CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-386
21-223/S-003

CHEMISTRY REVIEW(S)

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CHEMISTRY REVIEW

NDA 21-386

Zometa

Norvatis Pharmaceuticals Corporation

Yung-Ao Hsieh, Ph.D.

Division of Oncology Drug Products

Chemistry Review Data Sheet

1. NDA 21-386

2. REVIEW No.: 1

3. REVIEW DATE: 28-Nov-01

4. REVIEWER: Yung-Ao Hsieh, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSIONS BEING REVIEWED:

Submissions Reviewed	Document date
NDA 21-386	21-Aug-01
NDA 21-386 (BC)	19-Sep-01
NDA 21-386 (BL)	21-Nov-01

7. NAME & ADDRESS OF APPLICANT:

Name: Norvatis Pharmaceuticals Corporation

Address: 59 Route 10, East Hanover, NJ 07936-1080

Representative: Eileen A. Ryan, Associate Director, Drug Regulatory Affairs

Telephone: 973-781-7661

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Zometa
Non- Proprietary Name (USAN): Zoledronic Acid for injection
Chem. Type/Submission Priority:
- Chem. Type: biphosphonic acid
- Submission Priority: 1P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: a bone resorption inhibitor

11. DOSAGE FORM: sterile, lyophilized powder

12.STRENGTH/POTENCT: 4 mg

13.ROUTE OF ADMINISTRATION: intravenous infusion

14.Rx/OTC DISPENSED: _x_ Rx ___ OTC

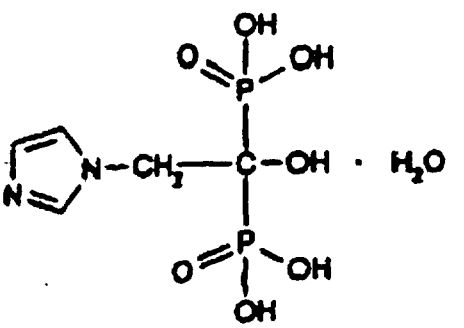
15.SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

___SPOTS products – Form Completed

_x_ Not a SPOTS product

16.CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

IUPAC Name: (1-Hydroxy-2-imidazol-1-yl-phosphonoethyl)phosphonic acid monohydrate
Other Name: 1-Hydroxy-2-(imidazol-1-yl)-ethylidene-1,1-bis phosphonic acid monohydrate
CAS Name: [1-Hydroxy-2-(1H-imidazol-1-yl)- ethylidene] bis phosphonic acid monohydrate
STRUCTURAL FORMULA:
MOLECULAR FORMULA: $C_5H_{10}N_2O_7P_2 \bullet H\,O$
MOLECULAR WEIGHT: 290.11



17.RELATED SUPPORTING DOCUMENTS: N/A

18.CONSULT STATUS: N/A

The Chemistry Review for NDA 21-386

The Executive Summary

I. Recommendations:

The application is recommended for approval from a chemistry point of view.

II. Summary of Chemistry Assessments:

A. Description of the Drug Product and Drug Substance:

The drug product is a sterile, lyophilized powder for reconstitution for intravenous infusion. Zometa contains zoledronic acid (4 mg), mannitol and sodium citrate. The drug substance, zoledronic acid is obtained by chemical synthesis. It is a biphosphonic acid derivative and a potent inhibitor of osteoclastic bone resorption. Zoledronic acid presents in the drug product in the form of a monohydrate. The drug product can be stored at 25°C/60% RH. An expiration dating of two years has been granted.

B. Description of How the Drug Product is Intended to be Used

Zometa is indicated for the treatment of hypercalcemia of malingancy and for the treatment of osteolytic, osteoblastic and mixed bone metastases of solid tumors and osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy.

C. Basis for Approvability Recommendation

NDA 21-386, was submitted as a Type 6 NDA, describing clinical trials with Zometa in the treatment of cancer patients with bone metastases. The CMC section of this NDA, including CMC data and information on the manufacture, control and release of the zoledronic acid drug substance and drug product, is cross-referenced to the original Zometa NDA 21-223, which was approved by the Division of Metabolic and Endocrine Products (HFD-510) for the treatment of hypercalcemia of maligancy.

This review covers the environment assessment information and labeling and package insert submitted in NDA 21-386. The Claim for Categorical Exclusion from the Environmental Assessment, submitted in the amendment [NDA 21-386 (BC), dated 19-Sep-01], was found acceptable. The samples of vial and carton labels and draft package insert submitted indicated that they are adequate for their intended use. Additionally, the CGMP compliance status of the manufacturing and testing facilities for both the drug substance and drug product is acceptable.

Based on the above observations, it is concluded that satisfactory CMC information has been provided for this NDA. Approval is recommended.

III. Administrative

A. Reviewer's Signature

Review Chemist, HFD-150
Yung-Ao Hsieh, Ph.D.

B. Endorsement Block

Y. A. Hsieh, Review Chemist:
R. H. Wood, Chemistry Team Leader:
D. Vause, Project Manager:

C. CC Block

Original NDA 21-386
HFD-150 Div. File
HFD-150/YAHsieh
HFD-150/RHWood
HFD-150/ DVause

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

2 pages