CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER for: 020560, S015

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

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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: