[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.

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,

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

Q:\crmal\vnk0217\520groprcsp

APPEARS THIS WAY ON ORIGINAL

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

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

February 25, 1998

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

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

Response to FDA Request for Information

Dear Dr. Ju:

Reference is made to the pending supplemental application cited above and to our telephone conversation of January 27, 1998. During this conversation, MRL was informed that the FDA intended to perform inspections at sites 082-010 (Dr. Patrice Poubelle, Canada), 082-012 (Dr. Jonathan Adachi, Canada), 083-001 (Dr. Ronald Emkey, U.S.), and 083-008 (Dr. Kenneth Saag, U.S.) and additional information regarding these sites was requested by the Agency. This information was submitted to the Agency on February 5, 1998 as a Response to FDA Request for Information.

Reference is also made to your January 27, 1998 facsimile communication requesting additional information regarding the supplemental application cited above and the Agency's Monitoring Survey. Further reference is made to your conversations with Ms. Susan Stauffer (Senior Director, Clinical Quality Assurance Resources - Merck Research Laboratories) on January 27 and 28, 1998 during which the Agency's Monitoring Survey was discussed and clarification was provided on the collection of the information required for this Monitoring Survey. During these conversations, it was also agreed that this Monitoring Survey information could be provided to the Agency separately from the site information.

With this letter, MRL is providing the requested information regarding the Agency's Monitoring Survey. This submission consists of the following:

1. Copy of the January 27, 1998 facsimile from the Agency to MRL.

2. Copies of form 1571 for the study sites which were conducted under the IND; 083-001 (Ronald Emkey, MD) and 083-008 (Kenneth Saag, MD).

3. A list of clinical studies and significant deviations from Good Clinical Practice standards; an overview of monitoring organizations; monitoring responsibilities and time periods.

4. Data tables to support Items II.B. and III.B. of the Monitoring Survey (Exhibit A).

5. Standard operating procedures for sponsor monitoring (Exhibit B).

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,

Michelle W. Kloss

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

q:carnal\mk0217\giop\giopreq1.doc

Attachments

Federal Express #1

cc letter only: Solomon Sobel, M.D., Dir. HFD-510, Federal Express #2
Mr. Randy Hedin, HFD-510, Federal Express #2

APPEARS THIS WAY ON ORIGINAL

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

BEST POSSIBLE COPY

ORIGINAL

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

Note: Information submitted by Merck not acted upon in return of this time.
/S/ [redacted] 3-20-98

These copies are
OFFICIAL FDA Copies
not desk copies.

MERCK
Research Laboratories

February 19, 1998

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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 20 1998
HFD-510

NDA 20-560/S-012: FOSAMAX

GENERAL CORRESPONDENCE

Dear Dr. Sobel:

Reference is made to the Supplemental NDA cited above and to a teleconference meeting between FDA and MRL on January 22, 1998 to discuss this supplemental application.

With this submission, we are providing the MRL Summary of this teleconference as minutes of the meeting cited above. We would be pleased to receive a copy of the Agency's minutes of this meeting as soon as they become available.

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

REVIEWS COMPLETED	
CSO ACTION:	
☐ LETTER ☒ N.A.I. ☐ MEMO	
/S/ [redacted]	5/4/98
CSO INITIALS	DATE

Sincerely,

Larry P. Bell for

Michelle W. Kloss, Ph.D
Director
Regulatory Affairs

/S/ [redacted]
3-27-98

Attachment
Federal Express #1

(1) Desk copy: Mr. Randy Hedin, CSO, HFD-510, Room 14B-19
Federal Express #2

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

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486-0004
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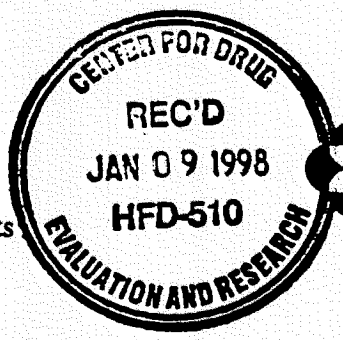

MERCK
Research Laboratories

January 9, 1998

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

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

FINAL BACKGROUND INFORMATION AND MEETING CONFIRMATION

Dear Dr. Sobel:

Reference is made to the Supplemental New Drug Application cited above submitted on November 26, 1997 regarding alendronate in the treatment and prevention of glucocorticoid-induced osteoporosis (GIOP) in men and women. Reference is also made to telephone conversations on April 8, 1994 and August 22, 1994 between Dr. Edwin Hemwall (MRL) and Dr. Samarendra Dutta (FDA) during which the design of the MRL clinical program for glucocorticoid-induced osteoporosis was discussed and to submissions on August 10, 1994, September 16, 1994, and April 9, 1997 providing the draft protocol, the finalized protocol, and the Data Analysis Plan for GIOP study protocol 083. Additional reference is made to a January 6, 1998 telephone conversation between Mr. Randy Hedin (FDA) and Dr. Michelle Kloss (MRL) during which the Agency questioned the appropriateness of bone mineral density (BMD) as the endpoint for the GIOP studies. Additional reference is made to your telephone conversation on January 6, 1998 with Dr. Bonnie Goldmann during which this topic was discussed and Dr. Goldmann requested to meet with the Agency, at the Agency's convenience, to discuss this issue further. During this conversation, it was agreed that this meeting would take place as soon as possible and that background information regarding MRL's position on this issue would be submitted by Friday, January 9, 1998. Reference is also made to a written meeting request and preliminary background information submitted January 7, 1998 to assess this topic.

With this submission, we are providing a full background package that summarizes MRL's position on this topic to facilitate discussion at this upcoming meeting. This communication also confirms our intent to participate in a meeting with Agency representatives on January 16, 1998 from 9:00 - 10:30 AM in a conference room to be determined in the Parklawn Building.

The Agency has stated its opinion that the pathophysiology of glucocorticoid-induced osteoporosis (GIOP) and that of postmenopausal osteoporosis are fundamentally different. As such, the Agency believes that the comprehensive data gathered on alendronate in postmenopausal osteoporosis may not be generalizable to GIOP and has questioned the appropriateness of bone mineral density (BMD) as an endpoint in the glucocorticoid-induced osteoporosis (GIOP) studies with alendronate;

it has commented that fracture endpoint studies in this population are needed. In this context, the Agency has stated its opinion that such fracture endpoint studies in glucocorticoid users are feasible since fractures in this population occur frequently and early in therapy. Additionally, the Agency has commented that the data from the alendronate GIOP studies suggest that there may be a greater incidence of fractures in patients on alendronate than in those on placebo.

As described in the attached background package, MRL believes that the pathophysiology of GIOP and that of postmenopausal osteoporosis are more similar than dissimilar. In light of this similar pathophysiology and the fact that BMD has clearly been validated as a predictor of fracture risk reduction for alendronate, MRL believes that BMD is the most appropriate endpoint for studies of alendronate in glucocorticoid users and that fracture endpoint studies in this population are neither feasible nor necessary. Additionally, the fracture data from the alendronate GIOP studies do, in fact, demonstrate a trend toward fracture risk reduction, consistent with the fracture risk reduction observed with alendronate in patients with postmenopausal osteoporosis. Finally, we believe that alendronate is a rational treatment for GIOP and fills an urgent medical need that is currently unmet. This position is shared by two outside consultants with whom we have discussed this issue and whose letters on this topic are attached in Appendix 1 and 2.

At the upcoming meeting, we are planning a brief presentation of our position on this topic followed by discussion.

The following individuals from Merck Research Laboratories will attend this meeting:

Dr. Larry Bell	Regulatory Affairs
Dr. Anastasia Daifotis	Clinical Research
Ms. Marie Dray	Regulatory Agency Relations
Dr. Bonnie Goldmann	Regulatory Affairs
Dr. Harry Guess	Epidemiology
Dr. Michelle Kloss	Regulatory Affairs
Ms. Marie-Pierre Malice	Statistics
Dr. Leonard Oppenheimer	Statistics
Dr. C. P. Peter	Safety Assessment
Dr. Gideon Rodan	Bone Biology
Dr. John Yates	Clinical Research

Please direct any questions or need for additional information to Michelle W. Kloss, Ph.D. at (610) 397-2905 or, in my absence, Bonnie J. Goldmann, M.D. at (610) 397-2383.

Sincerely,

Michelle W. Kloss

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

Hand-Delivered

(10) Desk copies w/attachments:
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Mr. Randy Hedin, HFD-510, Room 14B-19
Hand-Delivered

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

Merck & Co., Inc.
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215 652 5000

January 7, 1998

MERCK
Research Laboratories

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

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

MEETING REQUEST AND PRELIMINARY BACKGROUND INFORMATION

Dear Dr. Sobel:

Reference is made to the Supplemental New Drug Application cited above submitted on November 26, 1997 regarding alendronate in the treatment and prevention of glucocorticoid-induced osteoporosis (GIOP) in men and women. Reference is also made to telephone conversations on April 8, 1994 and August 22, 1994 between Dr. Edwin Hemwall (MRL) and Dr. Samarendra Dutta (FDA) during which the design of the MRL clinical program for glucocorticoid-induced osteoporosis was discussed and to submissions on August 10, 1994, September 16, 1994, and April 9, 1997 providing the draft protocol, the finalized protocol, and the Data Analysis Plan for GIOP study protocol 083. Additional reference is made to a January 6, 1998 telephone conversation between Mr. Randy Hedin (FDA) and Dr. Michelle Kloss (MRL) during which the Agency questioned the appropriateness of bone mineral density (BMD) as the endpoint for the GIOP studies. Additional reference is made to your telephone conversation on January 6, 1998 with Dr. Bonnie Goldmann during which this topic was discussed and Dr. Goldmann requested to meet with the Agency, at the Agency's convenience, to discuss this issue further. During this conversation, it was agreed that this meeting would take place as soon as possible and that background information regarding MRL's position on this issue would be submitted by Friday, January 9, 1998.

With this submission, we are providing a written request to meet with the Agency to discuss this topic and, as requested by Mr. Hedin in the conversation cited above, we are providing a brief summary of MRL's position on this issue. A more complete background package regarding MRL's position will be submitted within several days as agreed to in your phone conversation with Dr. Goldmann cited above.

It is MRL's position that alendronate is a rational treatment for glucocorticoid-induced osteoporosis and that BMD, rather than fracture, is the most appropriate primary endpoint

for studies of alendronate in glucocorticoid-users. MRL believes that there are several reasons why a fracture endpoint approach is neither feasible nor necessary and these reasons are summarized below:

1. Similarity of GIOP and Postmenopausal Osteoporosis Disease States

The Agency has suggested that the disease states of GIOP and postmenopausal osteoporosis are quite different. It is MRL's position that these disease states are more similar than they are dissimilar. The mechanism of bone loss in glucocorticoid-induced osteoporosis differs only slightly (quantitatively, rather than qualitatively) from that in postmenopausal women and the rationale for using an effective inhibitor of bone resorption exists in both conditions. Bone tissue responds in only a very limited number of ways to various signals and the various forms of bone loss (estrogen-deficiency, immobilization, glucocorticoid-induced, etc.), although differing in terms of the stimulus for bone loss, are similar in terms of the cellular pathophysiology and responsiveness to antiresorptive treatment. Thus, both in GIOP and in women following menopause, the rate of bone resorption exceeds that of bone formation. Importantly, data from all prior epidemiology studies in general populations of both men and women indicate that there is a very strong relationship between low BMD and increased fracture risk. In our own GIOP studies, MRL has been able to confirm that the same relationship exists in glucocorticoid users as in those broader populations, since the GIOP patients with the lowest BMD in our studies were those who at baseline most often gave a history of fracture.

2. Established Safety of Alendronate in Bone

Results from numerous preclinical and clinical studies have repeatedly demonstrated the safety of alendronate in bone in that alendronate produces bone of normal quality. The evidence of normal bone quality comes both from bone biopsies in animals and man (in postmenopausal women, Paget's patients, and glucocorticoid users) as well as from biomechanical testing in animals (rats and baboons) which demonstrate favorable effects on bone strength. The extensive bone biopsy program with alendronate includes 72 biopsies in patients from the GIOP studies demonstrating bone of normal quality in these patients; these data are included in the supplemental application (S-012). Additionally, there is now clear evidence from multiple studies that, by producing increases in bone mineral density and producing bone of normal quality, alendronate maintains the structural integrity of bone and reduces the incidence of fractures in postmenopausal women with osteoporosis (FIT and Phase III).

3. Feasibility of GIOP Fracture Endpoint Studies

The Agency has suggested that fracture endpoint studies in GIOP may be appropriate and feasible since fractures tend to occur early and often in glucocorticoid-users. This conclusion, however, is difficult to confirm from the epidemiological literature and it

appears not to be substantiated by the fracture data derived from the alendronate GIOP studies. In these studies, there was a relatively low fracture incidence in the placebo group (which may in part reflect the fact that all patients received high dose calcium supplements and vitamin D treatment which decreased the loss in bone mass that has previously been reported in other GIOP studies); the overall incidence of fractures was low in this heterogeneous population of glucocorticoid users and the fractures did not occur early.

The GIOP studies were not prospectively powered for an endpoint of fracture. As expected, there were no statistically significant differences in the overall rate of fracture adverse events, serious events, drug-related events, or withdrawals due to fractures in any of these treatment groups. Even with the 560 patients included in the alendronate GIOP experience, there were too few fracture events to provide sufficient power to address the efficacy of alendronate on fracture risk in this population. The alendronate GIOP program was very complex, due to the underlying diseases, use of steroids and other concomitant medications, and the fact that many patients either were able to discontinue steroids or otherwise had significant changes in their health status. A second-year extension is underway; however, despite the best efforts of MRL to recruit as many of the original 560 patients as possible into the extension, only 215 patients entered the extension and approximately 60% of these are expected to complete two years of the study. Thus, from the standpoint of both the low fracture rate/large patient numbers required and lengthy duration needed to maintain patients on sufficient doses of steroids, it is not feasible to conduct a study in glucocorticoid users that is sufficiently powered to address the question of efficacy of alendronate on fracture risk.

We are looking forward to meeting with the Agency on this matter. For this upcoming meeting, attendees (approximately 10-11) from Merck will include representatives from Clinical Research, Preclinical Bone Biology, Biostatistics, Epidemiology, and Regulatory Affairs; a specific list of Merck participants will be provided to the Agency once a meeting date has been determined. Please direct any questions or need for additional information to Michelle W. Kloss, Ph.D. at (610) 397-2905 or, in my absence, Bonnie J. Goldmann at (610) 397-2383.

Sincerely,

Michelle W. Kloss

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

Federal Express #1

(8) Desk copies: Mr. Randy Hedin, HFD-510, Room 14B-19
Fax/Federal Express #2

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SNC-92

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

These copies are ORIGINAL
OFFICIAL FDA Copies
not desk copies.

Merck & Co., Inc.
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West Point PA 19486-0004
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Tel 610 397 2905
215 652 5000

December 22, 1997

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

/S/ [redacted]

MERCK
Research Laboratories

DEC 24 1997
HFD-510

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

GENERAL CORRESPONDENCE

Dear Dr. Sobel:

Reference is made to the above supplemental NDA submitted on November 26, 1997 and to a December 19, 1997 telephone conversation between Mr. Randy Hedin (FDA) and Dr. Michelle Kloss (MRL) confirming January 7, 1998 as the date for a demonstration session on the electronic submission of this supplemental NDA for Dr. Jonathan Levine (at 9:00 AM) and Dr. Gloria Troendle (at 1:00 PM.) In preparation for this demonstration session, please note that user manuals for this electronic submission were submitted to the Agency on December 18, 1997.

Please direct questions or need for additional information to Michelle W. Kloss, Ph.D. (610/397-2905) or, in my absence, Bonnie J. Goldmann (610/397-2383).

/S/ [redacted]

Sincerely,

Michelle W. Kloss

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

Federal Express #1

(1) Desk copy: Mr. Randy Hedin, HFD-510, Room 14B-19
Federal Express #2

(1) Desk copy: Dr. Gloria Troendle, HFD-510, Rm. 14B-31
Federal Express #3

(1) Desk copy: Dr. Jonathan Levine, HFD-715, Rm. 15B-45
Federal Express #4

REVIEWS COMPLETED
CSO ACTION
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

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Used
/S/ [redacted]
2-20-98

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

Merck & Co., Inc.
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West Point PA 19486-0004
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December 18, 1997

MERCK
Research Laboratories

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)
Supportive Documentation - Electronic Submission

Dear Dr. Sobel:

Reference is made to the above referenced Supplemental New Drug Application (sNDA) submitted on November 26, 1997 and to the electronic submission for the above referenced sNDA submitted on December 12, 1997.

With this letter we are providing hard copy documentation to assist the reviewers in using the electronic submission.

Specifically, Volume 1 contains the User Manual for the documentation portion of the electronic submission. Volume 2 contains the User Guide for the SAS Programs and Datasets.

Please direct questions or need for additional information to Michelle W. Kloss, Ph.D. (610/397-2905) or, in my absence Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely,

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

q\baf\mk217\elect

Attachments

Federal Express #1

Desk Copies: (3): Mr. Randy Hedin, HFD-510, Room 14B-04: Federal Express #1
(1): Dr. Gloria Troendle, HFD-510, Room 14B-04: Federal Express #1
(1): Dr. Jonathan Levine, HFD-715, Room 15B-45, Federal Express #2

NDA SUPPL FOR

ORIGINAL

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

NDA SUPPLEMENT

Merck & Co., Inc.
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West Point PA 19486-0004
Fax 610 397 2516
Tel 610 397 2905
215 652 5000

November 26, 1997

MERCK
Research Laboratories

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: 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 Title 21 of the Code of Federal Regulations, Merck Research Laboratories (MRL) is submitting a Supplemental New Drug Application for FOSAMAX™ (alendronate sodium tablets).

This submission provides clinical efficacy and safety documentation supporting the use of FOSAMAX™ for the treatment and prevention of glucocorticoid-induced osteoporosis in men and women. The Data Analysis Plans for the two primary clinical studies were submitted to the agency on April 9, 1997 (IND [redacted]

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 54 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 Prescription Drug User Fee Act of 1992; User Fee I.D. No. [redacted] was sent to the Mellon Bank, Three Mellon Bank Center, 27th Floor [redacted] Pittsburgh, PA 15259-0001, on November, 12, 1997.

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 as previously agreed are being provided in electronic format only (see attached "Statement of Organization"). The electronic version of this submission will be submitted on or before December 12, 1997 to the Technology Support Services Staff (TSSS). Any differences between paper copy and electronic versions will be noted in the documentation accompanying the electronic version. Copies of the documentation provided with the electronic submission will be submitted to the NDA. As in the past, MRL will work with FDA to arrange orientation to the electronic submission for all relevant 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, Bonnie J. Goldmann, M.D., (610/397-2383)

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Sincerely, yours,

Michelle W. Kloss

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

Q:BF\MK-0217\GIOPCOV

Attachment

Federal Express #

Desk Copy (Letter and Patent Information only)
Mr. George Scott
5516 Nicholsen Lane, Room 238
Rockville, MD 20895

Federal Express #

APPEARS THIS WAY ON ORIGINAL