[redacted]

[redacted]

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

Merck & Co., Inc
P.O. Box 4, BLA-20
West Point PA 19486-0004
Fax 610 397 2516
Tel 610 397 2905
215 652 5000

May 21, 1998

MERCK
Research Laboratories

Solomon Sobel, M D., Director
Division of Metabolism and Endocrine
Drug Products, HFD-510, Room 14B04
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-560/S-012: FOSAMAX™
(Alendronate Sodium Tablets)

AMENDMENT TO PENDING APPLICATION

Dear Dr. Sobel:

Reference is made to the supplemental application cited above and to a telephone conversation between Mr. Randy Hedin (FDA) and Dr. Larry Bell (MRL) on May 20, 1998 during which the Agency requested that MRL submit a request for a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.31(b). With this submission, we are providing this information.

Pursuant to 21 CFR 314.50(k)(3), a complete field copy of the Chemistry, Manufacturing and Controls technical section (Item 4) has been submitted to the FDA Philadelphia District Office. This field copy is a true copy of Item 4 as contained in the archival copy and review copies of this application.

Categorical exclusion granted

/s/ [redacted]

5-20-98

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

Please direct questions or need for additional information to Michelle W. Kloss, Ph.D. (610/397-2905) or, in my absence, Larry P. Bell, M.D. (610/397-2310).

Sincerely yours,

APPEARS THIS WAY ON ORIGINAL

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

Q:\carnafvmk0217\520groprespp

Attachment

FAX/Fed Ex #1

Desk Copies w/Attachment:
Mr. Randy Hedin, HFD-510, Room 14B-04 - Federal Express #1

Ms. Debra Pagano
Philadelphia District Office
Food & Drug Administration
U.S. Custom House Room 900
2nd and Chestnut Street
Philadelphia, Pennsylvania 19106-2973 - Federal Express #2

F. Environmental Assessment - Categorical Exclusion

F.1. Date

May 20, 1998

F.2. Name of Applicant

Merck Research Laboratories
Merck and Co., Inc.

F.3. Address

Sumneytown Pike
West Point, PA 19486

F.4. Description of Proposed Action

F.4.a. Requested Action - Categorical Exclusion

Merck Research Laboratories, Division of Merck and Co., Inc. is filing a Supplemental New Drug Application for FOSAMAX™ (Alendronate Sodium Tablets). FOSAMAX™ is approved for the Treatment and Prevention of Postmenopausal Osteoporosis. This supplement supports the indication for FOSAMAX™ in the Treatment and Prevention of Glucocorticoid-Induced Osteoporosis.

Merck is requesting a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.31(b). The production of FOSAMAX™ meets the requirements of a categorical exclusion under 21 CFR §25.31(b) because the estimated concentration of drug

[redacted]

[redacted]

F.4.a. **Requested Action - Categorical Exclusion (Cont.)**

substance alendronate sodium at the point of entry, referred to as the Expected Introduction Concentration (EIC), into the aquatic environment will be below 1 part per billion (ppb). To the best of the firm's knowledge no extraordinary circumstances exist in regards to this action.

EA is adequate
i.e. Categorical Exclusion
is fine

/S/ [redacted]
5-21-98

Concurred
/S/ [redacted] 5-21-98

Meeting Date: January 22, 1998 Time: 3:00 - 3:30 pm Location: Conf. Rm. C

NDA 20-560/S-012 Fosamax (alendronate sodium) Tablets

Type of Meeting: Teleconference

External participant: Merck Research Laboratories

Meeting Chair: Dr. Troendle

External participant lead: Dr. Michelle Kloss

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Dr. James Bilstad, Director, ODE II
Dr. Solomon Sobel, Director, DMEDP
Dr. Gloria Troendle, Deputy Director, DMEDP
Dr. Bruce Schneider, Medical Reviewer, DMEDP
Dr. Leo Lutwak, Medical Reviewer, DMEDP
Dr. Elizabeth Barbehenn, Pharmacology Reviewer, DMEDP
Mr. Randy Hedin, CSO, DMEDP

External participant Attendees and titles:

Dr. Anastasia Daifotis, Clinical Research, Endocrine and Metabolism
Dr. Harry Guess, Epidemiology
Dr. Michelle Kloss, Regulatory Affairs
Dr. John Yates, Clinical Research, Endocrine and Metabolism
Dr. Larry Bell, Regulatory Affairs
Dr. Leonard Oppenheimer, Biostatistics
Dr. Gideon Rodan, Bone Biology
Dr. Elizabeth Stoner, Clinical Research, Endocrine and Metabolism
Dr. M.J. van Zwieten, Safety Assessment

Meeting Objectives:

This meeting was requested by Merck to discuss our request that they withdraw the supplement for corticosteroid induced osteoporosis.

Discussion Points and Decisions (agreements) reached:

- Merck Research Laboratories agreed to provide the Agency a comprehensive document that will include the following:

1. A summary and discussion of the preclinical animal models for glucocorticoid-induced osteoporosis (GIOP).

2. A summary and discussion of the data on biochemical markers, bone turnover, bone quality (biopsy/histomorphometry), and fracture incidence observed with alendronate in clinical trials in both postmenopausal osteoporosis and glucocorticoid-induced osteoporosis.

3. An in-depth analysis of the fracture data, including narratives of the fracture situations, in the alendronate GIOP studies.

4. A summary/discussion of the assumptions used in the calculations regarding the number of patients required to conduct a fracture endpoint study in the GIOP population.

- The Sponsor further agreed to investigate conducting a GIOP preclinical animal model study as soon as possible (presumably the Wistar rat strain model). It was agreed that the timeline for submission of data from such a study would be approximately 4 months.

- The Division stated that it has filed the application, and is considering it a priority review.

Unresolved or issues requiring further discussion:

- None

Action Items:

- None

Signature, minutes preparer: /S/ [redacted]

Concurrence Chair: /S/ [redacted]

cc: NDA Arch
HFD-510
Attendees
HFD-510/EGalliers
HFD-511/RHedin/2.24.98/N20560.M20

Concurrences: LLutwak/BSchneider/GTroendle/5.5/SSobel/5.6/JBilstad/5.12.98

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-560/S-012

Merck Research Laboratories
P.O. Box 4, BLA-20
West Point, PA 19486-0004

DEC - 2 1997

Attention: Michelle W. Kloss, Ph.D.

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-012
Date of Supplement:	November 26, 1997
Date of Receipt:	November 26, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on January 25, 1998, 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/ [redacted]

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

[redacted]

[redacted]

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

June 16, 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-012: FOSAMAX™
(Alendronate Sodium Tablets)

Response to FDA Request for Information

Dear Dr. Sobel:

Reference is made to the pending supplemental new drug application cited above and to the Agency's May 26, 1998 Approvable Letter for this supplemental application which requested the submission of additional information. Reference is also made to an amendment to this supplemental application submitted on December 15, 1998 in response to the May 26, 1998 Approvable Letter. Further reference is made to two June 15, 1999 telefaxes from the Agency which addressed proposed labeling and a proposed Phase IV study. Finally, specific reference is made to two teleconferences on June 15, 1999 and June 16, 1999 between Merck Research Laboratories (MRL, a Division of Merck & Co., Inc.) and the FDA (Dr. Solomon Sobel, Dr. Gloria Trocndle and Mr. Randy Hedin) in which labeling, a proposed Phase IV study commitment, and the potential to generate pediatric data relevant to the above referenced supplemental application were discussed.

During these teleconferences, agreement between MRL and the Agency was reached regarding labeling for this supplemental application. Please note that the term "corticosteroid" has been changed to "glucocorticoid" for consistency with the rest of the label. A clean copy of the product circular for S-012 is attached, incorporating these agreements. A mock up of the product circular showing revision marks is also provided. A clean copy and a mock up of the patient package insert (PPI) is also provided for your convenience. An electronic copy of the product circular for S-012 is also being provided. It is formatted in Word 6.0.

As discussed in the June 15, 1999 teleconference, MRL acknowledges the Agency's request to generate Phase IV data relevant to this supplement [redacted]

MRL acknowledges the Agency's interest in the generation of pediatric data related to this supplemental indication. In response to this interest, MRL commits to generate and submit to the Agency a proposed pediatric study request.

Questions concerning this submission should be addressed to Michele R. Flicker, MD, PhD (610/397-3193) 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:RC\MK-0217\GIOP\request2

[redacted]

Attachments
Diskette

Fax/Federal Express

Desk Copies
Dr. Gloria Troendle, HFD-510, Room 14B-04 - Federal Express
Mr. Randy Hedin, HFD-510, Room 14B-04 - Federal Express

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

NDA SUPP AMEND
SE1-012 BKL

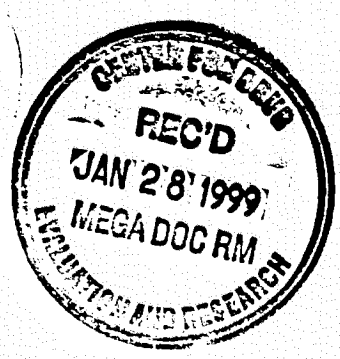
Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2310
215 652 5000
Email larry_bell@merck.com

These copies are OFFICIAL FDA Copies
not desk copies.

MERCK
Research Laboratories

January 27, 1999

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



NDA 20-560/S-012: FOSAMAX™
(Alendronate Sodium Tablets)

RESPONSE TO FDA REQUEST FOR INFORMATION

Reference is made to the pending supplemental new drug application cited above and to the Agency's May 26, 1998 Approvable Letter for this supplemental application which requested the submission of additional information. Reference is also made to a December 15, 1998 amendment to this pending supplemental application submitted in response to the May 26, 1998 Approvable Letter. Additional reference is made to telephone conversations between Mr. Randy Hedin (FDA) and Dr. Michelle Kloss (MRL) on January 21 and 22, 1999 in which Mr. Hedin requested that Attachments 1 (proposed draft labeling) and 2 (Clinical Study Report) contained within the December 15, 1998 amendment be provided to the Agency electronically.

By copy of this letter, as requested, Merck Research Laboratories (MRL; a division of Merck & Co., Inc) is providing one (1) Compact Disk (CD) which contains Attachments 1 (proposed draft labeling) and 2 (Clinical Study Report) of the December 15, 1998 submission cited above. To facilitate the electronic review of Attachment 2, please note that we have also provided Attachments 3 and 7 (Case Report Forms and Case Report Tabulations, respectively) on this CD, since these items pertain to Attachment 2 (Clinical Study Report).

The information on this CD [redacted] is to be copied to the StorageWorks Building Block (SBB) [redacted] currently installed on the MRL-dedicated network server in use at the Agency for the MK-0217 Glucocorticoid Induced Osteoporosis (GIOP) Supplemental NDA.

The reviewers from the Endocrine & Metabolic Drug Products Division and the Division of Biometrics who should be provided access to the electronic submission from their desktops are as follows:

Gloria Troendle, M.D.	HFD-510	PKLN 14B04
Leo Lutwack, M.D.	HFD-510	PKLN 14B04

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

When an action has been taken on this submission and the CDs are no longer needed, MRL will make arrangements to retrieve them 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 CDs are free of computer viruses and we authorize the use of anti-virus software, as appropriate.

There are five attachments to this letter:

Attachment 1	A 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 CDs 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 Bell, M.D.
Senior Director
Regulatory Affairs

Q:carnal\mk0217\giop\eleccov

Attachments
Enclosures:
Compact Disk (CD) [redacted]

Federal Express #1

[redacted] APPEARS THIS WAY ON ORIGINAL

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
G. Troendle, M.D. HFD-510, Room 14B-04 - Federal Express #3
L. Lutwak, M.D. HFD-510, Room 14B-03 - 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

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

December 15, 1998

MERCK

Solomon Sobel, M D., 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-012: FOSAMAX™
(Alendronate Sodium Tablets)

AMENDMENT TO PENDING SUPPLEMENTAL APPLICATION

Dear Dr. Sobel:

Reference is made to the pending supplemental new drug application cited above and to the Agency's May 26, 1998 Approvable Letter for this supplemental application which requested the submission of additional information. Additional reference is made to correspondence dated August 3, 1998 in which MRL provided an overview of MRL's plans regarding responses to the items outlined in the May 26, 1998 Approvable Letter, and in which MRL requested Agency concurrence with these plans. Reference is also made to a September 1, 1998 telephone conversation between Mr. Randy Hedin (FDA) and Dr. Michelle Kloss (MRL) in which Mr. Hedin stated that the Agency was in agreement with MRL's plans as outlined in the August 3, 1998 communication.

With this submission, we are providing a complete response to the May 26, 1998 Approvable Letter for this pending supplemental application. This response is in accordance with the plans outlined by MRL in the August 3, 1998 communication noted above

This submission includes an Overview section which provides a comprehensive summary of MRL's responses to the comments cited in the May 26, 1998 Approvable Letter. Following this Overview are four main components which provide detailed responses to each of the specific comments in the Approvable Letter: (1) the complete Clinical Study Report of the (preplanned) combined results from both double-blind extensions of the Glucocorticoid-Induced Osteoporosis (GIOP) Studies (protocols 082/083) through 2 years, including electronic datasets (Attachments 2, 3, 4, and 7); (2) revised draft labeling for this supplemental application (Attachment 1); (3) a five-year CIOMS II report of the worldwide postmarketing experience with alendronate (Attachment 5); and (4) a comprehensive review of safety information available from all Merck osteoporosis clinical trials with alendronate since the time of filing supplemental application S-012 on November 26, 1997 (Attachment 6)

The following provides a listing of the documents contained within this submission:

Description	Volume
Overview	1
Attachment 1: Proposed draft labeling	2
Attachment 2: MRL Clinical Study Report: Two 12-Month, Randomized, Double-Blind, Placebo-Controlled, Multicenter Extension Studies to Evaluate the Continued Safety and Efficacy of Two Doses of Oral Alendronate Sodium for the Prevention and Treatment of Glucocorticoid-Induced Bone Loss. (Protocols 082/083)	3-5
Attachment 3: Case Report Forms for patients in Protocols 082 and 083 who either died or discontinued the study due to an adverse experience.	6
Attachment 4: Electronic Datasets for the combined GIOP studies (provided electronically on CD, [redacted]	7
Attachment 5: Periodic Safety Update Report for: Alendronate Sodium Tablets	8-11
Attachment 6: Comprehensive Review of Alendronate Safety in Clinical Trials	12-13
Attachment 7: Case Report Tabulations for protocols 082/083. (provided electronically on CD, [redacted]	14

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.

We consider the filing of this amendment 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.

Questions concerning this submission should be addressed to 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\GIOP\amendcov

Attachments

Federal Express #1

Desk Copies
Dr. Bruce Schneider (vols. 1-6, 8-13), HFD-510, Rm. 14B-04 - Federal Express #2
Dr. Gloria Troendle, (vols. 1-6, 8-13), HFD-510, Room 14B-04 - Federal Express #3
Mr. Randy Hedin, (vol. 1-6, 8-13), HFD-510, Room 14B-04 - Federal Express #4

Desk Copy with CD
Dr. Jonathan Levine (vols. 1-5, 14: CD [redacted] HFD 725, Rm. S123
- Federal Express #5

APPEARS THIS WAY ON ORIGINAL