CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-575

CHEMISTRY REVIEW(S)

NDA 21-575

FOSAMAX®
(alendronate sodium)
ORAL [redacted] SOLUTION

Merck & Co., Inc.

Elsbeth Chikhale, Ph.D.
Division of Metabolic and Endocrine Drug Products

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Chemistry Review Data Sheet

1. NDA 21-575

2. REVIEW #: 1

3. REVIEW DATE: 2-SEP-2003

4. REVIEWER: Elsbeth Chikhale, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Information request	9-JUL-2003
Information request	22-JUL-2003
Information request	23-JUL-2003
T-con	31-JUL-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	15-NOV-2002
Amendment to original[1]	21-JUL-2003
Amendment to original[2]	25-JUL-2003
Amendment to original[3]	15-AUG-2003

[1]The 7/21/2003 amendment provides for a response to Agency Request for Information dated 7/9/03
[2]The 7/25/2003 amendment provides for a response to Agency Requests for Information dated 7/22/03 & 7/23/03
[3]The 8/15/2003 amendment provides for a response to Agency Request for Information dated 7/31/03

7. NAME & ADDRESS OF APPLICANT:

Name: Merck & Co., Inc.

Address: P.O. Box 2000
Maildrop: RY 33-720
Rahway, New Jersey 07065

Representative: Michelle R. Flicker, M.D., Ph.D., FACP
(Director, Regulatory Affairs)

Telephone: (732) 594-1502

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Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Fosamax oral ——— solution
b) Non-Proprietary Name (USAN): Alendronate sodium
c) Code Name/#: L-670,452
d) Chem. Type/Submission Priority:

- Chem. Type: 3 (new formulation)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

This is a 505(b)(1) submission

10. PHARMACOL. CATEGORY:

Bone/calcium-phosphorous metabolism

11. DOSAGE FORM: solution

12. STRENGTH/POTENCY: 70 mg/75 mL

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13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _x_ Rx ___ OTC

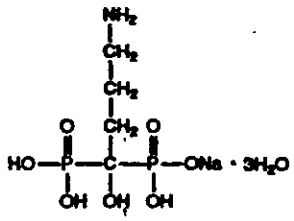
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product ___ Form Completed

__x__Not a SPOTS product

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

(4-amino-1-hydroxybutylidene) bisphosphonic acid monosodium salt, trihydrate



$C_4H_{12}NNaO_7P_2.3H_2O$
Molecular Weight: 325.12 (for trihydrate)

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	IV	[redacted]	[redacted]	1	Adequate	July 10, 2003	Reviewed by Elsbeth Chikhale, Ph.D.
[redacted]	III	[redacted]	[redacted]	3	Adequate	September 26, 2000	Reviewed by Don Klein, Ph.D.
[redacted]	III	[redacted]	[redacted]	3	Adequate	November 3, 2000	Reviewed by Raymond Frankewich Ph.D.
[redacted]	III	[redacted]	[redacted]	3	Adequate	February 14, 2003	Reviewed by J. Salemme, Ph.D.
[redacted]	III	[redacted]	[redacted]	3	Adequate	March 31, 2001	Reviewed by David Lin, Ph.D.
[redacted]	III	[redacted]	[redacted]	3	Adequate	April 5, 2002	Reviewed by J. Boal, Ph.D.
[redacted]	III	[redacted]	[redacted]	3	Adequate	February 14, 2003	Reviewed by J. Salemme, Ph.D.
[redacted]	III	[redacted]	[redacted]	7	Adequate	July 24, 1999	Reviewed by J. Vidra, Ph.D.
[redacted]	III	[redacted]	[redacted]	3	Adequate	April 30, 2001	Reviewed by Don Klein, Ph.D.
[redacted]	III	[redacted]	[redacted]	3	Adequate	March 23, 1999	Reviewed by R. Harapanhalli, Ph.D.
[redacted]	III	[redacted]	[redacted]	1	Adequate	July 21, 2003	Reviewed by Elsbeth Chikhale, Ph.D.
[redacted]	III	[redacted]	[redacted]	1	Adequate	July 10, 2003	Reviewed by Elsbeth Chikhale, Ph.D.

Chemistry Review Data Sheet

[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)

Comment: DMF — for the — was reviewed by J. Vidra Ph.D. in support of his review of DMF — or the — It was concluded (see review of DMF — dated 7/24/99 and review of DMF dated 8/13/99) that the — made from — — are found adequate as — . DMF —was later reviewed again in support of an NDA for an — solution, and was found inadequate — . Since the subject drug product for NDA 21-575 is an oral solution, it is concluded that the — can be considered acceptable for NDA 21-575. In addition — therefore the drug product is —

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-560	Alendronate sodium tablets

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	6-17-03	Elsbeth Chikhale, Ph.D.
Pharm/Tox	N/A		
Clinical Pharmacology and Biopharmaceutics	Acceptable	pending	Johnny Lau, Ph.D.
Methods Validation		pending	Elsbeth Chikhale, Ph.D.
ODS	N/A		
EA	Satisfactory (consult not needed)	9-2-03	Elsbeth Chikhale, Ph.D.
Microbiology	Microbial limits test is performed according to USP<61> and USP<1111>.	9-2-03	Elsbeth Chikhale, Ph.D.

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 21-575

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 21-575 is recommended for **approval** from the standpoint of chemistry, manufacture and controls.

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

None

II. Summary of Chemistry Assessments

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

1) Drug Product

The proposed drug product is described as an oral ——— solution (pH 6.8) containing 91.35 mg of alendronate sodium trihydrate (drug substance) equivalent to 70 mg free acid per bottle. In addition to the drug substance, the drug product solution also contains an artificial raspberry flavor, citrate buffer, antimicrobial preservatives (sodium propylparaben and sodium butylparaben), and an artificial sweetener, all dissolved in 75 mL purified water. The finished drug product is provided in a unit of use (75 mL) bottle ——— The drug product manufacturing is ——— The approval of this NDA is based on the equal bioavailability of the 70 mg oral ——— solution and the 70 mg tablets already approved under NDA 20-560. Since the primary packaging component, ——— he main safety/quality concern during the CMC review was the assurance that ———

2) Drug Substance

——— It is a fine white, crystalline, nonhygroscopic powder, freely soluble in water, but practically insoluble in organic solvents. The drug substance is adequately stable when stored at room temperature. The drug substance, alendronate sodium (trihydrate), is identical to the drug substance approved under NDA 20-560 for Fosamax® tablets. The CMC information is provided (by reference) in NDA 20-560.

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

The drug product (alendronate sodium oral ——— solution) has to be taken at least 30 minutes before the first food or drink (other than water) of the day or any other oral medication or supplementation. The recommended dose for the drug product is 70 mg (one 75 mL unit dose) weekly. The proposed storage is at 25°C (room temperature), and the proposed expiry date is 24 months, which is supported by sufficient stability data and found acceptable.

C. Basis for Approvability or Not-Approval Recommendation

The drug substance, alendronate sodium, is identical to the drug substance used for a different dosage form, Fosamax Tablet (NDA 20-560). The drug product manufacturing process and in-process controls of the clinical batches and the to-be-marketed batches are practically the same. The oral solution drug product batches used for the clinical bioavailability studies have the same formulation/composition and packaging as the proposed commercial formulation and are considered equivalent from a chemical as well as biopharmaceutical stand point. The drug product specifications (release and stability) are the same (except for the assay for the preservatives), so that drug product quality is assured at release and during the 2 year shelf life. Sufficient stability data are provided to support the proposed expiry period of 2 years for the drug product, when stored at the recommended storage conditions (25°C). No trends (upward or downward) were observed, as indicated by the stability data submitted. The cGMP status of all manufacturing and control facilities is acceptable per EER dated 6/17/03. The deficiencies noted in the information request letters dated 7/9/03, 7/22/03 and 7/23/03 and discussed in the 7/31 t-con, have been addressed satisfactorily.

III. Administrative

A. Reviewer's Signature

Elsbeth Chikhale, Ph.D.

B. Endorsement Block: in DFS

C. cc Block: in DFS

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37 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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

/s/

Elsbeth Chikhale
9/4/03 01:08:47 PM
CHEMIST

Mamta Gautam-Basak
9/4/03 01:22:06 PM
CHEMIST
Concur, approvable from the CMC standpoint.