CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER for: 020560, S018

ADMINISTRATIVE DOCUMENTS and CORRESPONDENCE

Merck & Co., Inc.
West Point PA 19486

November 24, 1999

MERCK
Research Laboratories

Solomon Sobel, MD, Director
Division of Metabolism and Endocrine Drug Products
HFD-510, Room 14B-04
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-560/S-015, S-018: FOSAMAX™
(Alendronate Sodium Tablets)

AMENDMENT TO PENDING SUPPLEMENTAL APPLICATIONS

Dear Dr. Sobel:

Reference is made to the pending supplemental new drug applications cited above for FOSAMAX™ (Fracture Intervention Trial (FIT), 4-Year Data) submitted September 3, 1998 and FOSAMAX™ (Estrogen/HRT) submitted January 28, 1999. Reference is also made to the Agency's September 3, 1999 Approvable Letter for S-015 and to the November 9, 1999 amendment to this supplemental application. Further reference is made to multiple conversations between members of the Agency and Merck Research Laboratories (MRL, a division of Merck & Co., Inc.), and to a November 24, 1999 teleconference in which all remaining issues regarding the above referenced supplements were resolved.

Attached, as agreed, is a revised mockup package circular which incorporates all agreed changes, as well as clean running text of the Patient Package Insert.

Labeling

In response to the Agency's proposal for additional language in the Precautions section, MRL agrees to the following language. The new section now reads (p. 21 of the mockup):

[redacted]

In addition, the sentence "No other specific drug interaction studies were performed." was deleted from the Clinical Pharmacology section (p. 4 of the mockup).

[redacted]

Promotion

Although Merck does not intend to encourage the concomitant use of FOSAMAX™ with HRT, Merck and the Agency have agreed that Merck retains the right to promote. Specifically, as discussed, Merck retains the right to distribute publications (without disclaimers) which contain data based upon the use of FOSAMAX™ with HRT.

Carcinogenesis Language

Upon receipt and review of Dr. Steigerwalt's information, MRL will work with him to resolve any remaining carcinogenesis language issues. It is MRL's understanding that resolution of these issues is not a requirement for approval of supplements S-015 and S-018.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct any further requests or questions to Michele R. Flicker, MD, PhD (732-594-1502) or, in my absence, Steve Caffe, MD (610-397-2835).

Sincerely yours,

Michele R. Flicker

Michele R. Flicker, MD, PhD
Director
Regulatory Affairs

Q:\flicker\projects\fosamax\estrogen\Amend1124

Attachments: Mockup package circular
Patient Package Insert

Fax/Federal Express

Desk Copy with Attachments: Ms Enid Galliers, HFD-510, Room 14B-04 – Federal Express #1

NDA 20-560 FOSAMAX®
Alendronate sodium
Patent Information

Item 13

PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

1.	Active Ingredient	Alendronate sodium
2.	Dosage	5 mg and 10 mg
3.	Trade Name	FOSAMAX®
4.	Dosage Form Route of Administration	Tablet Oral
5.	Applicant Firm Name	Merck Research Laboratories
6.	NDA Number	20-560
7.	Approval Date	
8.	Exclusivity - Date First ANDA Could Be Submitted	Three (3) years from this NDA approval date or five (5) years from September 29, 1995 (September 29, 2000)
9.	Applicable Patent Numbers	US Patent 4,621,077 Expires August 6, 2007 US Patent 5,358,941 Expires December 2, 2012 US Patent 5,681,590 Expires December 2, 2012 US Patent 5,804,570 Expires February 17, 2015 US Patent 5,849,726 Expires June 6, 2015

NDA 20-560 FOSAMAX®
Alendronate sodium
Patent Information

Item 14

Pursuant to the provisions of Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. Section 355 (b)(1)], attached hereto please find the patent information for the above-identified application.

The undersigned declares that U.S. Patent Nos. 4,621,077, 5,358,941, 5,681,590, 5,804,570, and 5,849,726 cover the formulation, composition and/or method of use of FOSAMAX® (alendronate sodium tablet). This product is the subject of this application for which approval is being sought.

U.S. Patent No. 4,621,077, having an expiration date of August 6, 2007, claims a method of use. This patent is owned by Merck & Co., Inc., Rahway, NJ.

The undersigned declares that U.S. Patent No. 4,621,077 covers the formulation, composition, and/or method of use of FOSAMAX®. This product is the subject of this application for which approval is being sought.

U.S. Patent No. 5,358,941, having an expiration date of December 2, 2012, claims a drug product. This patent is owned by Merck & Co., Inc., Rahway, NJ.

The undersigned declares that U.S. Patent No. 5,358,941 covers the formulation, composition, and/or method of use of FOSAMAX®. This product is the subject of this application for which approval is being sought.

U.S. Patent No. 5,681,590, having an expiration date of December 2, 2012, claims a drug product. This patent is owned by Merck & Co., Inc., Rahway, NJ.

The undersigned declares that U.S. Patent No. 5,681,590 covers the formulation, composition, and/or method of use of FOSAMAX®. This product is the subject of this application for which approval is being sought.

U.S. Patent No. 5,804,570, having an expiration date of February 17, 2015, claims a method of use. This patent is owned by Merck & Co., Inc., Rahway, NJ.

The undersigned declares that U.S. Patent No. 5,804,570 covers the formulation, composition, and/or method of use of FOSAMAX®. This product is the subject of this application for which approval is being sought.

U.S. Patent No. 5,849,726, having an expiration date of June 6, 2015, claims a drug, drug product, and method of use. This patent is owned by Merck & Co., Inc., Rahway, NJ.

NDA 20-560 FOSAMAX®
Alendronate sodium
Patent Information

Item 14

The undersigned declares that U.S. Patent No. 5,849,726 covers the formulation, composition, and/or method of use of FOSAMAX®. This product is the subject of this application for which approval is being sought.

1/19/99

Anthony D. Sabatelli
Senior Patent Attorney

Date

Attachment

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY FOR NDA # 20-560 SUPPL # 018

Trade Name Fosamax Generic Name alendronate

Applicant Name Merck HFD # 510

Approval Date If Known 24 NOV. 1999

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /___/ NO /✓/

b) Is it an effectiveness supplement?

YES /✓/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? 3

e) Has pediatric exclusivity been granted for this Active Moiety?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /X/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active

moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20 560 _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /✓/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 097

Study 077

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 097 _____

Study 072 _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # [ ] YES /✓/ | NO /___/ Explain: _____

Investigation #2

IND # [ ] YES /✓/ | NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ | NO /___/ Explain _____

_____	_____
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

/S/

Signature

Title: CSO

11/24/99

Date

/S/

Signature of Division Director

11-24-99

Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20560	**Trade Name:**	FOSAMAX (ALENDRONATE SODIUM)10+40MG TABS
Supplement Number:	18	**Generic Name:**	ALENDRONATE SODIUM
Supplement Type:	SE1	**Dosage Form:**	TAB
Regulatory Action:	AP	**Proposed Indication:**	The supplemental application provides clinical efficacy and safety documentation for taking Fosamax with estrogen/hormone replacement therapy.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

The supplement is for the use of Fosamax with estrogen/hormone replacement therapy in postmeopausal women and would be contraindicated in pediatric patients.

Same as above.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, RANDY HEDIN

/S/

Signature

11/2/99

Date

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-560/S-018

FEB 16 1999

Merck Research Laboratories
Sumneytown Pike P.O. Box 4 BLA-20
West Point, PA 19486

Attention: Michelle W. Kloss, Ph.D.
Director, Regulatory Affairs

Dear Dr. Kloss:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Fosamax® (Alendronate Sodium Tablets)
NDA Number:	20-560
Supplement Number:	S-018
Date of Supplement:	January 28, 1999
Date of Receipt:	January 28, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on March 29, 1999, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely

/S/

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Merck & Co., Inc.
West Point, PA 19486

November 23, 1999

MERCK
Research Laboratories

Solomon Sobel, MD, Director
Division of Metabolism and Endocrine Drug Products
HFD-510, Room 14B-04
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-560/S-015, S-018: FOSAMAX™
(Alendronate Sodium Tablets)

AMENDMENT TO PENDING SUPPLEMENTAL APPLICATIONS

Dear Dr. Sobel:

Reference is made to the pending supplemental new drug applications cited above for FOSAMAX™ (Fracture Intervention Trial (FIT), 4-Year Data) submitted September 3, 1998 and FOSAMAX™ (Estrogen/HRT) submitted January 28, 1999. Reference is also made to the Agency's September 3, 1999 Approvable Letter for S-015 and to the November 9, 1999 amendment to this supplemental application.

Reference is also made to the November 18, 1999 teleconference in which members of the Agency and Merck Research Laboratories (MRL, a division of Merck & Co., Inc.) discussed the labeling for pending supplements S-015 and S-018. Further reference is made to a November 22, 1999 teleconference between the Agency and MRL in which the Agency requested that additional language be added to the Precautions section. Specific reference is made to a November 23, 1999 teleconference between Dr. Sol Sobel (FDA) and Dr. Bonnie Goldmann (MRL) in which progress towards resolution of outstanding issues occurred.

It is MRL's understanding that for S-015 all issues have been resolved and no further dialogue is necessary.

As a result of the November 23, 1999 teleconference, MRL believes the positions of the Agency and that of MRL to be very close together on labeling, Phase IV, and promotional issues.

Labeling

In response to the Agency's proposal for additional language in the Precautions section, MRL proposes the following language with a reference to the Clinical Pharmacology section of the label. The new section now reads:

[redacted]

Promotion

Although Merck does not intend to encourage the concomitant use of FOSAMAX™ with HRT, we cannot commit to not promote, since this might be interpreted to preclude the use of publications. As discussed with the Agency, Merck wishes to reserve the right to distribute publications (without disclaimers) which contain data based upon the use of FOSAMAX™ with HRT.

Carcinogenesis Language

MRL proposes that Dr. Steigerwalt's request to modify the existing carcinogenesis language not be discussed at the present time. After Dr. Steigerwalt has had the opportunity to review the data, MRL will work with him to resolve any remaining issues.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct any further requests or questions to Michele R. Flicker, MD, PhD (732-594-1502) or, in my absence, Steve Caffe, MD (610-397-2835).

Sincerely yours,

Michele R. Flicker

APPEARS THIS WAY
ON ORIGINAL

Michele R. Flicker, MD, PhD
Director
Regulatory Affairs

Attachments: Fax –November 19, 1999: Mr. Randy Hedin (301-443-9282)
Mockup package circular

Fax/Federal Express

Desk Copy with Attachments: Mr Randy Hedin, HFD-510, Room 14B-04 – Federal Express #1

Q flicker\projects\fosamax\estrogen\Amend1122c

Michele R. Flicker, MD,PhD,FACP

Merck & Co., Inc.
P.O. Box 2000
Rahway NJ 07065
Tel 732 594 1502
Fax 732 594 1030
Email michele_flicker@merck.com

November 19, 1999

Solomon Sobel, MD, Director
Division of Metabolism and Endocrine Drug Products
HFD-510, Room 14B-04
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

MERCK
Research Laboratories

NDA 20-560/S-015, S-018: FOSAMAX™
(Alendronate Sodium Tablets)

AMENDMENT TO PENDING SUPPLEMENTAL APPLICATIONS

Dear Dr. Sobel:

Reference is made to the pending supplemental new drug applications cited above for FOSAMAX™ (Fracture Intervention Trial (FIT), 4-Year Data) submitted September 3, 1998 and FOSAMAX™ (Estrogen/HRT) submitted January 28, 1999. Further reference is made to the Agency's September 3, 1999 Approvable Letter for S-015 and to the November 9, 1999 amendment to this supplemental application. The draft labeling submitted with the November 9, 1999 amendment to S-015 also included the draft labeling for supplement S-018. Reference is also made to the Agency's November 10, 1999 facsimile transmission which requested additional revisions to the draft labeling provided for supplement S-018. Finally, reference is made to the November 18, 1999 teleconference in which the Agency and Merck Research Laboratories (MRL, a division of Merck & Co., Inc.) discussed and resolved all pending S-015 and S-018 labeling issues.

With this submission, MRL is providing a revised package circular and patient package insert which reflect the revisions agreed upon at the teleconference. Key elements of the revised package circular include the:

- Histomorphometry results from S-018 (Estrogen/HRT)
  (in response to the November 10, 1999 Agency request)
- Description of the S-015 (FIT-4) study population completion rate
  (in response to the September 3, 1999 Approvable letter)
- Adverse event table based on S-015
  (in response to the September 3, 1999 Approvable letter)

Because there are many parameters by which bone turnover may be assessed histomorphometrically, MRL believes the second sentence in the histomorphometry paragraph (revised mock-up, p.15) is incomplete without defining the parameter used to generate the percentage values cited for bone turnover suppression. In this case, the parameter was mineralizing surface. Thus, although not yet incorporated into this faxed version of the package circular mockup, MRL plans to add the clarifying phrase "(as assessed by mineralizing surface)" to the second sentence of the above-mentioned histomorphometry results language. The histomorphometry paragraph will then read:

"Histomorphometric studies of transiliac biopsies in 92 subjects showed normal bone architecture. Compared to placebo there was a 98% suppression of bone turnover (as assessed by mineralizing surface) after 18 months of combined treatment with FOSAMAX and HRT, 94% on FOSAMAX alone, and 78% on HRT alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence and fracture healing have not been studied."

MRL will send a new mockup with this last revision, as well as the clean running text versions of the package circular and patient package insert, on Monday, November 22, 1999.

MRL wishes to express its appreciation to the Agency for a productive and collaborative teleconference.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct any further requests or questions to Michele R. Flicker, MD, PhD (732-594-1502) or, in my absence, Steve Caffe, MD (610-397-2835).

Sincerely yours,

Michele R. Flicker

Michele R. Flicker, MD, PhD
Director
Regulatory Affairs

Q:\daly\Amend1118

Attachments

Fax 18-Nov-1999: Mr. Randy Hedin (301-443-9282)

Michele R. Flicker, MD,PhD,FACP

Merck & Co., Inc.
P.O. Box 2000
Rahway NJ 07065
Tel 732 594 1502
Fax 732 594 1030
Email michele_flicker@merck.com

November 3, 1999

Solomon Sobel, MD, Director
Division of Metabolism and Endocrine Drug Products
HFD 510, Room 14B-04
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

MERCK
Research Laboratories

NDA 20-560/S-018: FOSAMAX™
(Alendronate Sodium Tablets)

Response to Request for Information

Dear Dr. Sobel:

Reference is made to the pending supplemental new drug application cited above for FOSAMAX™ (estrogen/HRT) submitted January 28, 1999. Further reference is made to a telephone conversation among Mr. Randy Hedin (FDA), Dr. Bruce Schneider (FDA) and Dr. Michele Flicker (Merck Research Laboratories, Inc (MRL), a division of Merck & Co., Inc.) on November 2, 1999. During this conversation, the Agency questioned apparent inconsistencies between the patient numbers presented in Table 34 (pp. 88-89) and the associated text (p. 86, Reference 2) for FACET Protocol 097.

With this submission, MRL addresses the consistency between patient numbers in Table 34 and the associated text. Numerical differences were usually due to patients who may have received x-rays, but for whom the reports were not available to MRL.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

We hope this explanation proves helpful and resolves your concerns. Please direct any further requests or questions to Michele R. Flicker, MD, PhD (732 594-1502) or, in my absence, Steve Caffé, MD (610-397-2835).

Sincerely yours,

Michele Flicker

Michele R. Flicker, MD, PhD
Director
Regulatory Affairs

Michele R. Flicker, MD,PhD,FACP

Merck & Co., Inc.
P.O. Box 2000
Rahway NJ 07065
Tel 732 594 1502
Fax 732 594 1030
Email michele_flicker@merck.com

October 27, 1999

Solomon Sobel, MD, Director
Division of Metabolism and Endocrine Drug Products
HFD-510, Room 14B-04
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

MERCK
Research Laboratories

NDA 20-560/S-018: FOSAMAX™
(Alendronate Sodium Tablets)

Response to Request for Information

Dear Dr. Sobel:

Reference is made to the pending supplemental new drug application cited above for FOSAMAX™ (estrogen/HRT) submitted January 28, 1999. Further reference is made to several telephone conversations among Mr. Randy Hedin (FDA), Dr. James Gebert (FDA), and Dr. Michele Flicker (MRL, a division of Merck & Co., Inc.) on October 15th, 18th, and 20th, 1999. In those conversations the Agency questioned apparent discrepancies between the SAS analysis dataset bone mineral density (BMD) values and the case report form BMD values provided in this supplemental NDA. Of particular concern were lumbar spine and femoral neck values for certain patients from Protocol 072, especially patients with allocation numbers 10 and 13.

With this submission, MRL is providing an analysis of the probable origin of the differences between case report form BMD values and statistical analysis dataset values. Possible sources for these differences include: 1) the use of longitudinal correction factors for all body sites; 2) adjustments in calculating BMD values when there is a prevalent vertebral fracture; and 3) adjustments for missing vertebral, hip or wrist areas in the BMD scans.

We hope this analysis proves helpful and resolves your concerns. Please direct any further requests or questions to Michele R. Flicker, MD, PhD (732-594-1502) or, in my absence, Steve Caffé, MD (610-397-2835).

Sincerely yours,

Michele Flicker

Michele R. Flicker, MD, PhD
Director
Regulatory Affairs

Q:daly\Resp1027

Attachment

Fax/Federal Express #1

Desk Copies: Ms. Julie Rhee, HFD 510, Room 14B-04 - Federal Express #1
Mr. Randy Hedin, HFD-510, Room 14B-04 - Federal Express #1
Dr. James Gebert, HFD-715, Room 10B-45 - Federal Express #2

NDA 20-560/S-018: FOSAMAX™ (Alendronate Sodium Tablets)
Response to Request for Information
Possible Sources of Discrepancies Between Case Report Form BMD Values and Statistical Analysis Dataset BMD Values

There are several possible sources of discrepancies between case report form BMD values and statistical analysis dataset values. These are the use of longitudinal correction factors for all body sites, adjustments in calculating BMD values when there is a prevalent vertebral fracture, and adjustments for missing vertebrae, hip or wrist areas in the BMD scans.

Since its inception, the FOSAMAX clinical development program employed quality control (QC) centers that are blinded to treatment allocation to process bone mineral density data. As the study progresses, bone mineral density scans from investigator sites are sent to the QC centers which evaluates the results of scans prior to submission of data to Merck Research Laboratories. (More details on the role of these centers can be found in our study protocols.) MRL then includes the QC processed data into the study database, and case report form BMD values are generated from this database. Near the end of the trial, the QC center generates longitudinal BMD correction factors which provide an adjustment for measurement drift over time at a study site. The QC center provides MRL with a report that documents the appropriate correction factors. During the preparation of the original treatment NDA, a decision was made to apply these correction factors to the statistical analysis datasets rather than the study database. This adjustment is done in our data setup programs that create SAS datasets from the study database. Thus, the application of correction factors is one source of discrepancy between the statistical dataset BMD value and the case report form value.

For Protocol 072, all investigator sites used Hologic machines. Medical Data Management (MDM, Waltham, MA.) served as the BMD quality control center for this trial. The availability of the correction factors was briefly described in the clinical study report (Section 6f., p. 24) and the longitudinal correction factors can be found in Appendix 4.20 of the same report.

The correction factors were applied in the following manner for this protocol. The Hologic machine indicates the start date for any correction factor for a study site. Thus for each patient at a study site, the date of the BMD scan is compared with the start date of a correction factor for the site. If the date of the scan is after the start date, then the correction factor is applied in a multiplicative manner. This will result in a discrepancy between the statistical analysis dataset value and the case report form value.

EXAMPLE 1.

Consider allocation number 10 in Protocol 072. This patient had a bone mineral density measurement on day 749 (6/5/97). The lumbar spine BMD case report value was 0.762 gm/cm^2 and the statistical data analysis set value was 0.76517 gm/cm^2.

A correction factor of 1.00416 was applied to BMD measurements made with the Hologic densitometer at the study center that included patient number 10 for all measurements made from 5/12/97 onwards.

Thus, since the measurement date for this patient was 6/5/97, the multiplicative correction factor was applied. The value of 0.762 now becomes 0.762 x 1.00416 = 0.76517 (rounded to 5 decimal places).

There are several other possible BMD adjustments. Lumbar spine BMD values may be distorted if a prevalent fracture exists at lumbar sites L1-L4. Although this is a rare event, in such an instance, the fractured site is not used in the calculation of lumbar spine BMD at all time points (i.e. the data for this vertebra is deleted from all subsequent BMD calculations). Also, the number of vertebrae scanned for an individual may be inconsistent across time and adjustments need to be made. For this situation, data is carried forward from the last recorded value. Unfortunately, these ground rules do not appear to have been provided with the Estrogen Combination submission. The ground rules can be found in Appendix [3.3] of the two-year Protocol 035/037 extension CSR that was previously submitted to the agency. These are reproduced verbatim in the Appendix. These ground rules are a bit complex and the example below will illustrate their use.

EXAMPLE 2.

In Protocol 072, several conventions were applied for allocation number (AN) 13. AN 13 had a prevalent of L2 vertebral fracture and subsequently fractured vertebra L1 on day 420 (6/17/96). Up to day 420, convention one was applied. Her lumbar spine BMD values were recalculated based on her L1, L3, and L4 AREA and BMC information:

BMD=(L1BMC+L3BMC+L4BMC)/(L1AREA+L3AREA+L4AREA).

For study days beyond 420 both conventions above were applied. Thus, L1BMC and L1AREA were deleted due to fracture and the last available values of L1BMC and L1AREA prior to Day 420, which was Day 379, were used instead.

Here is an example of Day 568 (12/19/96). The lumbar spine BMD case report value was 0.825 (gm/ cm^2) and the statistical analysis dataset value was 0.78842.

	L1	L2	L3	L4
BMC(gm)	7.34*	NA**	12.37	13.79
AREA(cm^2)	11.84*	NA**	14.48	16.17

* : carried forward from Day 379.
** : deleted due to prevalence fracture.

Lumbar Spine BMD=(7.34+12.37+13.79)/(11.84+14.48+16.17)=0.78842

APPENDIX: BMD GROUND RULES

The ground rules for handling fracture vertebra and missing vertebra are reproduced below verbatim from Appendix [3.3] of the two-year Protocol 035/037 extension CSR that was previously submitted to the agency.

Situation: Vertebrae are fractured
Convention: If a vertebra was fractured, all BMD measurements of that vertebra occurring after the time-point of fracture were deleted. For lumbar spine, BMD was re-computed based on the remaining vertebrae measured. Since this deletion would result in inconsistent vertebrae being scanned over time, the following data handling convention would also apply:

Situation: Vertebrae scanned over time are inconsistent
Convention: If the number of vertebrae used to calculate PA lumbar spine was inconsistent over time in the baseline relative day range, then the last value in the range was considered the baseline value, rather than the average of values in the baseline day range.
If the number of vertebrae used to calculate PA lumbar spine was inconsistent over time in the on-treatment portion of the study, previous on-treatment vertebral area, bone mineral content, bone mineral density measurements were carried forward if this would provide consistency over time.

(In addition, for hip and wrist BMD measurements, if the same side of the hip (left vs. right) or the same wrist (left vs. right) were not measured over time, then all measurements not consistent with the baseline measurement were deleted.)

RANDY H.

Michele R. Flicker, MD,PhD,FACP

DESK COPY

Merck & Co., Inc.
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Tel 732 594 1502
Fax 732 594 1030
Email michele_flicker@merck.com

October 1, 1999

MERCK
Research Laboratories

Solomon Sobel, MD, Director
Division of Metabolism and Endocrine Drug Products
HFD-510, Room 14B-04
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-560/S-018: FOSAMAX™
(Alendronate Sodium Tablets)

Response to Request for Information

Dear Dr. Sobel:

Reference is made to the pending supplemental new drug application cited above for FOSAMAX™ (estrogen/HRT) submitted January 28, 1999. Further reference is made to a September 10, 1999 telephone conversation between Dr. James Gebert (FDA) and Dr. Michele Flicker (MRL, a division of Merck & Co., Inc.) in which Dr. Gebert indicated that the SAS program supporting this supplement was not yielding accurate lumbar spine results as compared to the submitted table 18 for protocol 097 (located in volume 4, published page number 321).

By desk copy with CD to Dr. Gebert, we are providing the corrected SAS datasets and programs.

We apologize for any inconvenience this may have caused. Please direct any questions to Michele R. Flicker, MD, PhD (732-594-1502) or, in my absence, Larry P. Bell, MD (610-397-2310).

Sincerely yours,

Michele R. Flicker

Michele R. Flicker, MD, PhD
Director
Regulatory Affairs

Q:\carnal\mk-0217\responses\s018_res2

Federal Express #1

Desk Copy with CD: Dr. James Gebert, HFD-715, Room 10B-45 - Federal Express #2

Desk Copy (Letter Only): Mr. Randy Hedin, HFD-510, Room 14B-04 - Federal Express #1

Merck & Co., Inc.
West Point, PA 19486

DUPLICATE

NDA SUPP AMEND
SE8-018/BM

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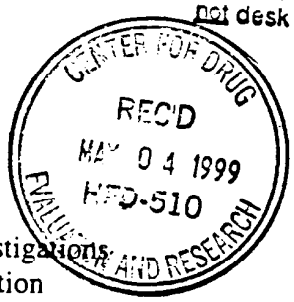

May 3, 1999

MERCK
Research Laboratories

H.W. Ju, M.D.
HFD-344, Room 125
Division of Scientific Investigations
Food and Drug Administration
7520 Standish Place
Rockville, Maryland 20855

NDA 20-560/S-018: FOSAMAX™
(Alendronate Sodium Tablets)
Response to FDA Request for Information

Dear Dr. Ju:

Reference is made to the pending supplemental new drug application cited above and to an April 16, 1999 telephone conversation between Dr. H.W. Ju (FDA) and Dr. Michele Flicker (MRL, a Division of Merck & Co., Inc.). During this conversation, MRL was informed that the FDA intended to perform inspections at sites 072-012 (Dr. Clark McKeever), 097-007 (Dr. Mark T. Ettinger) and 080-003 (Dr. Robert Jaffe). To facilitate these inspections, the Agency requested additional relevant clinical and monitoring information described below.

With this letter, MRL is providing the requested information. The site-specific clinical information consists of four volumes, two for Dr. McKeever's site, and one each for Dr. Ettinger's site and Dr. Jaffe's site as noted above. The site-specific information for each investigator includes the following:

- Form 1572 for the principal investigator
- Copy of the protocol
- Cover letter used in the past to communicate and summarize changes for each protocol amendment
- Total # patients entered for that investigator
- Total # patients completed
- Total # dropouts and reason for each dropout
- List of protocol violators and associated explanations
- Data listing for adverse reactions
- Primary individual efficacy data listings (listings which were submitted to the NDA)
- Case Report Forms (see next page)

For the Case Report Forms (CRF) section, the list of allocation number enrollment precedes the CRFs. CRFs were requested for the following:

- For site 072-012, the CRF for the 1st, 20th, 40th, and 65th patient enrolled
- For site 097-007, the CRF for the 1st, 10th, 20th, and 35th patient enrolled
- For site 080-003, the CRF for the 1st, 5th, 10th, and 13th patient enrolled

During our preparation of the above materials, three subjects were identified who are not reflected in the final study database. One of those subjects is from study 080-003; the other two from study 080-005. The patient from study 080-003 is the only patient who actually received study drug. Her inclusion in that study report would have influenced the number of subjects enrolled (N = 14 rather than 13 at that site), the number dropped (N = 1 rather than 0 at that site) and possibly the listing of adverse events and protocol violators (N = 2 rather than 1). The primary efficacy analysis per protocol and the conclusions of the study would remain unchanged.

Because these three patients are not included in the final database, additional explanatory information has been attached to the front of the first study 080 volume.

Additionally, we are attaching the two copies of the Monitoring Survey as requested. The Monitoring Survey consists of three sections which are as follows:

- Section I – List of Clinical Studies
- Section II – Monitoring Organizations
- Section III – Standard Operating Procedures

If you have any questions or need further information, please contact Michele Flicker, M.D., Ph.D. (610-397-3193) or, in my absence, Larry P. Bell, M.D. (610-397-2310).

Sincerely yours,

Michele R. Flicker

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

Attachments

Federal Express #1

Desk Copies (letter only):
NDA 20-560, HFD-510, Room 14B-04 -Federal Express #2
Mr. Randy Hedin, HFD-510, Room 14B-04 -Federal Express #2

q:carnal/mk0217/responses/ju-res

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486-0004
Tel 610 397 2905
Fax 610 397 2516

March 24, 1999

MERCK

H.W. Ju, M.D.
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Food and Drug Administration
7520 Standish Place
Rockville, Maryland 20855

NDA 20-560/S-018: FOSAMAX™
(Alendronate Sodium Tablets)
Response to FDA Request for Information

Dear Dr. Ju:

Reference is made to the pending supplemental new drug application cited above and to a March 17, 1999 telephone conversation between Dr. H.W. Ju (FDA) and Dr. Larry Bell (MRL, a Division of Merck & Co., Inc.) in which you requested additional information regarding clinical studies contained in this supplement. Further reference is made to a March 22, 1999 voice mail message from you to Dr. Bell in which further clarification was made as to the information to be provided. With this submission, we are providing the requested information as follows:

Tab A: Protocol 072:

1) The Title page (indicating the full title and protocol number)
2) Appendix 3.4 of the Protocol 072 Clinical Study Report which includes the complete investigator list, noting the full address of each site and the number of patients enrolled
3) Table A: Patient Listing of Adverse Experiences (production table)

Tab B: Protocol 097:

1) The Title page (indicating the full title and protocol number)
2) Appendix 3.5 of the Protocol 097 Clinical Study Report which includes the complete investigator list, noting the full address of each site and the number of patients enrolled
3) Table B: Patient Listing of Adverse Experiences (production table)

Tab C: Protocol 080 (Non-Alendronate Clinical Pharmacology Study):

1) The Title page (indicating the full title and protocol number)
2) Appendix 3.4 of the Protocol 080 Clinical Study Report which includes the complete investigator list, noting the full address of each site and the number of patients enrolled
3) Table C: Patient Listing of Adverse Experiences (production table)

Additionally, we are attaching Volume 2 of the supplement as you requested. Volume 2 contains the Synopsis of Application.

Please direct any questions to Michelle Kloss, Ph.D. (610-397-2905) or, in my absence, Larry P. Bell, M.D. (610-397-2310).

Sincerely, yours,

Larry P Bell

for Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Q:carnal\mk-0217\responses\est_res

Attachments
Enclosure (Volume 2 of NDA 20-560/S-018)
Federal Express #1

cc w/attachments:
Solomon Sobel, M.D., HFD-510, Room 14B-04 - Federal Express #2
Mr. Randy Hedin, HFD-510, Room 14B-04 - Federal Express #2

APPEARS THIS WAY
ON ORIGINAL

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486-0004
Tel 610 397 2905
Fax 610 397 2516

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March 1, 1999

MERCK

Solomon Sobel, M D., Director
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HFD-510, Room 14B-04
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

MAR 02 1999

NDA 20-560/S-018: FOSAMAX™
(Alendronate Sodium Tablets)

Response to Request for Information

Dear Dr. Sobel:

Reference is made to the supplemental new drug application cited above for FOSAMAX™ that was hand delivered on January 28, 1999. Further reference is made to a February 24, 1999 telephone call from Mr. Randy Hedin (FDA) in which he indicated that the Medical and Statistical review copies (Items 8 and 10, respectively) could not be found. Mr. Hedin requested that MRL (a Division of Merck & Co., Inc.) resubmit the Medical and Statistical review copies to the Agency.

By desk copy with attachments to Mr. Hedin, we are providing the requested review copies.

Please direct any questions to Michelle Kloss, Ph.D. (610-397-2905) or, in my absence, Larry P. Bell, M.D. (610-397-2310).

Sincerely yours,

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Q:carnal\mk-0217\responses\s018_res

Federal Express

Desk Copy with Attachments:
Mr. Randy Hedin, HFD-510, Room 14B-04 - Federal Express

Larry P. Bell, M.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc
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Tel 610 397 2310
215 652 5000
Email larry_bell@merck.com

February 5, 1999

[illegible] OFFICIAL FDA [illegible] desk copies.

SUPPL NEW CORRESP
SE8-018
SUC

Solomon Sobel, M D., Director
Division of Metabolism and Endocrine Drug Products
Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20850

MERCK
Research Laboratories

Supplemental New Drug Application

NDA 20-560 FOSAMAX™ (Alendronate Sodium Tablets)

By copy of this letter, Merck Research Laboratories (MRL) is providing one (1) Compact Disk (CD) which contains the supplemental New Drug Application (sNDA) for NDA 20-560 FOSAMAX™ (Alendronate Sodium Tablets), submitted in hardcopy on January 28, 1999.

This supplemental application provides clinical efficacy and safety documentation for FOSAMAX™ when taken in combination with estrogen/hormone replacement therapy (i.e., estrogen with or without progestin).

The information on this CD is to be copied to the StorageWorks Building Block (SBB) currently installed on the MRL-dedicated network server in use at the Agency for the Glucocorticoid-Induced Osteoporosis Supplemental New Drug Application disk labeled MK217G electronic submission

A list of reviewers from the Metabolic & Endocrine Drug Products Division and Division of Biometrics who should be provided access to this electronic submission from their desktops may be obtained from Mr. Randy Hedin, Project Manager.

Please notify MRL's Regulatory Agency Relations (RAR) Office (301/881-9000) when the disk installation is successfully completed and access from the reviewers' desktops is functional.

When an action has been taken on this submission and the CD is no longer needed, MRL will make arrangements to retrieve it from the FDA. We understand that, in the future, information submitted in electronic form may be retained indefinitely by the Agency, as an archival copy of the application, in the event that a complete paper submission is not filed.

We have taken precautions to ensure that any software on the CD is free of computer viruses and we authorize the use of anti-virus software, as appropriate.

There are five attachments to this letter:

Attachment 1	An NDA Table of Contents of the accompanying electronic submission.
Attachment 2	A Difference Report identifying differences between the electronic version of this submission and the hard copy submission.
Attachment 3	Installation Instructions detailing how to copy the contents of the CD onto the server.
Attachment 4	Documentation regarding the development procedures performed at MRL for this electronic submission.
Attachment 5	A complete list of file names.

During the time that the electronic submission is actively being used, MRL will provide technical support. Any questions relating to this electronic submission should be addressed to me (610/397-2310) or, in my absence, Margo Herron (301/881-9000).

Sincerely,

Larry P. Bell, M.D.
Senior Director
Regulatory Affairs

Q:carnal\mk0217\estrogen\eleccov

Attachments
Enclosures:
Compact Disk (CD)

Federal Express #1

cc (cover letter only):
K. Edmunds, Division of Technology Support Services Staff, HFD-70 Federal Express #2
S. Sobel, M.D. HFD-510, Room 14B-04, Federal Express #3
R. Hedin, R. Ph. HFD-510, Room 14B-04, Federal Express #3

cc (cover letter with attachments):
NDA 20-560, HFD-510 (2 copies), Federal Express #4

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

SE8
5/018

Merck & Co., Inc.
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Fax 610 397 2516
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215 652 5000

DESK COPY

January 28, 1999

MERCK
Research Laboratories

Solomon Sobel, M D., Director
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HFD-510, Room 14B-04
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-560: FOSAMAX™
(Alendronate Sodium Tablets)

Supplemental New Drug Application

Dear Dr. Sobel:

Pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act and in accordance with 21 CFR 314.70 (b), Merck Research Laboratories (MRL) is submitting a Supplemental New Drug Application (sNDA) for FOSAMAX™ (alendronate sodium tablets).

This supplemental application provides clinical efficacy and safety documentation for FOSAMAX™ when taken in combination with estrogen/hormone replacement therapy (i.e., estrogen with or without progestin). The contents of this application include complete Clinical Study Reports for a clinical pharmacology study and two clinical studies as well as a comprehensive Clinical Summary. Draft labeling text is also provided which incorporates the revisions supported by this application.

This application is formatted as required in Title 21, paragraph 314.50 of the Code of Federal Regulations. It consists of a complete "archival" copy (blue binders), comprising 28 volumes, and review copies for each of the two (2) technical sections (one technical review copy for each Item) as described in the Statement of Organization, which is attached to this letter.

In accordance with the Food and Drug Administration Modernization and Accountability Act of 1997 (FDAMA); User Fee I.D. No[ ]was sent to the Mellon Bank, Three Mellon Bank Center, 27th Floor (FDA 360909), Pittsburgh, PA 15259-0001, on January 18, 1999.

Merck is requesting a categorical exclusion from the requirements to prepare an Environmental Assessment for this supplemental application under 21 CFR §25.31(a). The supplement meets the requirements of a categorical exclusion under 21 CFR §25.31(a) because it will not increase the use of the active moiety, alendronate sodium. To the best of the firm's knowledge no extraordinary circumstances exist in regards to this action.

This sNDA is being provided in both paper copy and electronic format, with the exception of Items 11 and 12 (Case Report Tabulations and Case Report Forms), which are being provided in electronic format only (see attached "Statement of Organization").

This application is also being submitted electronically in accordance with the Guidance for Industry - Archiving Submissions in Electronic Format - NDAs, published September, 1997.

This sNDA is being submitted in the following formats:

FORMAT	INFORMATION INCLUDED	MEDIA FORMAT	DATE OF SUBMISSION
Paper	(all information except CRTs and CRFs)	Paper	January 28, 1999
Electronic Archival Files	sNDA Table of Contents, Case Report Tabulations, Case Report Forms	CD	January 28, 1999
Electronic Submission	(all information)	CD	February 5, 1999 (to Technology Services Support Staff)

As noted in the Guidance document, this letter is being included as *cover.pdf* and includes:

- Appropriate regulatory information
- A description of the submission
- A description of which portions of the submission are presented only in paper, only in electronic format, or both paper and electronic format *(see above)*
- A description of the electronic submission including the contents of the media, their number and format, a description of the file types and the total size of the submission
  The electronic archival files for Case Report Tabulations and Case Report Forms are provided on 1 CD. The files are provided in .PDF and .PDF catalogue index format. The total file size is approximately 193 MB.
- Verification that the submission is virus free with a description of the software used to check the files for viruses
  Merck Research Laboratories (MRL) has employed Norton anti-virus (NAV) software and has scanned all files. No viruses were detected.
- A description of any deviation from the specifications in the guidance document
  There are no deviations from the specifications as noted in the guidance document.

MRL will work with the FDA to arrange orientation to the electronic submission for all interested Agency reviewers.

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 debarred under sections 306(a) or (b) of the Act.

MRL would like to meet with the FDA approximately 90 days following receipt of this application. The purpose of this meeting will be to discuss the general progress and status of the review of this application and to determine if there are any important deficiencies identified at that time. MRL will contact the FDA to arrange for this meeting.

We consider the filing of this Supplemental New Drug Application to be a confidential matter and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining written permission from Merck & Co., Inc.

If you have any questions or need further information, please contact Michelle W. Kloss, Ph.D. (610/397-2905) or, in my absence, Larry P. Bell, M.D., (610/397-2310)

Sincerely, yours,

Michelle W. Kloss

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Q:RC\MK-0217\Estrogen\COVER

Attachment

Hand Deliver

Desk Copy
Mr. Randy Hedin, HFD-510, Room 14B-04 - Federal Express #1

Desk Copy (Letter and Patent Information Only)
Ms. Mary Ann Holovac, HFD-93, 5600 Fishers Lane
Rockville, MD 20857 – Federal Express #2