CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-575

ADMINISTRATIVE DOCUMENTS

NDA 21-575 FOSAMAX®

Patent Information

Item 13

PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

1. Active Ingredient	Alendronate sodium
2. Dosage(s)	70 mg
3. Trade Name	FOSAMAX®
4. Dosage Form	Oral —— solution
Route of Administration	Oral
5. Applicant Firm Name	Merck Research Laboratories
6. NDA Number	NDA 21-575
7. Approval Date	Pending
8. Exclusivity	Three (3) years from this NDA approval date or five (5) years from October 20, 2000 (October 20, 2005)
9. Applicable Patent Numbers	US Patent 4,621,077 Expires August 6, 2007 US Patent 5,462,932 Expires May 17, 2014 US Patent 5,994,329 Expires July 17, 2018 US Patent 6,015,801 Expires July 17, 2018 US Patent 6,225,294 Expires July 17, 2018

APPEARS THIS WAY
ON ORIGINAL

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A. This section should be completed for each individual patent

U.S. Patent Number: 5,462,932

Expiration Date: May 17, 2014

Type of Patent - indicate all that apply:

1. Drug Substance (Active Ingredient) __ Y ✓ N
2. Drug Product (Composition/Formulation) ✓ Y __ N
3. Method of Use ✓ Y __ N

Name of Patent Owner: MERCK & CO., INC., Rahway, NJ

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

B. The following declaration statement is required if the above listed patent has Composition/ Formulation or Method of Use claims.

The undersigned declares that United States Patent Number 5,462,932

covers the composition, formulation and/or method of use of alendronate sodium

(name of drug product). This product is:

- __ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act

  OR

- ✓ the subject of this application for which approval is being sought.

A. This section should be completed for each individual patent

U.S. Patent Number: 6,015,801

Expiration Date: July 17, 2018

Type of Patent - indicate all that apply:

1. Drug Substance (Active Ingredient) __ Y ✓ N
2. Drug Product (Composition/Formulation) __ Y ✓ N
3. Method of Use ✓ Y __ N

Name of Patent Owner: MERCK & CO., INC., Rahway, NJ

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

B. The following declaration statement is required if the above listed patent has Composition/ Formulation or Method of Use claims.

The undersigned declares that United States Patent Number 6,015,801

covers the composition, formulation and/or method of use of alendronate sodium

(name of drug product). This product is:

- __ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act

  OR

- ✓ the subject of this application for which approval is being sought.

Respectfully submitted,

By /J. Antonio Garcia-Rivas/
J. Antonio Garcia-Rivas
Attorney for Applicants

Merck & Co., Inc.
P.O. Box 2000 - RY60-30
Rahway, NJ 07065-0907
(732) 594- 1513

Date: November 15, 2002

A copy of the above information should be submitted to the FDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

In accordance with 21 C.F.R. §314.53(d)(4), the applicant shall submit two copies of each submission of patent information to:

Central Document Room
Center For Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Room 2-14
12420 Parklawn Dr.
Rockville, MD 20857

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IN DUPLICATE

FOSAMAX® 70mg (Alendronate Sodium) Oral Solution
Item 16 - Debarment Certification

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc. did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

Michele R. Flicker

October 31, 2002

Michele R. Flicker, M.D., Ph.D. FACP
Director
Regulatory Affairs

Date

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NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-575	Efficacy Supplement Type SE-	Supplement Number N/A	
Drug: Fosamax Oral Solution		Applicant: Merck Research Labs.	
RPM: Randy Hedin		HFD-510	Phone # 827-6392
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	None
❖ User Fee Goal Dates	September 18, 2003
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	( ) Paid
• User Fee waiver No clinical data.	( ) Small business ( ) Public health ( ) Barrier-to-Innovation (X) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	Completed
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	PM January 16, 2003

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	None
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	September 12, 2003
• Original applicant-proposed labeling	November 11, 2002
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	See PM Labeling Review.
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	September 12, 2003
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	None
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Complete
❖ Memoranda and Telecons	Complete
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	None
• Pre-NDA meeting (indicate date)	None
• Pre-Approval Safety Conference (indicate date; approvals only)	None
• Other	Complete
❖ Advisory Committee Meeting	
• Date of Meeting	None
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	None

Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	
❖ Clinical review(s) *(indicate date for each review)*	August 28, 2003
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	None Needed
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See Team Leader Memo
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Complete
❖ Statistical review(s) *(indicate date for each review)*	None
❖ Biopharmaceutical review(s) *(indicate date for each review)*	September 8, 2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	None
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	No Studies
• Bioequivalence studies	No inspection requested
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	September 4, 2003
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	September 4, 2003
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	September 4, 2003
❖ Facilities inspection (provide EER report)	Date completed: June 17, 2003 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (X) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	March 13, 2003
❖ Nonclinical inspection review summary	None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	None
❖ CAC/ECAC report	None

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

/s/

Randy Hedin
9/17/03 02:41:19 PM

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ON ORIGINAL

45 Day Meeting Checklist
NONCLINICAL PHARMACOLOGY/TOXICOLOGY

NDA 21-575 Fosamax (alendronate sodium) 70 mg weekly oral solution for post-menopausal osteoporosis

ITEM	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	X		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	X		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	X		
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA. (genotox, reprotox, adequate duration of chronic tox, carcinogenicity)	X		Have electronic files of the carcinogenicity studies been submitted for statistical review? Fosamax (alendronate sodium) is approved, this supplement is for a change in formulation; once weekly oral solution.

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?	X		
6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	X		The sponsor has indicated clinical bioequivalence with the 70 mg once weekly tablet formulation and has provided local esophageal irritation studies in dog (single and 5 week repeated dose) to support safety.
7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	X		
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	X		

ITEM	YES	NO	COMMENT
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	X		
10) Reasons for refusal to file:			

Supervisory Pharmacologist

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/s/

Karen Davis-Bruno
12/17/02 02:43:27 PM
PHARMACOLOGIST

APPEARS THIS WAY
ON ORIGINAL

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA Number, Requested Trade Name, Generic Name and Strengths (modify as needed for an efficacy supplement and include type):

Applicant: Merck Research Laboratories

Date of Application: November 15, 2002
Date of Receipt: November 18, 2002
Date of Filing Meeting: December 17, 2002
Filing Date: January 17, 2002

Indications requested: The treatment and prevention of post-menopausal osteoporosis

Type of Application: Full NDA __X__ Supplement _____
(b)(1) _____X____ (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S___X___ P_____
Resubmission after a withdrawal or refuse to file __No___
Chemical Classification: (1,2,3 etc.)__3___
Other (orphan, OTC, etc.)____Rx___

Has orphan drug exclusivity been granted to another drug for the same indication? YES NO X

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

If the application is affected by the application integrity policy (AIP), explain.

User Fee Status: Paid ____X_____ Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES___X___ NO_____
User Fee ID#__4444_____
Clinical data? YES _____ NO ___X___ Referenced to NDA# _____
Date clock started after UN _____NA_____

User Fee Goal date: ____September 18, 2003___

Action Goal Date (optional) _____

- Does the submission contain an accurate comprehensive index? YES X NO
- Form 356h included with authorized signature? YES X NO
  If foreign applicant, the U.S. Agent must countersign.

- Submission complete as required under 21 CFR 314.50? YES X NO
  If no, explain:

- If electronic NDA, does it follow the Guidance? YES X NO NA
  If an electronic NDA: all certifications must be in paper and require a signature.

- If Common Technical Document, does it follow the guidance? YES NO NA X

- Patent information included with authorized signature? YES X NO

- Exclusivity requested? YES; If yes, _____years NO X

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES X NO
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, ..."

- Financial Disclosure included with authorized signature? YES X NO
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- Has the applicant complied with the Pediatric Rule for all ages and indications? YES X NO
  If no, for what ages and/or indications was a waiver and/or deferral requested:

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES X NO

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES X NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers:

End-of-Phase 2 Meeting? Date___ NO X
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date___ NO X
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? YES NO X

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?
YES NO X

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?
NA

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? YES NO NA X

Advisory Committee Meeting needed? YES, date if known _____ NO X

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
YES NO NA X

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES X NO
  If no, did sponsor submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) package submitted? YES X NO

- Parenteral Applications Consulted to Sterile Products (HFD-805)? YES NO NA X

If 505(b)(2), complete the following:

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)? (Normally, FDA will refuse-to-file such applications.)
YES NO

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?
If yes, the application must be refused for filing under 314.54(b)(1) YES NO

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?
YES NO
If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

  YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  YES NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

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

/s/

Randy Hedin
1/16/03 09:53:22 AM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Merck & Co., Inc.
Sumneytown Pike, BLA-20
P.O. Box 4
West Point, PA 19486

2. TELEPHONE NUMBER *(Include Area Code)*

(484) 344-7597

3. PRODUCT NAME

Fosamax 70mg (Alendronate Sodium) oral Solution

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N 021-575

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☐ YES ☒ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4444

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Dennis M. Erb	Dennis M. Erb, Ph.D. Executive Director, Regulatory Affairs	November 1, 2002

FORM FDA 3397 (4/01)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See Tables C-1 and C-2 in Item 19	"Alendronate Sodium - 70 mg
	[redacted], Oral [redacted] Solution"	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
David Arkowitz	Controller, MRL Financial Services
FIRM/ORGANIZATION: Merck & Co., Inc.	
SIGNATURE	DATE

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

28 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Randy Hedin
7/24/03 10:49:49 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

Division of Metabolic and Endocrine Drug Products

PROJECT MANAGER LABELING REVIEW

Application Number: NDA 21-575

Name of Drug: Fosamax (alendronate sodium) Solution

Sponsor: Merck Research Laboratories

Material Reviewed

Submission Dates:

- November 15, 2002, submission containing draft labeling text for the combined tablet and solution package insert (PI), and patient package insert.

Background and Summary Description:

This new drug application (NDA) proposes an additional new oral solution formulation for Fosamax (alendronate sodium).

Review

The submitted draft printed labeling of text for the Package Insert (PI) (Identifier Number 79570, No Issued Date), was compared to the currently approved FPL of the text for the PI (Identifier Number 7957020, Issued July 2002). The following changes are noted:

Package Insert

- The phrase "AND ORAL [redacted] SOLUTION" is added to the name. The firm has been informed that the term [redacted] is not acceptable, and has agreed to remove the term.

- The paragraph, "Each bottle of the oral [redacted] solution contains 91.35 mg of alendronate monosodium salt trihydrate, which is the molar equivalent to 70 mg of free acid. Each bottle also contains the following inactive ingredients: sodium citrate dihydrate and citric acid anhydrous as buffering agents, sodium saccharin, artificial raspberry flavor, and purified water. Added as preservatives are sodium propylparaben 0.0225% and sodium butylparaben 0.0075%." is added to the DESCRIPTION section.

- The sentence "FOSAMAX 70 mg oral [redacted] solution and FOSAMAX 70 mg tablets are [redacted] added to the CLINICAL PHARMACOLOGY section. This is not acceptable (see Biopharm review).

- The sentence "Patients at increased risk of aspiration should not receive FOSAMAX oral [redacted] solution." Is added to the CONTRAINDICATIONS section.

- The phrase, " [redacted] ." in the **WARNINGS** section is changed to " . . . the recommended amount of water, . . ."

- The term "tablet" is changed to "dose" throughout the label and minor editorial changes are made throughout the label to accommodate the new dose. This is acceptable.

- In the *Dosing Instructions* subsection of the **PRECAUTIONS** section the sentence "To facilitate gastric emptying patients should drink at least 2 oz (a quarter of a cup) of water after taking FOSAMAX oral [redacted] solution." is added.

- In the *General* subsection of the **PRECAUTIONS** section the sentence, [redacted] is changed to, "Other disorders affecting mineral metabolism (Such as vitamin D deficiency) should also be effectively treated," and the sentence, "In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with FOSAMAX." is added after the above sentence.

- In the *Post-Marketing Experience* subsection of the **ADVERSE REACTIONS** section the sentence, "Rarely, symptomatic hypocalcemia has occurred, generally in association with predisposing conditions" is added after the phrase, ". . . (myalgia, malaise and rarely, fever) have been reported with FOSAMAX, typically in association with initiation of treatment." Also in this subsection, the phrase "rarely severe skin reactions, including Stevens-Johnson syndrome and toxic-epidermal necrolysis" is added after the phrase *skin*: rash (occasionally with photosensitivity), pruritus."

- In the *Prevention of osteoporosis in postmenopausal women* subsection of the **ADVERSE REACTIONS** section the term, "abdominal [redacted] is replaced with, "abdominal distention."

- In the **DOSAGE AND ADMINISTRATION** section the sentence "FOSAMAX should only be taken upon arising for the day." is added to the second paragraph, and the phrase " [redacted] is deleted. In the

same paragraph the sentence "To facilitate gastric emptying FOSAMAX oral [redacted] solution should be followed by at least 2 oz (a quarter of a cup) of water." is added. The phrase "or one bottle of 70 mg oral [redacted] solution once weekly" is added to the recommended dosage for the treatment of osteoporosis in postmenopausal women, and the treatment to increase bone mass in men with osteoporosis sections of the **DOSAGE AND ADMINISTRATION** section.

- The phrases, "No. 3833 – Oral [redacted] Solution FOSAMAX, 70 mg, is a clear, colorless solution with a raspberry flavor and is supplied as follows: **NDC** 0006-3833-34 unit-of-use cartons of 4 single-dose bottles containing 75 mL each." And FOSAMAX Oral [redacted] Solution: Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Do not freeze." are added to the **HOW SUPPLIED** section.

The rest of the label is identical.

Patient Package Insert

- The phrase "AND ORAL [redacted] SOLUTION" is added to the name. The firm has been informed that the term " [redacted] is not acceptable, and has agreed to remove the term.

- In the How should I take once weekly FOSAMAX? section, number 1 is changed from "Choose the day of the week that best fits your schedule. Every week. [redacted] to "Choose the day of the week that best fits your schedule. Every week, take one dose of Fosamax (one tablet or one entire bottle of solution) on your chosen day. Number 2 is changed from "After getting up for the day and before taking your first food, beverage, or other medication, [redacted] " to "After getting up for the day and before taking your first food, beverage, or other medication, take your FOSAMAX with plain water only as follows:
  - TABLETS: Swallow one tablet with a full glass (6-8 oz) of plain water.
  - ORAL [redacted] SOLUTION: Drink one entire bottle of solution followed by at least 2 ounces (a quarter of a cur) of plain water."

  The next paragraph of the How should I take once weekly FOSAMAX? section, is changed from [redacted] 'Do not take FOSAMAX with:
  Mineral water
  Coffee or tea
  Juice."

- Wherever " [redacted] appears in the PPI it is changed to "taking your FOSAMAX."

- In the FOSAMAX is for: subsection of the What is FOSAMAX section the sentence "FOSAMAX tablets are for treatment and prevention, and FOSAMAX oral [redacted] . solution is for treatment of osteoporosis." is added.

- In the Who should not take FOSAMAX? section the phrase "Difficulty swallowing liquids should not take FOSAMAX oral [redacted] solution" is added.

- In the What are the possible side effects of FOSAMAX? section the phrase ". . [redacted] ." is changed to "the recommended amount of water. . ."

The rest of the label is identical.

Conclusions

The only changes to the label are noted above. An approval letter should be issued.

Reviewed by: Randy Hedin, R.Ph., Senior Regulatory Management Officer

APPEARS THIS WAY
ON ORIGINAL

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/s/

Randy Hedin
9/17/03 03:03:50 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

Team Leader Memorandum

NDA: 21-575

DRUG: Alendronate 70 mg oral solution

COMPANY: Merck

PRIMARY MEDICAL OFFICER: Theresa Kehoe, MD

PRIMARY MEDICAL OFFICER'S RECOMMENDATION: Approve

PRIMARY BIOPHARMACEUTICS REVIEWER: Johnny Lau, Pharm D

BIOPHARMACEUTICS REVIEWER'S RECOMMENDATION: Approve

DATE OF MEMO: September 4, 2003

I. Background

In this NDA submission, Merck Research Labs (MRL) is seeking approval of a 70 mg oral solution of alendronate. The company is not seeking a new indication for the oral solution, rather this dosage formulation will provide patients who have difficulty swallowing a tablet with an alternative to the 70 mg alendronate tablet, which when taken once-weekly, is indicated for the treatment of postmenopausal and male osteoporosis.

Because clinical studies were not considered necessary for evaluation of this new dosage formulation, data from 4 clinical pharmacology studies provide the basis for approval of this NDA. These studies are: 2 pilot studies to examine the bioavailabilities of the oral [redacted] solution formulations relative to marketed tablets (one study examined the 10 mg dose only); 1 to demonstrate the bioequivalence of the final formulation of the 70 mg oral [redacted] solution to the 70 mg marketed tablet (study 177), and 1 to examine the safety and dose proportionality of higher doses of the oral [redacted] solution, from 70 mg up to 375 mg.

Study 177 is the pivotal bioequivalence study that compared urinary excretion of alendronate following single doses of the 35 mg oral solution and the 70 mg oral solution to the 70 mg tablet.

Dr. Kehoe reviewed the safety data from the 4 clinical pharmacology studies and did not identify any safety signals from these data.

Dr. Karen Davis-Bruno has reviewed the pharmacology – toxicology studies conducted in dogs and summarizes the findings as follows:

"Daily exposure to an alendronate solution (0.2 mg/ml) at pH 2 resulted in esophageal irritation in dogs. Exposure of the esophagus once weekly for one month to alendronate 0.8 mg/ml at pH 2 was not irritating to the esophageal mucosa. Increasing the alendronate concentration to 3.73 mg/ml pH 6.8 resulted in no morphologic evidence of esophageal irritation. Together these studies suggest that weekly dosing of an oral [redacted] formulation (pH 6.8) is not irritating to the esophagus despite a higher concentration (3.73mg/ml) than used in a once-a-day dosing solution (0.2 mg/ml) in the dog. Significant esophageal irritation (ulceration/erosion) was observed with 7.47 mg/ml given once weekly for four weeks, however this represents a significantly higher exposure multiple (17X) compared to the proposed MRHD (70 mg). Lower doses tested in the dog model (3.73 and 0.93 mg/ml) did not show significant irritation which represents exposures ≤10X the MRHD."

She recommends that the NDA be approved.

II. Pivotal Bioequivalence Study 177

This was a 3-way crossover, fasted, single-dose bioequivalence study between 35 mg oral solution, 70 mg oral solution, and the 70 mg oral tablet. The primary objective was to compare the urinary excretion of alendronate following a 70 mg alendronate oral [redacted] solution to that following an alendronate 70 mg tablet. The secondary objective was to compare the urinary excretion of alendronate following a 35 mg alendronate oral [redacted] solution to that following an alendronate 70 mg tablet. One hundred fifteen healthy male and female subjects, aged 18 to 79 years, entered the study. One hundred and nine subjects provided data for the primary analysis.

The geometric mean ratio and 90% CI of the urinary excretion of alendronate for the 70 mg solution vs. the 70 mg tablet were 0.99 (0.89 – 1.00); and 0.84 (0.76 – 0.93) for the 35 mg solution vs. the 70 mg tablet. These data indicate that the 70 mg solution, but not the 35 mg solution, is equally bioavailable to the 70 mg tablet.

All 115 study participants were included in the safety analyses. Sixty-six subjects reported a total of 219 clinical adverse experiences. Clinical adverse experiences were generally similarly distributed among the 3 treatments. The most common drug-related adverse experiences were headache (reported by 2 subjects following the 70 mg tablet, 4 following the 70 mg solution, and 2 following the 35 mg solution), diarrhea (2 following the 70 mg tablet, 3 following the 70 mg solution, and 2 following the 35 mg solution), and nausea (2 following the 70 mg tablet, 1 following the 70 mg solution, and 3 following the 35 mg solution). No laboratory adverse experiences were reported. One subject reported a serious adverse experience consisting of viral gastroenteritis. This subject experienced gastrointestinal and flu-like symptoms beginning several hours following his initial dose of alendronate, and was sent by the investigator to an emergency department the morning of Day 2 when the severity of the symptoms increased. In the emergency department, the subject was diagnosed with viral gastroenteritis and was treated with ibuprofen and intravenous fluids. The subject was discontinued from the study. In addition, one subject was discontinued from the study for a clinical adverse experience of hives, which developed after completion of the second study period.

III. Overview of Safety from the 4 Clinical Pharmacology Studies

As shown in the following table, 152 subjects received at least one dose of the alendronate 70 mg oral solution, and 90 participants received at least one dose of 140 mg or higher of the alendronate oral solution.

Number of Subjects Exposed to Oral Alendronate Solution (Studies 163, 177, and 204)

	Marketed Tablet		Oral [redacted] Solution				
Single Dose Treatment	70 mg N	35 mg N	70 mg N	140 mg N	280 mg N	375 mg N	Placebo N
Randomized	127	127	157	30	30	30	30
Received Dose	123	120	152	27	25	25	25
Total Discontinuations	3	2	7	2	0	0	0
Discontinuations due to Adverse Experiences	1	0	1	0	0	0	0
Discontinuations due to other (withdrew consent; lost to follow-up)	2	2	6	2	0	0	0

[*] Since these were crossover studies, the same subjects received more than one treatment.

No subject died during these studies. None of the subjects who received the 70 mg oral solution had a serious adverse event and only one subject from this group discontinued due to adverse event: hives. This subject received the 70 mg tablet prior to the solution without problems. Allergic reactions have been reported with alendronate tablets and this information is provided in the current product labeling.

Although higher than placebo, compared with the 70 mg tablet, the incidence of GI adverse events such as nausea (6%), diarrhea (5%), and vomiting (3%) was very similar for subjects in the 70 mg solution group. For unknown reasons, there was a relatively high percentage of subjects (~14%) in both the 70 mg tablet and solution groups who

complained of headache; none of the placebo subjects complained of headache. None of the headache were serious or of clinical concern.

There were no clinically significant changes in laboratory parameters.

IV. 120-Safety Update

MRL submitted a Safety Update Report on 14 March 2003. There are no new clinical trial data with the 70 mg oral solution since submission of this NDA in November 2002.

During the period of this safety update, there were 6 reports with fatal outcome identified spontaneously from healthcare providers in which the patients were on therapy with alendronate tablet once weekly.

0208[redacted]00048	76/F	Cardiac arrest	A patient with hypertension, thyroid disorder and hypercholesterolaemia was placed on therapy with alendronate 70 mg once weekly on [redacted] for the treatment of osteoporosis. Concomitant therapy included lisinopril, levothyroxine sodium, atorvastatin, and benserazide hydrochloride/levodopa. On [redacted], the patient developed wheezing and dyspnea and was diagnosed on [redacted] with asthmatic bronchitis. Therapy with methylprednisolone was initiated the same day. During that night, the patient died from an unexpected cardiac arrest.
0208[redacted]00100	70/F	Decompensation cardiac and Renal failure acute	Information was received from a physician via an agency concerning a patient with chronic lymphocytic leukaemia, cardiac insufficiency, compensated chronic renal insufficiency, coronary artery disease, diabetic nephropathy, arterial hypertension, diabetes mellitus type II, depression, obesity and polyarthropathy and a history of fractured coccyx and recurrent pleural effusions, who, on [redacted], while hospitalized due to poor general condition with immobility and pain in the left hip, was placed on therapy with alendronate 70 mg once weekly for the treatment of osteoporosis. Concomitant therapy included unspecified calcium and vitamin D. Laboratory analysis revealed that blood hemoglobin was 10.7 g/dl (anaemia) and white blood cell was 67000 (leukocytosis); hence, treatment of chronic lymphocytic leukaemia with chlorambucil and prednisolone was discussed. While on unspecified pain therapy, the patient's condition improved, but she was still depressed; another antidepressive medication and outpatient psychiatric treatment was recommended. On [redacted], with a reduced fluid and food intake, the patient developed acute renal failure with decreased diuresis, anuria, elevation of renal function tests, and cardiac decompensation. The patient was dialyzed and placed on a respirator; the increasing pleural effusion was a symptom of the cardiac decompensation and was drained. As a consequence, the patient developed congestion pneumonia and was treated with antibiotics. The patient's condition markedly improved and she was transferred. Subsequently, the patient's general condition worsened and the patient died of acute renal failure and cardiac decompensation on [redacted]. The reporting physician felt that acute renal failure was possibly related to therapy with alendronate.
0210[redacted]00004	82/M	Dissecting aortic aneurysm	Information was received from a treatment observation program, concerning a patient with an aortic aneurysm, who was placed on therapy with alendronate 70 mg once weekly for the treatment of osteoporosis (therapy duration was not reported). Subsequently, the patient died of a dissecting aortic aneurysm. According to the physician there is definitely no causal relationship between death and therapy with alendronate.
0210[redacted]00007	83/M	Liver carcinoma	Information was received from a physician and an agency concerning a patient with dermatitis, spinal osteoarthritis, and a history of sciatica and oesophageal dysmobility, who, on [redacted], was placed on therapy with alendronate 70 mg once weekly for the treatment of osteoporosis. Concomitant therapy included zolpidem tartrate, mirtazapine, mineral oil, acetaminophen, hydrocortisone, cetostearyl alcohol (+) phenoxyethanol (+) sodium lauryl sulfate, cimetidine, hydroxyzine, quinine sulphate, betamethasone valerate, psyllium husk, calamine, and hypromellose. The same day, the patient experienced a swollen mouth, mouth drop, loss of feeling on one side, shuffling, abdominal pain, angioedema, difficulty with his speech, paraesthesia of his legs, and blurred vision. The physician stated that the patient "developed a severe allergic reaction to the alendronate sodium after the initial dose and developed angioedema, difficulty with his speech, paraesthesia of his legs and abdominal pains." The agency report stated "Oedema of lips, tongue, difficulty with speech and blurred vision. Paraesthesia of fingers and legs. Low abdominal pain." Alendronate was discontinued the same day and was treated with an antihistamine and prednisolone for the swollen mouth, difficulty with speech, blurred vision, abdominal pain, and paraesthesia of legs. Subsequently, the patient experienced severe pains and on [redacted] was hospitalized and diagnosed with carcinoma of the liver. On [redacted], the patient died from carcinoma of the liver with unknown primary; an autopsy was not performed. The patient's abdominal pains and severe pain continued until time of death. The physician felt that the abdominal pain, angioedema, difficulty with speech, and paraesthesia of legs were related to therapy with alendronate; however, he did not feel that the carcinoma of the liver and severe pain were related to therapy with alendronate.

0210[redacted]00003	82/F	Hypocalcaemia	Information was received from a physician via an agency concerning a patient with hyperlipidaemia, cardiac failure, hypertension, depression, Parkinson's disease, podagra, and decubitus ulcer who was placed on therapy with alendronate 70 mg once weekly for the treatment of osteoporosis. Concomitant therapy included pravastatin, enalapril, furosemide, propranolol, mianserin, and estriol. On [redacted], the patient was hospitalized due to diarrhoea and dehydration and hypocalcaemia were revealed. Serum calcium test was 1.66 mmol/L and corrected serum calcium test was 1.9 mmol/L. Other lab test results: serum C-reactive protein test 207-260 mg/L, serum alanine aminotransferase test 85 U/L, serum albumin test 28 g/L, serum creatine kinase test 556 U/L, serum uric acid test 1109 micromol/L, and white blood cell count 13.4 - 2.2 x 10^9/L. The patient received treatment with intravenous fluid, calcium, and magnesium. On approximately [redacted], alendronate therapy was discontinued. Urine production decreased and serum creatinine test increased with values of 285-309 micromol/L. The patient's condition gradually worsened, and she died as a result of hypocalcaemia on [redacted].
0208USA02188	80*/F	Oesophageal cancer	A patient was placed on therapy with alendronate 70 mg once weekly for the treatment of osteoporosis. The patient had discontinued alendronate and subsequently, died of unknown causes. The family felt that alendronate gave her esophageal cancer. The registered nurse reported that the patient's daughter told a friend that her mother died of esophageal cancer from alendronate. The friend of the patient's daughter then reported this information to the registered nurse. The registered nurse reported that she spoke with the patient's physician concerning the patient and the physician said "not a problem with [alendronate]."

Of these events, hypocalcemia is biologically plausible. The exact role alendronate may have played in this case of hypocalcemia is unclear because there is no information on the duration of alendronate use prior to the event, pre-alendronate serum calcium levels, or the extent of the patient's diarrhea prior to hospitalization. That she was also taking lasix further complicates interpretation of causality. The precautions section of the product labeling clearly states that hypocalcemia must be corrected before initiating therapy with alendronate.

To the extent that it provides some safety information, in a 30-day endoscopy study, the company reports that the mean gastric erosion scores following treatment with placebo, alendronate 40 mg tablet daily, alendronate 280 mg oral solution once-weekly, and aspirin 650 mg QID were 0.11, 0.53, 0.09, and 2.51, respectively. The incidence of GI adverse events such as diarrhea, nausea, vomiting, and abdominal pain were higher in the 280 mg group compared with the placebo group.

According to Merck, the post-marketing reporting rates for serious esophageal and upper GI adverse events are very similar for the once-daily and once-weekly regimens.

V. Labeling

The following are proposed additions to the labeling:

Description

- Each bottle of the oral [redacted] solution contains 91.35 mg of alendronate monosodium salt trihydrate.....

Clinical Pharmacology

- Fosamax 70 mg oral [redacted] solution and Fosamax 70 mg tablets are [redacted]

Contraindications

Patients at increased risk of aspiration should not receive Fosamax oral [redacted] solution.

Dosing Instructions

- To facilitate gastric emptying patients should drink at least 2 oz of water after taking Fosamax oral [redacted] solution.....

Dosage and Administration

- To facilitate gastric emptying [redacted]
- [the following appears with the 70 mg tablet once weekly information] one bottle of 70 mg oral [redacted] solution once weekly

How Supplied

- Oral [redacted] solution Fosamax, 70 mg, is a clear, colorless solution with raspberry flavor.....

-The proposed labeling language is acceptable from a clinical standpoint.

VI. Comments and Recommendation

Merck has provided sufficient evidence to support that the 70 mg oral solution of alendronate is equally bioavailable to the 70 mg alendronate tablet. Studies in dogs suggest that the ——— solution at a dose comparable to 70 mg once-weekly, is not irritating to the esophagus. There was no evidence from the clinical studies that the safety profile of the ——— solution differs from the tablet, albeit, a limited number of subjects were exposed to this formulation. If used as directed, there is no reason to believe that the oral solution will have a less favorable upper GI-safety profile than the 70 mg tablet.

I recommend that the 70 mg alendronate oral solution be approved for the treatment of postmenopausal and male osteoporosis.

Eric Colman, MD

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/s/

Eric Colman
9/16/03 11:58:40 AM
MEDICAL OFFICER

David Orloff
9/16/03 05:49:54 PM
MEDICAL OFFICER
Concur with Dr. Colman's recommendation to approve.

APPEARS THIS WAY
ON ORIGINAL

From: Hedin, Durand M
Sent: Wednesday, September 03, 2003 10:54 AM
To: 'Flicker, Michele R.'
Subject: Labeling comments for NDA 21-575, Fosamax Solution

Dear Dr. Flicker,

We have the following comments concerning the labeling for NDA 21-575, Fosamax Solution.

> Please change the statement in the *absorption* subsection of the CLINICAL PHARMACOLOGY section that reads, "FOSAMAX 70 mg oral [redacted] solution and FOSAMAX 70 mg tablet are [redacted] to read "FOSAMAX 70 mg oral solution and FOSAMAX 70 mg tablet are equally bioavailable." Also, please remove the term " [redacted] from the name of the product.

Sincerely,

Randy Hedin

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/s/

Randy Hedin
9/3/03 11:11:46 AM
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APPEARS THIS WAY
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-575

Merck & Co., Inc.
Attention: Michele Flicker, M.D. Ph.D.
Director, Regulatory Affairs
P.O. Box 2000, RY 33-720
Rahway, NJ 07065

Dear Dr. Flicker:

Please refer to the meeting between representatives of your firm and FDA on July 31, 2003. The purpose of the meeting was to discuss chemistry issues.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Randy Hedin
Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

Meeting Date: July 31, 2003 Time: 11:00 - 11:30 PM Location: 14-B-45

NDA 21-575 Fosamax Solution

Type of Meeting: Advice

External participant: Merck Research Laboratories

Meeting Chair: Dr. Mamta Gautam-Basak

External participant lead: Dr. Michele Flicker

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Division of Metabolism and Endocrine Drug Products:

Randy Hedin, R.Ph. Senior Regulatory Management Officer

Division of New Drug Chemistry II:

Mamta Gautam-Basak, Ph.D., Team Leader
Elsbeth Chikhale, Ph.D., Reviewer

External participant Attendees and titles:

Michele Flicker M.D., Ph.D., Director, Regulatory Affairs

Meeting Objectives:

The meeting was requested by the Division to discuss chemistry issues.

Discussion Points and Decisions (agreements) reached:

- The Division stated that Merck's response to comments one and two of our July 23, 2003 communication are acceptable.

- The Division also stated that Merck's response to comment three of our July 22, 2003 communication is acceptable.

- The Division stated regarding Merck's response to comment two of our July 22, 2003 correspondence concerning use of the European Pharmacopeia's method for uniformity specifications is not acceptable. Since acceptance criteria as per the USP test for content uniformity <905> are significantly different than those described in

the NDA, drug product specifications should be revised to conform to the current USP<905>.

- The Division further stated regarding Merck's response to comment four of our July 22, 2003 correspondence that we need revised drug product specification to include USP<905>.

- The Division stated the following regarding Merck's response to comment one of our July 22, 2003 correspondence concerning the [redacted]

  - We have contacted the s[redacted], and suggested that they submit a DMF. The [redacted] previously stated to the Division that they did not know how to submit a DMF, and Merck committed to have their chemists contact the ink supplier and provide guidance for the DMF submission.

  - The Division asked Merck to provide a certification from the [redacted] regarding compliance with 21 CFR.

  - The Division stated that changes to the [redacted] can not be reported in the annual report as proposed in response dated July 21, 2003.

Unresolved or issues requiring further discussion:

- None

Action Items:

- None

Signature, minutes preparer:

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Concurrence Chair:

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/s/

Randy Hedin
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APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Flicker:

We have the following comments concerning the chemistry review of Fosamax Solution, NDA 21-575. We would appreciate a prompt response to the requests for information.

- On page 20 you provide test results of the antimicrobial effectiveness (AME) test (table P-7). Provide the test method or reference to USP<51>, as appropriate.

- On page P-34 you have provided the tests and methods used to control the artificial raspberry flavor prior to use in manufacture. However, the acceptance criteria for those tests were not provided. Provide your acceptance criteria for artificial raspberry flavor.

If you have any questions contact me at 301-827-6392.

Sincerely,

Randy Hedin

From: Hedin, Durand M
Sent: Tuesday, July 22, 2003 9:27 AM
To: 'Flicker, Michele R.'
Subject: Chemistry Comments, NDA 21-575

Dear Dr. Flicker:

We have the following comments concerning the chemistry review of Fosamax Solution, NDA 21-575. We would appreciate a prompt response to the requests for information.

- Provide a list of components or ingredients used in the formulation of the ink /varnish. On page p-20 of the drug product section, you mention that "the secondary packaging components (printing ink and adhesive) were carefully selected to be suitable for pharmaceutical or food grade materials and ensure compliance with local regulations." However, no reference could be located in the submission. Provide reference to CFR or GRAS for the ink components, to support your claim.

- The "uniformity of dosage units" test should be performed according to the current (USP26/NF21) method USP<905>.

- The microbial limits test USP<61> should also include the absence of Staphylococus aureas, absence of Salmonella, and absence of Pseudomonas aeruginosa.

- Revised drug product specifications with above recommended changes should be submitted.

If you have any questions contact me at 301-827-6392.

Sincerely,

Randy Hedin

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/s/

Randy Hedin
7/22/03 09:43:15 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-575

Merck & Co., Inc.
Attention: Michele Flicker, M.D., Ph.D.
Director, Regulatory Affairs
P.O. Box 2000
Mail Drop: Ry 33-720
Rahway, NJ 07065

Dear Dr. Flicker:

Please refer to your November 15, 2002 new drug application (NDA), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosamax (alendronate sodium) Oral [redacted] Solution.

We have completed our filing review of your application. At this time, we have not identified any potential review issues. Our filing review is only a preliminary review and deficiencies may be identified during substantive review of your application.

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

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff
1/27/03 02:18:53 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-575

Merck & Co., Inc
Attention: Michele R. Flicker, M.D., PhD.
Director, Regulatory Affairs
P.O. Box 2000, Mail Drop: RY 33-720
Rahway, NJ 07065

Dear Dr. Flicker:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Fosamax® (alendronate sodium) Oral Solution
Review Priority Classification:	Standard (S)
Date of Application:	November 15, 2002
Date of Receipt:	November 18, 2002
Our Reference Number:	NDA 21-575

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 17, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 18, 2003.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Randy Hedin, R.Ph.
Senior Regulatory Management Officer
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