CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-080

CHEMISTRY REVIEW(S)

NDA 22-080

Reclast® (zoledronic acid) Injection

Novartis

Sheldon Markofsky, Ph.D.

Division of Metabolic and Endocrine Drug Products
(DMEDP, HFD-510)

and

Office of New Drug Quality Assessment I
Branch II

File: n22080aRev

Table of Contents

Chemistry Review Data Sheet

1 NDA 22-080

2 REVIEW #: 1

3 REVIEW DATE: 25-June-07

4 REVIEWER: Sheldon Markofsky, Ph.D.

5 PREVIOUS DOCUMENTS:

Document	Document Date
NDA 21-817 (Original)	21-Sept-2004
NDA 21-817 (Amendment)	17-Dec-2004
NDA 21-817 (Amendment)	20-Jan-2005
NDA 21-817 (Review)	08-March-2005
NDA 22-080 (ORIGINAL)	16-Oct-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
ORIGINAL NDA 22-080	16-Oct-2006
NDA 22-080 Amendment [1]	14-June-2007

1) The amendment, dated 6-14-07 revises a stability protocol to support post-approval changes.

Chemistry Review Data Sheet

1 NAME & ADDRESS OF APPLICANT:

Name:	Novartis Pharmaceuticals Corporation
Address:	One Health Plaza, East Hanover, NJ 07936-1080
Representative:	Lynn Mellor, Director Drug Regulatory Affairs
Telephone:	(862) 778-3665

2 DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Reclast®
b) Non-Proprietary Name (USAN): Zoledronic acid
c) Code Name/# (ONDC only): ZOL446
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 6
- Submission Priority: S

1 LEGAL BASIS FOR SUMBISSION: 505(b)(2)

2 PHARMACOL. CATEGORY: Bone/Calcium-phosphorus metabolism.

3 DOSAGE FORM: Injection

4 STRENGTH/POTENCY: 5 mg per 100 mL

5 ROUTE OF ADMINISTRATION: Intravenous injection (IV)

6 Rx/OTC DISPENSED: _x_Rx ___OTC

7 **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

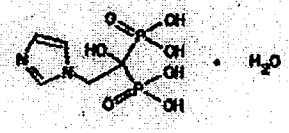
-----SPOTS product – Form Completed

__x Not a SPOTS product

Chemistry Review Data Sheet

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

Chemical Name	(1) Phosphonic acid, [1-hydroxy-2-(1*H*-imidazol-1-yl)ethylidene]bis-, monohydrate; (2) (1-Hydroxy-2-imidazol-1-ylethylidene)diphosphonic acid, monohydrate.
CAS Numbers	*CAS-165800-06-6.*



Molecular Info $C_5H_{10}N_2O_7P_2.H_2O$. 290.10.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS [2]	DATE REVIEW COMPLETED	COMMENTS
——	3	——		3	Adequate	10/10/02	
——	3	——		3	Adequate	08/07/98	

[1] Action codes for DMF Table:

1 – DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application 5 – Authority to reference not granted 6 – DMF not available 7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Original NDA for Zometa®	NDA 21-223	Approved August 20th, 2001
Zometa CMC Review # 1	NDA 21-223; Zometa® (zoledronic acid) for injection	Adequate (1st review cycle) S. Markofsky
NDA for Aclasta[1]	NDA 21-817	Approved 4-16-07
Aclasta[1] CMC Review # 1	NDA 21-817	March 8, 2005

1) The applicant _____ the name "Aclasta", and the approved drug product of NDA 21-817 is now called Reclast, which is also the name used in this NDA (22-080)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS*	**RECOMMENDATION**	**DATE**	**REVIEWER**
Biometrics	N/A		
EES	ACCEPTABLE	11-16-06	S. Adams for NDA 22-080
Pharm/Tox	ACCEPTABLE	2-23-05	G. Kuijpers
Biopharm	ACCEPTABLE	3-11-05	S. Suarez
LNC	N/A		
Methods Validation	Adequate	3-8-05	D. Lewis for NDA 21-817
EA	Categorical exclusion per 21 CFR 25.31(b)	6-25-07	S. Markofsky for NDA 22-080
Microbiology	APPROVAL	2-16-07	J. Metcalfe, Ph.D.

* The drug substance and drug product of NDAs 21-817 and 22-080 are identical. Therefore, most of the consults and related reviews shown in the above table are applicable to both NDAs..

19. ORDER OF REVIEW (OGD Only): N/A

The Chemistry Review for NDA 22-080

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA can be approved.

[Labeling will be finalized at a later date as part of the review team's labeling negotiation.]

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

The drug substance and drug product of NDAs 21-817 and 22-080 are identical, but the indications are different. The indication for NDA 22-080 is for the treatment of postmenopausal osteoporosis, whereas, NDA 21-817 is approved for the treatment of Paget's disease of bone in men and women. Accordingly, the Chemistry Manufacturing and Control (CMC) information for the approved NDA (21-817) supports this NDA (22-080). In addition, for the drug substance, (zoledronic acid), all CMC information is referenced to the approved NDA 21-223, Zometa (zoledronic acid) for injection. NDA 22-080, however, has been revised with added stability data for the drug product, an up-dated Categorical Exclusion from preparing an Environmental Assessment, and a new acceptable Establishment Inspection report for the relevant CMC related facilities.

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product, Reclast® (zoledronic acid) injection, is a small-volume parenteral (SVP) drug product providing 5 mg of zoledronic acid in a 100-mL injection, filled into a 100-mL ——vial ——— The drug product is ——— sterilized, and is intended for use as a single 5-mg infusion, once a year given intravenously, over no less than 15 minutes for the prevention of postmenopausal osteoporosis. There are two excipients in the drug product, sodium citrate ——— and mannitol ———. The drug substance, zoledronic acid (USAN) is utilized as the monohydrate in the drug product formulation on the basis of adequate solid-state stability and high aqueous solubility. All CMC information regarding zoledronic acid is adequate to support this NDA by reference to the approved NDAs 21-817 and 21-223.

Zoledronic acid is prepared by _____ by the NDA applicant, and is processed for drug product formulation by a _____ Morphic forms are not relevant to this application, since the drug product exists as a relatively dilute aqueous solution, and the drug substance is freely soluble in aqueous media. The retest date for zoledronic acid _____ is based on accumulated ICH stability data.

The drug product manufacturing process is relatively simple _____

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

The drug product is intended for use as a single IV infusion, to be administered once a year. The drug is recommended for administration as a single dose (5 mg).. The drug product provides 5.3 mg of zoledronic acid monohydrate (equivalent to 5 mg of anhydrous zoledronic acid) in 100 mL of _____ The drug product has been demonstrated to be compatible with the most commonly used dispensing apparatus (e.g., tubing and dispensing kits fabricated from various plastic materials).

The applicant has proposed an expiration dating period of 36 months with storage at controlled room temperature (25°C) with excursions permitted between 15 and 30°C. The expiry is satisfactorily supported by 36 months of acceptable ICH long-term stability data (25°C/60%RH) for the three registration batches.

The suitability of the proposed packaging for the drug product was addressed by the determination of extractables and leachables from the container closure for the exhibit batches in NDA 21-817 via a validated HPLC analytical method. All container components are either detectable by the method, or are present in the container closure system at levels so low that even 100% migration into the contents would result in levels below the reporting threshold (e.g., trace components in the label adhesive and labeling inks).

C. Basis for Approvability or Not-Approval Recommendation

The application is recommended for approval from the standpoint of CMC since the drug substance and drug product of NDAs 21-817 and 22-080 are identical, and NDA 21-817 has been approved. In addition, NDA 22-080 provided a satisfactory up-dated Categorical Exclusion from preparing an Environmental Assessment, and a new acceptable Establishment Inspection report has been received for the relevant CMC related facilities.

III. Administrative

A. Reviewer's Signature

Electronically, in DFS

B. Endorsement Block (OGD only)

N/A

C. CC Block (OGD only)

N/A

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✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1

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Sheldon Markofsky
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Ali Al-Hakim
6/26/2007 11:20:49 PM
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RECLAST
(zoledronic acid) injection
NDA 22- 080

Summary Basis for Recommended Action
From Chemistry, Manufacturing, and Controls

Applicant: Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Indication: treatment of postmenopausal osteoporosis

Presentation: RECLAST is a small volume parenteral drug (SVP) supplied sterile for single use as 5 mg zoledronic acid in a 100 mL injection, filled in a 100 mL _____

EER Status: Acceptable 16-NOV-2006

Consults:

Pharm/Tox -	Acceptable	23-FEB-2005
Biopharm -	Acceptable	11-MAR-2005
Microbiology –	Approval	16-FEB-2007
Methods Validation –	Adequate	8-MAR-2005 (NDA 21-817)

EA – Categorical exclusion granted under 21 CFR §25.31(b)

Original Submission: 16-OCT-2006

Drug Substance

Zoledronic acid (USAN) is a nitrogen-containing bis-phosphonate, is _____ by the applicant, and is the same as that in the approved NDA 21-223, Zometa (zoledronic acid) for injection and approved NDA 21-817 Reclast (zoledronic acid) injection.

All three NDAs have the same applicant, and this NDA includes a reference to the CMC information on the drug substance in the approved NDA 21-223.

All CMC information regarding zoledronic acid is adequate to support this NDA by reference to the approved NDA 21-223, Zometa® (zoledronic acid) for injection.

The retest date _____ for zoledronic acid is based on accumulated ICH stability data.

Conclusion: Drug substance is satisfactory

Drug product

The drug product is the same as in the approved NDA 21-817. Both NDAs have the same applicant, and this new NDA 22-080 includes a reference to the CMC information on the drug product in the pending NDA. The drug product is a small-volume parenteral that is terminally sterilized.

The active ingredient, zoledronic acid monohydrate (5.330 mg), is formulated with mannitol USP (4950.0 mg) and sodium citrate USP (30.0 mg) in 100 mL water for injection USP to give 5 mg zoledronic acid per 100 mL clear, colorless, sterile solution.

A 36-month expiry at 25° C/60% RH is proposed and supported by real-time long-term data on three primary commercial-scale product batches.

Conclusion: Drug product is satisfactory.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Overall Conclusion: From a CMC perspective, the application is recommended for **Approval,** pending agreement on product labeling.

Ali Al-Hakim, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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/s/

Ali Al-Hakim
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_____ Deliberative Process

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