

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-817

CHEMISTRY REVIEW(S)

Memorandum

Date: 13-MAR-2007
From: Su (Suong Tran), PhD, Pharmaceutical Assessment Lead, Branch II/DPA I/ONDQA
Through: Blair Fraser, PhD, Director, DPA I/ONDQA
To: NDA 21-817 NAME (zoledronic acid) Injection
Letter date: 13-OCT-2006

Subject: Complete Response to the 22-FEB-2006 Approvable Letter

Background:

- NDA 21-817 NAME (zoledronic acid) Injection was found Approvable on 22-FEB-2006 because of clinical deficiencies. The CMC recommendation at that time was "Approval" pending the DMETS' review of the proposed proprietary name. That recommendation included the review of CMC information in the package insert and packaging labels.
- The Complete Response dated 13-OCT-2006 includes labeling (copied at the end of this review).

Reviewer's comments:

- Compared to the CMC information in the package insert and packaging labels that was previously found acceptable (refer to previous Chem. Reviews), the labeling submitted in the Complete Response has the revisions listed below. These revisions are acceptable. The text size of the established name is acceptable (more than half the size of the proprietary name).

Conclusion:

The final CMC recommendation for NDA 21-817 (zoledronic acid) Injection is APPROVAL.

This recommendation does not cover the review of the proprietary name, graphics, and colors of the product labeling; refer to the recommendations from DMETS and DDMAC (Office of Drug Safety) on these non-CMC items.

3 Page(s) Withheld

 Trade Secret / Confidential

 X Draft Labeling

 Deliberative Process

Withheld Track Number: Chemistry- 1

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Suong Tran
3/19/2007 08:42:38 AM
CHEMIST

labeling review; no issue

Blair Fraser
3/19/2007 08:48:58 AM
CHEMIST



NDA 21-817

Aclasta® (zoledronic acid) Injection

Novartis

David B. Lewis, Ph.D.

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

27 Page(s) Withheld

X Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

Withheld Track Number: Chemistry-2



Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	8
C. Basis for Approvability or Not-Approval Recommendation.....	9
III. Administrative.....	9
A. Reviewer's Signature.....	9
B. Endorsement Block.....	9
C. CC Block	9
Chemistry Assessment	10
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	10
S DRUG SUBSTANCE [zoledronic acid, Novartis].....	10
P DRUG PRODUCT [Aclasta® (zoledronic acid) Injection].....	12
A APPENDICES	32
R REGIONAL INFORMATION	32
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	33
A. Labeling & Package Insert	33
B. Environmental Assessment Or Claim Of Categorical Exclusion	35
III. List Of Deficiencies To Be Communicated.....	36



Chemistry Review Data Sheet

1. NDA 21-817
2. REVIEW #: 1
3. REVIEW DATE: March 8th, 2005
4. REVIEWER: David B. Lewis, Ph.D.
5. PREVIOUS DOCUMENTS: None

Previous Documents

None

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

ORIGINAL NDA
AMENDMENT
AMENDMENT

Document Date

21/09/2004
17/12/2004
20/01/2005

- The amendment of December 17th, 2004 provided updated stability information for the drug product.
- The amendment of January 20th, 2005 provided a response to the items from the request for information communicated to the applicant on January 7th (method validation for the HPLC assay and identity of label adhesive and printing ink components).
- The amendment of January 21st, 2005 contained responses to a request for information drafted by the microbiology staff, and was addressed in the consult microbiology review. This amendment was not addressed in this (CMC) review.



Chemistry Review Data Sheet

7. 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

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Aclasta®
- b) Non-Proprietary Name (USAN): Zoledronic acid
- c) Code Name/# (ONDC only): ZOL446
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: 3030400, Bone/Calcium-phosphorus metabolism.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 5 mg per 100 mL

13. ROUTE OF ADMINISTRATION: Intravenous injection (IV)

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product



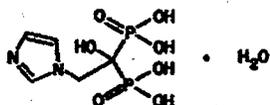
CHEMISTRY REVIEW



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

$C_5H_{10}N_2O_7P_2 \cdot H_2O$. 290.10.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE	STATUS	DATE REVIEW COMPLETED	COMMENTS
				3	Adequate	10/10/02	
				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



Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Original NDA for Zometa®	NDA 21-233	Approved August 20 th , 2001
Zometa CMC Review # 1	NDA 21-233; Zometa® (zoledronic acid) for injection	Adequate (1 st review cycle) S. Markofsky
Request for Information	NDA 21-817	Communicated to the applicant on January 7 th (attached to end of the review)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	ACCEPTABLE	31/01/2005	J. D' Ambrogio
Pharm/Tox	pending		G. Kuijpers, Ph.D.
Biopharm	pending		S. W. "Johnny" Lau, Ph. D.
LNC	N/A		
Methods Validation	Adequate*		
ODS	NOT ACCEPTABLE	31/01/2005	Kristina C. Arnwine, PharmD
EA	Categorical exclusion per 21 CFR 25.31(b)		D. Lewis
Microbiology	APPROVAL	14/02/2005	J. Metcalfe, Ph.D.

* The analytical method were found to be adequate for release and stability studies

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



The Chemistry Review for NDA 21-817

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application may be approved upon the submission of acceptable labeling (pending labeling review by all disciplines).

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

None

II. Summary of Chemistry Assessments

NDA 21-817 provides CMC information for Aclasta® (zoledronic acid) injection, 5 mg/100 mL, which is closely related to NDA 21-233, Zometa® (zoledronic acid) for injection, from the same applicant. *CMC information regarding the drug substance was reviewed and found adequate for NDA 21-233, and remains adequate for this NDA (no changes in manufacture, controls, or facilities).* The manufacturing processes and release specifications for Aclasta® are essentially identical to those, which were approved for Zometa® and are acceptable for this NDA (_____)

_____ The application was reviewed by the microbiology staff and found acceptable on the basis of sterility assurance. The manufacturing and testing facilities for the drug substance and product were evaluated by the Office of Compliance (OC), and found acceptable to support this application.

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

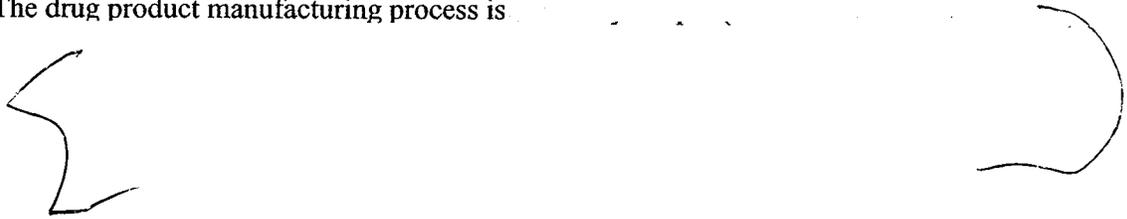
The drug product, Aclasta® (zoledronic acid) injection, is a _____ drug product providing 5 mg of zoledronic acid in a 100-mL injection, filled into a 100-mL plastic vial equipped with a rubber stopper and aluminum crimp. The proposed proprietary name, Aclasta® was reviewed, and found NOT ACCEPTABLE by the Division of Medication Errors and Technical Support (DMETS); the DMETS opinion was that the drug product should use the same proprietary name as the NDA 21-223 product, Zometa. *This opinion will be addressed in the final DMEDP labeling meeting.* The drug product is terminally sterilized, and is intended for use as a single injection for the treatment of Paget's disease of bone (one dose represents an entire round of treatment). There are two excipients in the drug product, citric acid _____ and mannitol _____



Executive Summary Section

The drug substance, zoledronic acid (USAN) is utilized as the monohydrate in 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 NDA 21-233, Zometa® (zoledronic acid) for injection. 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



Three (3) different formulations were utilized in clinical trials for this NDA; these formulations include a 4 mg freeze-dried powder (approved drug product, Zometa®, NDA 21-223), a 5 mg per 5 mL concentrate for dilution & injection), and the 5 mg per 100 mL ready-to-use injection (the proposed commercial formulation for this NDA). A comparison between the 5 mg/5 mL concentrate and the 5 mg/100 mL infusion indicates the following: the concentrate utilized _____ while the proposed NDA 21-817 formulation utilizes mannitol. The target quantities of the active ingredient and of citric acid _____

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

The drug product is intended for use as a single injection, to be administered by IV infusion once daily. *The drug is recommended for administration as a single dose (5 mg); clinical trials in support of this application monitored patients for six (6) months after the administration of this single dose.* 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 30 months with storage at controlled room temperature (25°C) with excursions permitted between 15 and 30°C. The expiry is supported by 18 months of acceptable ICH long-term and intermediate stability data for three exhibit batches accompanied by 6 months of acceptable ICH accelerated stability data on the same batches. The submitted stability data exhibited very little variability and change, allowing the expiry to be extrapolated to 30 months per the recommendations of ICH Q1E, *Evaluation of Stability Data*.



Executive Summary Section

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 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 on the basis of the following:

- Adequate CMC information for the drug substance (by reference to NDA 21-233)
- Adequate CMC information for the drug product (batch formula, controls, and analytical test results)
- Demonstration of container/closure suitability *via* determination of extractables and leachables in the drug product
- Submission of stability data that supports the proposed expiration date of 30 months
- Acceptable cGMP status for all manufacturing and testing facilities

III. Administrative

A. Reviewer's Signature

Electronically, in DFS

B. Endorsement Block

See DFS

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

See DFS

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

David Lewis

3/18/05 12:15:31 PM

CHEMIST

The application may be approved from the standpoint of CMC.

Mamta Gautam-Basak

3/18/05 12:29:45 PM

CHEMIST

Concur