CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020560/S012

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-560/S-012

Merck Research Laboratories
Attention: Michelle Kloss, Ph.D.
Director, Regulatory Affairs
P.O. Box 4, BLA-20
West Point, PA 19486-0004

MAY 26 1998

Dear Dr. Kloss:

Please refer to your supplemental new drug application dated November 26, 1998, received November 26, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosamax (alendronate sodium) 10 and 40 mg Tablets.

We acknowledge receipt of your submissions dated December 18 and 22, 1997, and January 7 and 9, February 19 and 25, March 6, and May 21(2) and 22, 1998. The User Fee goal date for this application is May 26, 1998.

The supplemental application provides for a new indication, the treatment and prevention of glucocorticoid-induced osteoporosis in men and women.

We have completed the review of this supplemental application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit:

1. Additional information about the two year double-blind extension studies. A more thorough and audited presentation of data from this recent submission should be provided to the Division. Please also include the following in the submission:

   A. Include time exposures (patient-months of treatment), dropout rates, and the numbers of patients who remained at risk at the end of two years.

   B. Fracture results should be presented in terms of patient-months of therapy.

2. A data base including both the initial treatment as presented in the one year studies of the NDA, and the two year double blind extensions. The following should be included with the data base:

   A. Present an analysis of subgroups based on the underlying disease condition and its interaction with the bone density endpoints and fractures.

   B. Provide an analysis of the NDA data that dissects out the contribution to

efficacy results of postmenopausal patients who are, and are not on hormone replacement therapy. Provide similar analyses for premenopausal patients and for men.

Also, revision of the draft labeling submitted on November 26, 1998, will be required. The duration of treatment should be limited to one year reflective of the treatment period of the 560 patients in the studies presented in the original NDA.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will certainly facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

This change may not be implemented until you have been notified in writing that this supplemental application is approved.

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

Sincerely yours,

/S/ [redacted]

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

NDA 20-560 FOSAMAX®
Alendronate sodium

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, and 5,681,590 cover the formulation, composition and/or method of use of FOSAMAX® (alendronate sodium tablet), 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 the use of FOSAMAX® for inhibiting bone resorption. This patent is owned by Merck & Co., Inc., Rahway, NJ.

The undersigned declares that U.S. Patent No. 4,621,077 covers the method of using FOSAMAX®. The subject of this application for which approval is being sought is covered by this patent.

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

The undersigned declares that U.S. Patent No. 5,358,941 claims a formulation 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 formulation of FOSAMAX®. This patent is owned by Merck & Co., Inc., Rahway, NJ.

The undersigned declares that U.S. Patent No. 5,681,590 claims a formulation of FOSAMAX®. This product is the subject of this application for which approval is being sought.

A claim of patent infringement could be asserted if a person not licensed by the owner of any of U.S. Patent Nos. 4,621,077, 5,358,941, or 5,681,590 engaged in the manufacture, use, or sale of FOSAMAX®.

11/18/97

Anthony D. Sabatelli — Date
Senior Patent Attorney

Attachment

EXCLUSIVITY SUMMARY for NDA # 20-560 **SUPPL #** 012

Trade Name Fosamax **Generic Name** alendronate sodium

Applicant Name Merck **HFD-** 510

Approval Date, if known _____

JUN 16 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.) SE1

   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?

_____

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 /✓/ OTC Switch /___/

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 /✓/

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 /✓/ 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 M082

Study M063

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 14082 _____

Study 14083 _____

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 # [redacted] YES /✓/ NO /___/ Explain: _____

Investigation #2

IND # [redacted] 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 _____

Investigation #2

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/ [redacted]
Signature

6/15/99
Date

Randy Hedin
Name (type or print)

CSO.
Title

/S/ [redacted]
Signature of Division Director

6/16/99
Date

Solomon Sobel
Name (type or print)

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

APPEARS THIS WAY ON ORIGINAL

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

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:	12	**Generic Name:**	ALENDRONATE SODIUM
Supplement Type:	SE1	**Dosage Form:**	TAB
Regulatory Action:	AP	**Proposed Indication:**	Fosamax is indicated for the treatment of corticosteroid induced osteoporosis in men and women receiving corticosteroids in a daily dosage equivalent to 7.5 mg or greater of prednisone.

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	Inadequate for ALL pediatric age groups
Formulation Status	-
Studies Needed	-
Study Status	-

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

COMMENTS:

Firm plans to do pediatric studies in the future.

The Division discussed the issue of pediatric studies with the firm, and the firm plans on doing studies in the future.

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

/S/ [redacted]

Signature

6/15/99

Date

[redacted] APPEARS THIS WAY ON ORIGINAL