

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-762

CHEMISTRY REVIEW(S)



NDA 21-762

**FOSAMAX™ PLUS
(alendronate sodium and vitamin D₃) Tablets**

Merck & Company, Inc.

David B. Lewis, Ph.D.

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



Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	8
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s).....	9
B. Description of How the Drug Product is Intended to be Used	9
C. Basis for Approvability or Not-Approval Recommendation.....	10
III. Administrative	10
A. Reviewer's Signature.....	10
B. Endorsement Block.....	10
C. CC Block.....	10
Chemistry Assessment.....	11
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data	11
S DRUG SUBSTANCE [alendronate sodium, Merck and company and — vitamin D3 —	11
P DRUG PRODUCT [FOSAMAX PLUS™ tablets].....	20
A APPENDICES	45
R REGIONAL INFORMATION	45
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1.....	46
A. Labeling & Package Insert.....	46
B. Environmental Assessment Or Claim Of Categorical Exclusion	48
III. List Of Deficiencies To Be Communicated.....	50



Chemistry Review Data Sheet

1. NDA: 21-762
2. REVIEW # 1
3. REVIEW DATE: March 22nd, 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
AMENDMENT
AMENDMENT

Document Date

24/05/2004
04/06/2004
22/07/2004
11/11/2004
19/01/2005

- The amendment of June 4th, 2004 addressed the assigned number for the — DMF
- The amendment of July 22nd, 2004 provided a letter of authorization allowing FDA reference to — DMF — to support this NDA.
- The amendment of November 11th, 2004 provided information regarding alternate dissolution media for alendronate and vitamin D₃ dissolution testing in the drug product.
- The amendment of January 19th, 2005 provided an updated “justification of specifications” section for the drug product.



CHEMISTRY REVIEW



Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Merck & Co., Inc.
Address: P.O. Box 2000, Rahway, NJ 07065
Representative: Michele R. Flicker, M.D., Ph.D., FACP
Telephone: (732) 594-1502

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: FOSAMAX™ PLUS
- b) Non-Proprietary Name (USAN): alendronate sodium and cholecalciferol
- c) Code Name/#: N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 2
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: treatment of osteoporosis in postmenopausal women, increase in bone mass in men with osteoporosis, —

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: each tablet contains 91.37 mg of alendronate sodium (equivalent to 70 mg of the free acid) and 70 µg of cholecalciferol (equivalent to 2800 I.U. of vitamin D₃).

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

Not a SPOTS product

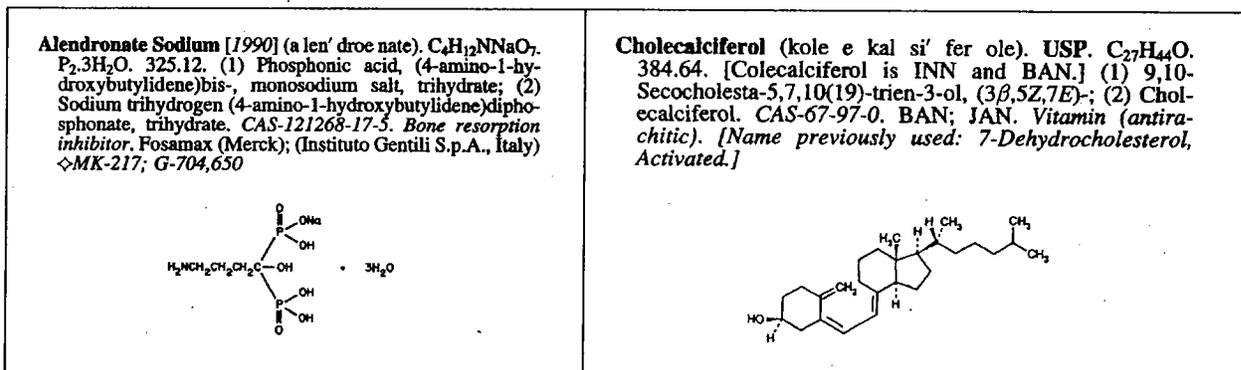
One excipient, magnesium stearate, is —



Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: The nomenclature for the drug substance is as follows:

- INN/USAN Name: Alendronate Sodium (USAN) and cholecalciferol, USP (USAN).
- Inverted IUPAC Names: Phosphonic acid, (4-amino-1-hydroxybutylidene)bis-, monosodium salt, trihydrate [*alendronate sodium*], and (3 β ,5Z,7E)-9,10-secocholesta-5,7,10(19)-trien-3-ol [*cholecalciferol*].
- Other chemical names: Sodium trihydrogen (4-amino-1-hydroxybutylidene)diphosphonate, trihydrate [*alendronate*]; 7-dehydrocholesterol, activated [*cholecalciferol*]
- CAS Registry Number: [121268-17-5] (alendronate sodium) and [67-97-0] (cholecalciferol)
- Structural Formula: C₄H₁₂NNaO₇P₂•3H₂O (325.12 g/mol, *alendronate sodium*) and C₂₇H₄₄O (384.6 g/mol, *cholecalciferol*).
- Chemical structure(s):



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE	STATUS	DATE REVIEW COMPLETED	COMMENTS
—	II	/	/	1	Adequate	20/12/2004	IR letter communicated to holder*
—	III			7			
/	III			7			
/	III			7			
/	III			7			



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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* Minor information requests were communicated to the DMF holder; responses are pending. However, these deficiencies do not constitute approvability issues for this NDA.

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)

The Type III packaging DMF's, which were referenced in the application, were not reviewed due to the current ONDC policy regarding container closure components for solid oral dosage forms. All of the container closure components (and the raw materials from which they were fabricated) meet the current 21 CFR requirements for food storage safety (*information contained within the referenced DMF's*).

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Original NDA for FOSAMAX	NDA 20-560	Submitted on March 31 st , 1995 and approved on September 29 th , 1995.
CMC Review for FOSAMAX	NDA 20-560 CMC review # 1	Adequate (S. Markofsky, September 1995)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	ACCEPTABLE	22/03/2005	S. Adams
Pharm/Tox	Approval	25/06/2004	K. Davis-Bruno, Ph.D.
Biopharm	<i>Pending*</i>		
LNC	N/A		
Methods Validation	ACCEPTABLE **	22/03/2005	D. Lewis, Ph.D.
ODS	NOT ADEQUATE ***	06/07/2004	C. Hoppes, R.Ph., M.P.H.
EA	Adequate (categorical exclusion)		D. Lewis, Ph.D.
Microbiology	N/A		

* The Clinical Pharmacology and Biopharmaceutics (Biopharm) Staff is expected to request that the applicant submit a new method for the determination of vitamin D3 dissolution for the drug product. This submission is to be requested post-approval. The CMC staff will review the method, once received from the applicant.

** The analytical methods are suitable for release and stability studies.

*** The Office of Drug Safety (ODS) rejected the proposed proprietary name, FOSAMAX PLUS. This was communicated to the applicant, after which, an alternate name, FOSAMAX PLUS D, was proposed. The acceptability of this name will be addressed in final labeling meeting (scheduled for March 28th, 2005).



The Chemistry Review for NDA 21-762

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval, pending the submission of adequate labeling for the drug product (including the submission of an acceptable proprietary name).

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

The Office of Clinical Pharmacology and Biopharmaceutics (Biopharm) is expected to request the applicant submit a new method for determining vitamin D₃ dissolution in the drug product. This method is expected to be submitted post-approval (Phase 4), and will be reviewed by CMC staff, when submitted.

I. Summary of Chemistry Assessments

NDA 21-762 covers a combination drug product, containing *alendronate sodium* and *cholecalciferol* (Vitamin D₃). Alendronate sodium is the drug substance for the approved drug product, FOSAMAX® (NDA 20-560, same applicant), and all chemistry, manufacturing and controls (CMC) information regarding alendronate sodium is adequate for this NDA by reference to NDA 20-560. Cholecalciferol is a vitamin and is not manufactured under *current drug GMP's*; however, the applicant _____, which is supplied from outside sources, is manufactured under current drug GMP's, and is described in a currently-maintained DMF _____ DMF _____ was reviewed and an information request (IR) letter was issued in January 2005. *However, the requests for information communicated to the DMF _____ holder are considered relatively minor, and are not critical to the approvability of this NDA. The DMF holder's response is pending.* **Note:** Cholecalciferol complies with the current USP monograph requirements, and process impurities derived from _____ Vitamin D₃ _____ are addressed in the drug product specifications. The proposed proprietary name was reviewed by the Office of Drug safety (ODS), Division of Medication Errors (DMETS), and found unacceptable for the drug product. **Note:** An alternate proprietary name was proposed, and will be addressed during the final labeling meeting (scheduled for March 28th, 2005). The drug substance and product manufacturing and testing facilities were submitted to the Office of Compliance (OC) for cGMP status; *OC evaluation is ACCEPTABLE per EER dated March 22nd, 2005.*



Executive Summary Section

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

The drug product has the proposed name of FOSAMAX™ PLUS (Alendronate Sodium – 70 mg/2800 I.U. Vitamin D₃ combination) Tablets, and is an solid oral dosage form (tablet) containing alendronate sodium (a bisphosphonate, which specifically inhibits osteoclast-mediated bone resorption) and cholecalciferol (vitamin D₃), a nutritional supplement (vitamin). *The proposed proprietary name was consulted to the Office of Drug Safety for review, and was found unacceptable. The drug product actually contains 91.37 mg of alendronate monosodium salt trihydrate, which corresponds to 70 mg of free acid (alendronic acid) and 70 µg of cholecalciferol, which is equivalent to 2,800 I.U. (International Units) of vitamin D. However, the expression of alendronate quantity (70 mg) is based on the approved FOSAMAX label (NDA 20-560), in which the strength is expressed as the corresponding amount of free acid, with the conversion statement, "each tablet contains 91.37 mg of alendronate sodium equivalent to 70 mg of the free acid) below the nomenclature.*

The drug substances in FOSAMAX™ PLUS are alendronate sodium (USAN), a synthetic bone resorption inhibitor and cholecalciferol, USP (USAN, also known as vitamin D₃). CMC information for alendronate sodium is adequate by reference to NDA 20-560 (FOSAMAX®, manufactured by the same applicant, approved in September 1995). CMC information was not reviewed for cholecalciferol, which is considered to be a food substance, is not manufactured under current drug GMP's, and is not described in a current Drug Master File (DMF). *Cholecalciferol, however, does comply with the requirements of several compendia (USP, EP, and FCC).* Cholecalciferol is supplied to the NDA applicant from outside sources as —

CMC information regarding — was reviewed in DMF — while the DMF holder's responses to an information request letter are still pending, the requested information is not considered critical to the approval of THIS NDA, and will be reviewed when available from the DMF holder. The retest period for alendronate is unchanged from that approved for FOSAMAX™ tablets (NDA 20-560) and the retest period for — is — which is supported by stability data contained in DMF —

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

The recommended dose of FOSAMAX™ PLUS is *one tablet once weekly*. The drug product is proposed for marketing in blister packages of 4, bottles of 4 and 12, and unit-dose (blister) packages of 20. —

— There is only one strength of FOSAMAX PLUS, a combination of 91.7 mg of alendronate sodium (equivalent to 70 mg of the free acid) and 2,800 I.U. of vitamin D (as cholecalciferol). The proposed dosing schedule is one tablet once weekly (thus, a bottle containing 4 tablets represents a 1-month supply). The proposed expiration dating period is 18 months with storage at room temperature (25°C with excursions permitted between 15 and 30°C). This expiry is supported by — of acceptable long-term ICH stability data

**Executive Summary Section**

accompanied by — of associated accelerated ICH stability data and a statistical analysis of the quantitative attributes (95% confidence level, extrapolated to 18 months). Stability data was included for each of the proposed package presentations.

C. Basis for Approvability or Not-Approval Recommendation

All CMC-related information is adequate, either by reference to approved NDA 20-560 (FOSAMAX®) or from the information provided in this NDA. The manufacturing and testing facilities for the drug substances and drug product have been found ACCEPTABLE regarding cGMP status by the Office of Compliance. Submitted stability data is adequate to support the proposed expiration dating period for the drug product (18 months).

The labeling will be finalized *via* TeleCon with the applicant (scheduled for March 28th, 2005).

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: David Lewis, Ph.D.

ChemistryTeamLeaderName/Date: M. Gautam-Basak, Ph.D.

ProjectManagerName/Date: R. Hedin, R. Ph.

C. CC Block

40 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) 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/

David Lewis

3/24/05 10:40:00 AM

CHEMIST

Recommended for approval on the basis of CMC.

Mamta Gautam-Basak

3/25/05 08:19:53 AM

CHEMIST

Concur, recommend approval from the CMC standpoint (minor labeling
comments to be forwarded)

Reason : BASED ON PROFILE

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 22-MAR-05
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :
FROSST IBERICA SA
VIA COMPLUTENSE, 140
ALCALA DE HENARES, , SP 28805

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 04-JUN-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 1036761 FEI : 1036761
MERCK AND CO INC
4633 MERCK RD W
WILSON, NC 278939613

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 03-JUN-04
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 2650235 FEI : 1000131917
MERCK CO INC
RD 2 KM 60.3 BO SAB HOYO
ARECIBO, PR 00688

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 03-JUN-04

Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 9611927 FEI : 3002807653
MERCK SHARP AND DOHME DIV MERCK AND CO INC
SHOTTON LANE
CRAMLINGTON, , UK

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile : CTX OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 29-JUN-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9610180 FEI : 3002807560
MERCK SHARP AND DOHME IRELAND LTD
TIPPERARY, CLONMEL COUNTY, EI

DMF No: AADA:

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-JUN-04

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

