date	
Proprietary Name / Established Name	N/A Zoledronic Acid Injection
Dosage forms / Strength	4 mg/100 mL
Proposed Indication(s)	Multiple treatment of: 1. Hypercalcemia of Malignancy 2. 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
Recommended	Approval

1. Introduction

NDA 203231 (**Zoledronic Acid**) was submitted in accordance with section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act to the Agency on August 30, 2011.

The original CTDL recommendation for the NDA was an **Approval** action as indicated in CTDL review no. 2 by Dr. Nallaperumal Chidambaram dated November 05, 2012. However, the approval recommendation was revised to **Complete Response (CR)** by the CMC reviewer, Dr. Joyce Crich; see **addendum to CMC Review # 2** dated February 11, 2013. The CR was based on unsatisfactory results of methods validation studies performed by FDA's Division of Pharmaceutical Analysis (DPA), St. Louis, MO.

Therefore, this CTDL(review no. 3) 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. 2).

Method Validation

The Complete Response letter sent to the sponsor sent on March 01, 2013 contains 3 CMC deficiencies related to methods validation, specifically HPLC methods for assay, unknown impurities and known impurities. However, CMC review #3 indicated these deficiencies were addressed satisfactorily in the resubmission (amendments 29, 30, 32-33) submitted by the sponsor.

Response to deficiency # 1 was evaluated and found acceptable because the sponsor modified injection volume for the HPLC method, modified the placebo solution and adjusted the pH of the mobile phase. All these modifications mentioned above successfully addressed the deficiencies

Response to deficiency # 2 was evaluated and found acceptable because the applicant did extensive investigational work to identify the source of this peak and to characterize the unknown impurity identified by FDA's St. Louis lab. As stated in the response, this unknown peak is not from an unknown impurity, but a (b) (4) the API, Zoledronic Acid (b) (4) used in the mobile phase of the HPLC methods for Assay and for unknown impurities.

Response to deficiency # 3 was evaluated and found acceptable because the applicant corrected errors identified in the Method Validation Report by FDA's St. Louis Lab for HPLC Method for Known Impurities (SAGENT Pharmaceuticals, Inc., Method ID: MCP429.USP-8.1) and updated Modules 3.2.P.5.2 Analytical Procedures and 3.2.P.5.3 Validation of HPLC Method for Known Impurities.

Since the Complete Response letter was issued by the Agency on 01-MAR-2013, St. Louis Lab did additional method validation to further verify the deficiencies and wrote corresponding summaries of this work. These summaries were entered in DARRTS dated 17-APR-2013, 24-MAY-2013 and June 24, 2013 (Note that the 24-JUN-2013 document is dated 25-MAR-2013, however, it was entered in DARRTS on 24-JUN-2013). ONDQA CMC reviewer, Dr. Joyce Crich, reviewed and assessed the applicant's amendments No. 28, 29, 32 and 33 as well as St. Louis validation summaries. Dr. Crich concluded, in CMC review # 3, that the responses to the 3 deficiencies outlined in the CR letter were adequately addressed by the applicant.

Therefore, all issues related to methods validation have been resolved and the NDA is recommended for approval.

This CDTL memo serves to summarize the critical issues noted in all review disciplines and recommends an "approval" 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 21-223), single-use ready-to-use bottle and is currently marketed by Novartis. 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, ready-to-infuse solution of zoledronic acid (4 mg/100 mL of 0.9% NaCl solution) in a 100 mL flexible (b) (4) infusion bags equipped with one (b) (4)

(b) (4) tube and twist off port (b) (4)
, which are placed in aluminum over-pouches.

Dosing Regimen and Administration

See CTDL review no. 2; no new information is provided.

3. Chemistry, Manufacturing and Controls (CMC)

General product quality considerations

The methods validations were conducted by FDA St. Louis Laboratory. Dr. Joyce Crich reported in her CMC review 3 that the method validations were acceptable. See related discussion above.

ONDQA Biopharm review

See CTDL review no. 2; 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 02, 2012

Microbiology

See CTDL review no. 2; no new information is provided.

4. Nonclinical Pharmacology/Toxicology

See CTDL review no. 2; no new information is provided.

5. Clinical Pharmacology

See CTDL review no. 2; no new information is provided.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

See CTDL review no. 2; 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: None

Financial disclosures: None submitted or needed

Other GCP issues: None

DSI audits: Not applicable

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

Methods Validation: See discussion above

Any other outstanding regulatory issues: None

12. Labeling

See CTDL review no. 2; no new information is provided

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

This reviewer recommends Approval of 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 including the status of manufacturing sites.

Recommendation for Postmarketing Risk Management Activities

None

Recommendation for other Postmarketing Study Commitments

None

Recommended Comments to Applicant

Based on provided stability data, a 24-month expiration dating period is granted for Zoledronic acid injection 4 mg/100 mL in the proposed container closure system and when stored at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

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/s/

ALI H AL HAKIM
07/31/2013