CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-223

CHEMISTRY REVIEW(S)

DIVISION OF Metabolism and Endocrine DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 21-223 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 9-11-00

SUBMISSION TYPE	DOCUMENT DATE	CDER Date	ASSIGNED DATE
NDA (Original)	12-21-99	12-21-99	12-23-99
Amendment	2-2-00	2-3-00	2-4-00
Amendment	3-21-00	3-22-00	3-24-00
Amendment	4-14-00	4-17-00	4-19-00
Amendment	4-20-00	4-25-00	4-26-00
Amendment	5-10-00	5-12-00	5-15-00
Amendment	5-17-00	5-18-00	5-19-00
Amendment	6-2-00	6-5-00	6-7-00

NAME & ADDRESS OF APPLICANT:
Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME:
Proprietary: Zometa
Nonproprietary: Zoledronic acid for injection
Chem. type/Ther. Class: 1P

PHARMACOL.CATEGORY/INDICATION:
Treatment of tumor induced hypercalcemia

DOSAGE FORMS:
Lyophilized powder in — vials, to be diluted

STRENGTHS: 4 mg

ROUTE OF ADMINISTRATION: I.V.

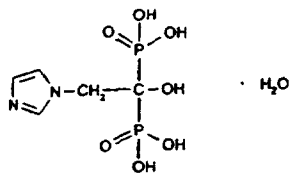
DISPENSED: _X_ Rx __ OTC

SPECIAL PRODUCTS: ____Yes _X_ No
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

APPEARS THIS WAY
ON ORIGINAL

CHEMICAL NAMES, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

IUPAC name: (1-hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate
Other name: 1-Hydroxy-2-(imidazol-1-yl)-ethylidene-1,1-bisphosphonic acid monohydrate
CAS name: [1-Hydroxy-2-(1H-imidazol-1-yl)-ethylidene]bisphosphonic acid monohydrate



Molecular weight: 290.11 $C_5H_{10}N_2O_7P_2 \cdot H_2O$ CAS # 165 800-06-6

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date
DMF	[redacted]	[redacted]	Adequate	5-23-00, 4-2-97

RELATED DOCUMENTS: IND [redacted]

CONSULTS: Microbiology

REMARKS/COMMENTS:

ZOMETA™ is a product of zoledronic acid monohydrate [redacted]/zoledronate, a bisphosphonic acid, which is a potent inhibitor of osteoclastic bone resorption. The proprietary name "Zometa" was found acceptable by the Office of Post-Marketing Drug Risk Assessment (OPDRA). This Review for Zometa (Zoledronic acid for injection) covers the original submission, dated 12-21-99, which was given a Priority Review Status. The User Fee Due Date was extended to 9-21-00 because of the submission of a major amendment in the clinical area. This Review also covers the amendments , which are described below:

The amendment, dated 2-2-00, provided additional information on Manufacturing, Packaging and Control facilities. Updated stability information was submitted in the 3-21-00 and 4-20-00 amendments. The amendment, dated 4-14-00, revised the vial label. Clarification of a test method, used to monitor the stability of the drug substance, was provided in the 5-10-00 amendment. Responses to Microbiology deficiencies, noted in Microbiology Review #1, were provided in the amendment dated 5-17-00. [Microbiology Review #2 deemed these responses satisfactory and recommended approval on the basis of sterility assurance.] Finally, responses to the chemistry deficiencies communicated in a Facsimile Transmission (FAX) to the applicant (attached to hard copy), dated 5-25-00, were provided in the 6-2-00 amendment.

The cGMP compliance status for this NDA is acceptable. (See attachment to hard copy.)

CONCLUSIONS & RECOMMENDATIONS:

Satisfactory CMC information has been provided, and the application is approvable from a Chemistry point of view.

cc:
Orig. NDA 21-223
HFD-510/Division File
HFD-510/Sheldon Markofsky/(Review Chemist)
HFD-510/R. Hedin (CSO)
HFD-510/D-G. Wu (Team Leader)
HFD-580/ S.Koepke

/S/ 9/11/00
/S/ 9-11-00
Sheldon Markofsky, Review Chemist

R/D Init by: Team Leader

filename:

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **NDA 21223/000**
Priority: **1P**
Org Code: **510**
Stamp: **21-DEC-1999** Regulatory Due: **21-SEP-2000**
Action Goal:
District Goal: **22-AUG-2000**
Applicant: **NOVARTIS PHARMS**
59 RT 10
EAST HANOVER, NJ 079361080
Brand Name: **ZOMETA (ZOLEDRONIC ACID FOR INJECTION)(4**
Established Name:
Generic Name: **ZOLEDRONIC ACID**
Dosage Form: **FIJ (FOR INJECTION)**
Strength: **4 MG**

FDA Contacts:
D. HEDIN (HFD-510) 301-827-6392 , Project Manager
S. MARKOFSKY (HFD-510) 301-827-6420 , Review Chemist
D. WU (HFD-510) 301-827-6375 , Team Leader

Overall Recommendation:

ACCEPTABLE on 25-AUG-2000 by M. GARCIA (HFD-322) 301-594-0095

Establishment: **2416082**
NOVARTIS PHARMA INC (CIBA)
OLD MILL RD
SUFFERN, NY 10901
DMF No:
AADA No:

Profile: **SVL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **02-FEB-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **FINISHED DOSAGE PACKAGER**

Establishment: **9692043**
NOVARTIS PHARMA INC (CIBA)
SCHAFFHAUSERSTRASSE
CH-4332 STEIN, , SZ
DMF No:
AADA No:

Profile: **CRU** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **01-FEB-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **DRUG SUBSTANCE MICRONIZER**
FINISHED DOSAGE MANUFACTURER

Profile: **SVL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **05-MAY-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **9611204**
NOVARTIS PHARMA INC (SANDOZ)
CH-4002
DMF No:
AADA No:

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

BASEL, , SZ

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **01-FEB-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **25-AUG-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON FILE REVIEW**
DISTRICT RECOMMENDATION

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
FINISHED DOSAGE STABILITY TESTER

Establishment: **9612715**
NOVARTIS PHARMA INC (SANDOZ)

DMF No:
AADA No:

RINGASKIDDY/CORK, RINGASKIDD

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **01-FEB-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**

Establishment: **9614433**
NOVARTIS PHARMANALYTICA SA

DMF No:
AADA No:

LOCARNO, , SZ

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **01-FEB-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE STABILITY TESTER**
FINISHED DOSAGE STABILITY TESTER

APPEARS THIS WAY
ON ORIGINAL

NDA 21-223
Zometa (zoledronic acid for injection)

Dear Ms. Cutler:

Please refer to your new drug application submitted December 21, 1999, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zometa (zoledronic acid for injection).

We also refer to your February 2, March 21, and April 14 and 20, 2000 submissions.

We have completed the chemistry of these submissions and have the following comments and information requests:

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, contact Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Cleared for Faxing: /S/ 5/25/00

Dr. Duu-Gong Wu, Team Leader

APPEARS THIS WAY
ON ORIGINAL