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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:

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<td>NDA 21-386 (BL)</td>
<td>21-Nov-01</td>
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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/POTENCY: 4 mg

13. ROUTE OF ADMINISTRATION: intravenous infusion

14. Rx/OTC DISPENSED: __Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
   ___ SPOTS products – Form Completed
   ___ 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)-ethyldene-1,1-bis phosphonic acid monohydrate
   CAS Name: [1-Hydroxy-2-(1H-imidazol-1-yl)- ethyldene] bis phosphonic acid monohydrate
   STRUCTURAL FORMULA:
   MOLECULAR FORMULA: C₈H₁₀N₂O₇P₂ • H₂O
   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 malignancy 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 malignancy.

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