

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**20-560/S016**

***Trade Name:*** Fosamax

***Generic Name:*** (alendronate sodium)

***Sponsor:*** Merck Research Laboratories

***Approval Date:*** October 19, 1999

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-560/S016**

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20-560/S016**

**APPROVAL LETTER**

NDA 20-560/S-016 & S-020


OCT 19 1999

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

Dear Dr. Flicker:

Please refer to your supplemental new drug application dated October 30, 1998, received November 2, 1998 (Supplement 016) and your supplemental new drug application dated April 26, 1999, received April 27, 1999 (Supplement 020), 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 submission dated June 22, 1999 (Supplement 016). Your submission of April 22, 1999, constituted a complete response to our March 2, 1999, action letter for Supplement 016. We also acknowledge receipt of your submissions dated June 22, 1999 (Supplement-016), and May 26, June 8, and August 17, 1999 (Supplement-020). Further, we refer to the October 6, 1999, telephone conversation between you and Mr. Randy Hedin of our Division in which you agreed to the change listed below concerning bullet three on page two of the physicians' sample blister package.

Supplement 016 proposes the following changes: A new physicians' sample blister package for the 10 mg strength of Fosamax Tablets, associated labeling for the new blister package, and two new  packaging sites for these physicians samples. The submission also requests a categorical exclusion from the requirement to prepare an environmental assessment for the tablets in these blister packages. Supplement 020 provides for a wax polish and a shape change.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text with the minor revision listed below. Accordingly, these supplemental applications are approved effective on the date of this letter.

The third bullet on page two of the carton in supplement 016 should be changed from, ~~\_\_\_\_\_~~ to  
"FOSAMAX increased the amount of spinal bone in more than 9 out of 10 patients with osteoporosis."

NDA 20-560/S-016 & S-020

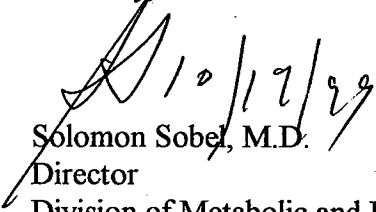
Page 2

The new labeling for the physicians' sample blister package must be identical, and include the minor revision indicated, to the submitted draft blister package submitted on April 22, 1999. This revision is a term of the approval.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

  
Solomon Sobel, M.D.

Director

Division of Metabolic and Endocrine Drug Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

RH 10/19/99

cc:

Archival NDA 20569/

HFD-510/Div. Files

HFD-510/R.Hedin

HFD-510/Reviewers and Team Leaders

HFD-095/DDMS-IMT

HFD-820/DNDC Division Director

DISTRICT OFFICE

Drafted by: RH/October 7, 1999

Initialed by: EChikhale/10.14/SMarkofsky/DWu/10.15/RShore for HAhn/EGalliers/10.18.99

final: RH 10.19.99

filename: N20560AP.L16

APPROVAL (AP)

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**20-560/S016**

**APPROVABLE LETTER**

MAR 2 1999

Merck and Company Inc.  
Attention: Dr. Michelle Kloss  
Director Regulatory Affairs  
Sunneytown Pike P.O. Box 4  
BLA-20  
West Point, PA 19486

Dear Dr. Kloss:

Please refer to your supplemental new drug application dated October 30, 1998, received November 2, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosamax (alendronate sodium tablets).

We acknowledge receipt of your submissions dated December 28, 1998, and January 20 and February 1, 1999.

This supplement proposes the following changes: A new physicians' sample blister package for the 10 mg strength of Fosamax Tablets, associated labeling for the new blister package, and two new alternative packaging sites for these physicians samples. The submission also requests a categorical exclusion from the requirement to prepare an environmental assessment for the tablets in these blister packages.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit draft Patient Starter Kit labeling revised as follows:

1. Please replace the bulleted phrase '~~\_\_\_\_\_~~' with '~~\_\_\_\_\_~~'

2. ~~\_\_\_\_\_~~

Fosamax has been shown to increase bone mineral density (BMD) by at best 5-7% depending on site and to decrease fracture incidence. These effects of Fosamax have been demonstrated over 3 years, and 5-year data are currently under review. The kyphosis that is so commonly seen in older women is the result of

factors in addition to loss of vertebral BMD and fractures. Age-related loss of muscle mass and strength is one such factor.

3. Please change the sentence that reads '\_\_\_\_\_ to \_\_\_\_\_ FOSAMAX tablet \_\_\_\_\_ with 6-8 oz. of plain water.' Also, please add statements instructing patients not to chew or suck on tablets, and not to take at bedtime, or before arising for the day.

4. The presentation of the \_\_\_\_\_ headlined with the statement \_\_\_\_\_ would be lacking in fair balance because it is not comparable to the presentation of the claims of efficacy. The efficacy claims are introduced with \_\_\_\_\_

Please revise the presentation of the risk information to be comparable to the presentation of the efficacy information.

5. The \_\_\_\_\_ does not include the \_\_\_\_\_ use of Fosamax. Please revise the \_\_\_\_\_ who should not take Fosamax, i.e., patients with: certain disorders of the esophagus, inability to stand or sit upright for at least 30 minutes, low levels of calcium in their blood, severe kidney disease, and allergy to Fosamax.

6. In the question that reads, '\_\_\_\_\_ add the words "AT LEAST" before "30 MINUTES." Also, in the \_\_\_\_\_

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 any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.



This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

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

Sincerely yours,

*3/2/99*  
Solomon Sobel, M.D.  
Director  
Division of Metabolic and  
Endocrine Drug Products (HFD-510)  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

*RH 3/2/99*

cc:

Archival NDA 20-560  
HFD-510/Div. Files  
HFD-510/R.Hedin  
HFD-510/Reviewers and Team Leaders  
HFD-95/DDMS  
DISTRICT OFFICE

Drafted by: RH/March 1, 1999

Initialed by: GTroendle/SMarkofsky/DWu/EGalliers/BSchneider/3.2.99

final:RH

filename: N20560AE.LT2

APPROVABLE (AE)

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**20-560/S016**

**MEDICAL REVIEW**

October 5, 1999

MEDICAL OFFICER'S REVIEW

sNDA 20560-016

**REVIEW OF SPONSOR'S RESPONSE TO OUR INITIAL COMMENTS  
REGARDING BLISTER PACKAGE FOR FOSAMAX**

I have reviewed the latest edition of Merck's Fosamax blister package. With one exception, I believe that they have responded adequately to our comments. In my initial review, I wrote. ~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~

In response, the sponsor changed the second bullet (page 2) to: ~~\_\_\_\_\_~~

**This change is acceptable.**

However, in the next bullet, "~~\_\_\_\_\_~~"  
~~\_\_\_\_\_~~

**This is not acceptable, for the reasons originally stated. The language should be identical to that in the second bullet ---e.g. "FOSAMAX increased the amount of spinal bone. ~~\_\_\_\_\_~~**

**in more than 9 out of 10 patients. ~~\_\_\_\_\_~~**

**Again, Fosamax has been shown to increase spine BMD in more than 9 out of 10 patients in clinical trials. ~~\_\_\_\_\_~~**

**The remainder of the blister package is acceptable.**

*Bruce Schneider*  
*Gloria Troendle*  
10/5/99

**BRUCE S. SCHNEIDER, MD**

**MEDICAL OFFICER  
DMEDP, HFD-510**

**CC Drs. Troendle, Sobel, Mr. Hedin, HFD-510 file**

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20-560/S016**

**CHEMISTRY REVIEW(S)**

FEB 12 1999

ORIGINAL

CHEMIST'S REVIEW	1. ORGANIZATION	2. NDA NUMBER
	DMEDP, HFD-510	20-560
3. NAME AND ADDRESS OF APPLICANT		4. SUPPLEMENT NUMBER, DATE
Merck & Co., Inc. Sumneytown Pike, BLA-20 P.O. Box 4 West Point, PA 19486		SCP-016, 30-Oct.-1998  User Fee Date: 3-2-99
5. NAME OF DRUG	6. NONPROPRIETARY NAME	8. AMENDMENTS/REPORT, DATE
Fosamax	Alendronate Sodium Tablets	
7. SUPPLEMENT PROVIDES FOR:		Amendment: 12-28-98 Amendment: 2-1-99 Correspondence: 1-20-99
1) A new physicians' blister package for the 10 mg strength of Fosamax tablets 2) Associated labeling for the new blister package 3) Two new <u>                    </u> packaging sites for these physicians samples 4) A Categorical Exclusion from the requirement to prepare an Environmental Assessment for the tablets in these blisters		
9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND/NDA/DMF
Treatment and prevention of osteoporosis	Prescription	
12. DOSAGE FORM	13. POTENCY	
Tablets (oral)	5, 10, & 40 mg tablets	
14. CHEMICAL NAME AND STRUCTURE		
See Chem. Rev. # 1		
15. COMMENTS:		
This Prior Approval Supplement provides for: 1) A new physicians' blister package for the 10 mg strength of Fosamax tablets 2) Associated labeling for the new blister package 3) Two new <u>                    </u> packaging sites for these physicians samples 3) A Categorical Exclusion from the requirement to prepare an Environmental Assessment for the tablets in these blisters. The labeling for this new physicians' blister package is also being reviewed by the appropriate Medical Officer (Dr. Bruce Schneider) and by Division of Drug Marketing, Advertising and Communications (DDMAC). <b>(Continued next page)</b>		
16. CONCLUSION AND RECOMMENDATIONS		
From a Chemistry point of view, the proposed supplement is acceptable. Issue an approval letter unless there are additional concerns raised by Dr. Schneider and (or) DDMAC.		
17. NAME	REVIEWER SIGNATURE	DATE COMPLETED
Sheldon Markofsky, Ph.D.	<i>Sheldon Markofsky</i>	2-12-99
DISTRIBUTION: ORIGINAL JACKET/CSO/REVIEWER/DIVISION FILE		

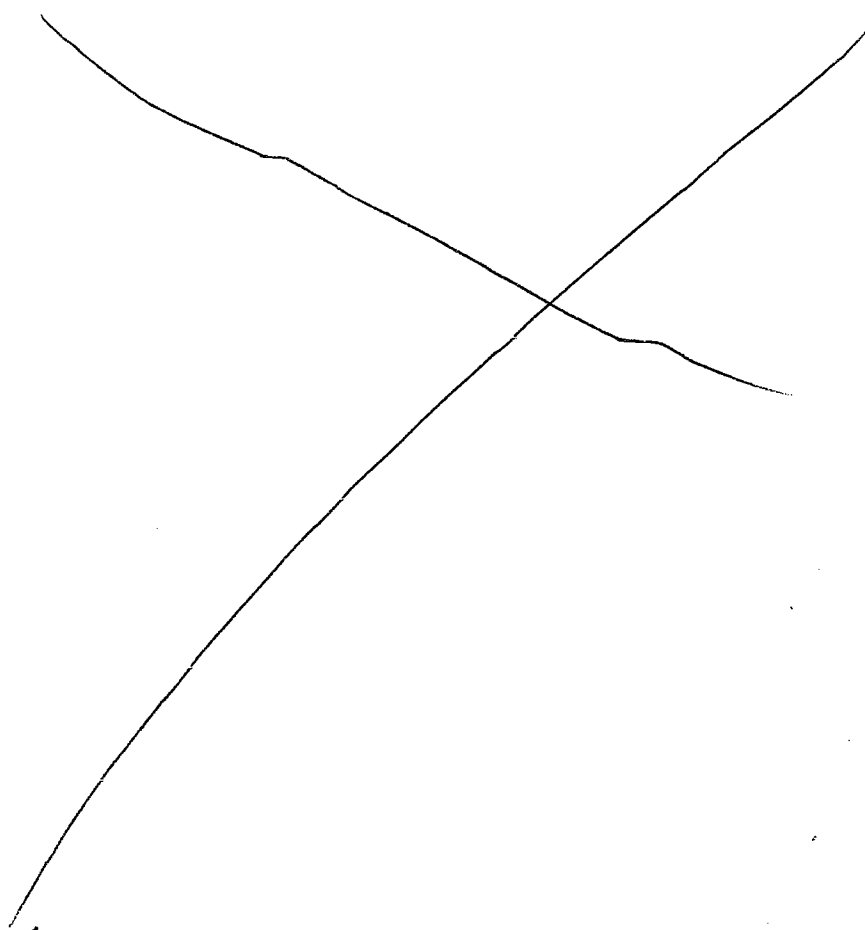
D/D initialed by:

*Duggan 2/12/99*

File name: n20560s.016a

15. COMMENTS (continued from page 1):

The amendments of 12-28-98 and 2-1-99 provide stability commitments for the new package. The correspondence, dated 1-20-99, provided a completely assembled sample blister package (minus the tablets). The relevant packaging facilities were given an acceptable cGMP status (See attached EES printout.)



2 Page(s) Withheld

X § 552(b)(4) Trade Secret /  
Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**20-560/S016**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



NDA 20-560/S-016 & 020  
Fosamax Tablets  
Dr. Michele Flicker.

**Date:**  
10/6/99

**CONTACT:**  
Dr. Michele Flicker  
610-397-3193

**MEMORANDUM OF TELECON**

I spoke with Dr. Flicker, concerning NDA 20-560/S-016 & 020. We discussed the third bullet on page two of the carton in supplement 016, and she agreed that the bullet should be changed ~~to~~ increased the amount of spinal bone to be consistent with the change in bullet number two. I stated that we would put this change in the approval letter as a condition of approval, and she agreed with this procedure.

  
Randy Hedim, CSO

cc: NDA Arch  
HFD-510  
HFD-510/RHedin/10.12.99/N20560.PH3

FEB 25 1999

Bone92

Alendronate, Merck, NDA 20560 /S-016  
Suggestions for Letter to Sponsor  
Re Advertising  
Jayne Peterson (DDMAC) and Bruce Schneider Reviews

The expression

\_\_\_\_\_  
Fosamax has been shown to increase BMD by at best 5-7% depending on site and to decrease fracture incidence. These effects of Fosamax have been demonstrated over 3 years, and 5-year data are currently under review. The kyphosis that is so commonly seen in older women is the result of factors in addition to loss of vertebral BMD and fractures. Age-related loss of muscle mass and strength is one such factor.

*Gloria Trowdle*  
2/25/99

cc: Orig NDA 20-560/S-016  
HFD-510

FEB 24 1999

February 24, 1999

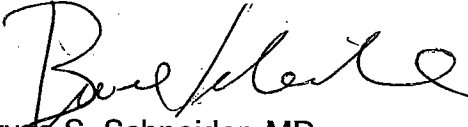
To: Jayne Peterson, DDMAC

Re: Fosamax blister package for patients

In general, I agree with the proposed changes. However, I would go a bit further.

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_ I also agree that  
withholding food for at least 30 minutes is an absorption/efficacy issue.

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
Fosamax treatment has been shown to increase BMD by at best 5-7%, depending on site, and to decrease fracture incidence as well. These effects of Fosamax have been demonstrated in 3-year studies, and 5-year data are currently under review. We have no data extending past 5 years. The kyphosis that is so commonly seen in older women is the result of many factors in addition to loss of vertebral BMD and presence of vertebral fractures. Age-related loss of muscle mass and strength is one such factor.

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
  
Bruce S. Schneider, MD  
Medical Officer, DMEDP, HFD-510

CC; Orig NDA 20-560/S-016  
HFD-510/div. file

FEB 18 1999

February 18, 1999

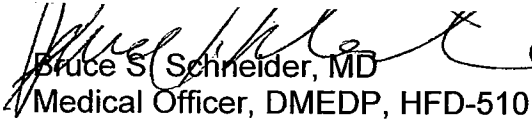
To: Jayne Peterson, DDMAC

Re: Fosamax blister package for patients

Jayne,

In general, I agree with the proposed changes.

I also agree that withholding food for at least 30 minutes is an absorption/efficacy issue.

  
Bruce S. Schneider, MD  
Medical Officer, DMEDP, HFD-510

cc: Orig NDA 20-560/S-016  
HFD-510/div. file

ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN  
SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Drug Marketing, Advertising, and Communications

DATE: February 3, 1999

TO: Randy Hedin  
Division of Metabolic and Endocrine Drug Products

FROM: Jayne E. Peterson, Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications

THROUGH: Tracy Acker, Acting Branch Chief  
Division of Drug Marketing, Advertising, and Communications

SUBJECT: NDA 20-560 *S-016*  
NAME OF DRUG: Fosamax 10 mg (alendronate sodium tablets)  
SPONSOR: Merck & Co., Inc.  
MACMIS#: 7392

BACKGROUND/RECOMMENDATIONS:

Merck submitted a proposed physicians' sample blister package for the 10 mg strength of Fosamax to the Division of Metabolic and Endocrine Drug Products (DMEDP) on October 30, 1999. Merck currently markets an individualized blister card with 31 tablets of the 10 mg strength for institutional use. This blister card provides for a blister package of 7 tablets for use as physicians' samples. In response to a December 9, 1998 request from the DMEDP, the Division of Drug Marketing, Advertising and Communications (DDMAC) has reviewed the proposed physicians' sample blister package and has the following comments:

• 

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In the Phase III clinical trials which investigated the use of Fosamax in the treatment of osteoporosis in postmenopausal women, increases in BMD were evident as early as three months. 

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This statement does not adequately convey the important precautionary and administration information that patients be directed to swallow the Fosamax tablet and that they should not chew or suck on the tablet. Therefore, DDMAC would recommend that Merck revise this statement to delete the word " " replace it with the word "swallow." Furthermore, DDMAC would recommend that Merck add the statement directing patients not to chew or suck on the tablet. Finally, DDMAC would recommend that Merck add the precautionary information that patients not take Fosamax at bedtime or before arising for the day.

- The presentation of the risk information in [redacted] of efficacy. The efficacy claims: [redacted] DDMAC would recommend that Merck revise the presentation of the risk information to be comparable to the presentation of the efficacy information.

- The [redacted] would be lacking in fair balance. [redacted] DDMAC would recommend that Merck revise the [redacted] to disclose those patients who should not take Fosamax, i.e., patients with: certain disorders of the esophagus, inability to stand or sit upright for at least 30 minutes, low levels of calcium in their blood, severe kidney disease and allergy to Fosamax.

- [redacted] does not adequately convey the precautionary information that after swallowing the Fosamax tablet, patients should wait at least 30 minutes before eating breakfast. DDMAC would recommend that Merck [redacted] to add the phrase, "at least" prior to the number "30." Furthermore, [redacted] that waiting at least 30 minutes after swallowing the Fosamax tablet and before eating breakfast, is critical, given the product's absorption, to Fosamax working at all. DDMAC would recommend that Merck revise the answer

NDA 20-560

Fosamax (alendronate sodium tablets)

to delete the word

---

Thank you for consulting with DDMAC on this issue. Please do not hesitate to call me if you have any questions, (301) 827-3901.

NDA 20-560  
Fosamax (alendronate sodium tablets)

File Name: C:/MYDOCUMENTS/Fosamaxblister12\_9

Draft:	Peterson	2/3/99
Consult:	Ostrove	2/7/99
Concur:	Acker	2/10/99

CC: HFD 40/NDA 20-560  
HFD 40/Chron/Peterson x2/Acker

MACMIS File ID #:	7391
MACMIS Type Code:	CONS
MACMIS Action Code:	INFO

Close out: Yes

FOI Status: NOT RELEASABLE



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

June 22, 1999

ORIGINAL

NDA SUPP AMEND

BL  
SCP-016

Mr. Randy Hedin, Senior Regulatory Manager  
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-016: FOSAMAX™  
(Alendronate Sodium Tablets)

Response to Request for Information

Dear Mr. Hedin:

Reference is made to the pending supplemental New Drug Application cited above for a Physicians' Sample Blister Package, also known as Patient Starter Kit. Further reference is made to the Agency's March 2, 1999 Approvable letter for this supplemental application and to an April 22, 1999 submission in which Merck Research Laboratories (MRL, a Division of Merck & Co., Inc.) provided an Amendment to Pending Supplement in response to the April 22, 1999 Approvable letter. Reference is also made to a June 21, 1999 telephone conversation between Mr. Randy Hedin and Dr. Michele Flicker (MRL) in which Mr. Hedin requested an additional desk copy of the above referenced supplemental application and amendment.

With this submission, we are providing the requested desk copies as well as a copy of the above referenced Approvable letter.

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

SKM  
1-10-00

REVIEWS COMPLETED
CSO ACTION:
<input checked="" type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS: <i>SK</i> DATE: <i>10/19/99</i>

Q:RCvmk-0217/response

Attachments

Federal Express #1

Desk Copy (Letter Only): NDA 20-560, HFD-510, Room 14B-04 - Federal Express #1

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

April 22, 1999

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ORIGINAL

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

AL  
5cp-016  
NDA SUPPLEMENT  
 **MERCK**

**NDA 20-560/S-016: FOSAMAX™  
(Alendronate Sodium Tablets)**

**Amendment to Pending Supplemental Application**



Dear Dr. Sobel:

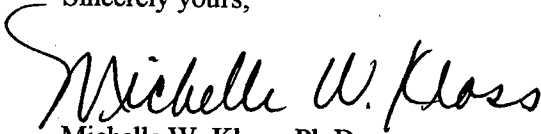
Reference is made to the pending supplemental new drug application cited above. Further reference is made to the Agency's March 2, 1999 Approvable Letter for this supplemental application which requested that Merck & Co., Inc. submit revised draft Patient Starter Kit labeling in accordance with Agency comments noted in this Approvable letter.

With this submission, we are providing, for Agency review and approval, a complete response to the items cited in the March 2, 1999 Approvable Letter for this supplemental application. This submission includes an Overview/Summary of Revisions section (Attachment 1) which provides a comprehensive summary of our responses to the Agency's comments and 20 mounted copies of the revised draft Patient Starter Kit labeling (Attachment 2).

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, Ph.D.  
Director  
Regulatory Affairs

Q:RC\mk-0217\amends\016amn4

Attachments

Federal Express #1

Desk Copy: Mr. Randy Hedin, CSO, HFD-510, Room 14B-04 Fed. Ex. #1

REVIEWS COMPLETED	
CSO ACTION:	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> METAD
PAT	

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

ORIGINAL Sep-016  
BM

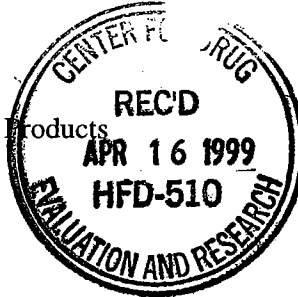
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NDA SUPP AMEND

April 15, 1999



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



*Handwritten signature and date: 12-28-99*

**NDA 20-560: FOSAMAX™ (Alendronate Sodium Tablets)  
Response to Request for Information**

Dear Dr. Sobel:

Reference is made to the new drug application cited above for FOSAMAX™ and to the March 9, 1999 submission in which Merck Research Laboratories (MRL, a Division of Merck & Co., Inc.) provided cancer data from all randomized, placebo-controlled phase 2 and 3 clinical trials of postmenopausal and corticosteroid-induced osteoporosis as requested by the Agency. Further reference is made to a March 18, 1999 facsimile communication from Dr. Solomon Sobel (FDA) to Dr. Michelle Kloss (MRL) which requested that MRL provide additional information. Specifically, the Agency has requested that MRL submit four tables for each of the seven main clinical trials of alendronate in osteoporosis; the complete details of the request are attached. The trials identified are 035 and 037 (osteoporosis treatment), 029, 038, and 055 (osteoporosis prevention), 051 (fracture intervention trial), and 082/083 (corticosteroid-induced osteoporosis)

With the attachment to this submission, we are providing the requested information. 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,

*Handwritten signature: Michelle W. Kloss*  
Michelle W. Kloss, Ph.D.  
Director  
Regulatory Affairs

*Handwritten: SB 7 12-28-99*

Q:\carnal\mck-0217\responses\apr\_res

Attachment

Federal Express #1

Desk Copies (2):

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

*Handwritten: NC RW statement 1/5/00*

REVISIONS COMPLETED  
CSO ACTION:  LETTER  M.A.I.  MEMO  
*Handwritten initials and date: 1/6/00*  
CSO INITIALS \_\_\_\_\_ DATE \_\_\_\_\_

SCP-016 C

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

SUPPL NEW CORRESP

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

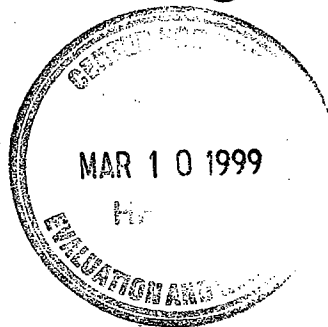
These copies are  
**OFFICIAL FDA Copies**  
~~not desk copies.~~

ORIGINAL



March 9, 1999

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  
9201 Corporate Blvd.  
Rockville, MD 20850



**NDA 20-560/S-016: FOSAMAX™**  
**(Alendronate Sodium Tablets)**

*[Handwritten signature]*  
3/18/99

Dear Dr. Sobel:

Please refer to your letter dated March 2, 1999 and received by MRL on March 9, 1999 indicating that the above-captioned supplement is approvable. With this letter, we wish to notify you of our intent to file an amendment to this application.

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.

*587  
3-25-99*

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-04 - Federal Express #2

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> M.A.I. <input type="checkbox"/> MEMO
<i>W</i>	<i>3/26/99</i>
CSO INITIALS	DATE

q:\kloss\fosamax\fdaltrs\sobel3-9-99

*No  
Rev Payment  
3/25/99*

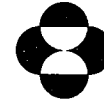
Michelle W. Kloss, Ph.D.  
Director  
Regulatory Affairs

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 1, 1999

**These copies are  
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not desk copies**

**ORIGINAL**



**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  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

**NDA SUPP AMEND**

*SCP-016 BSC*

**NDA 20-560/S-016: FOSAMAX™  
(Alendronate Sodium Tablets)**

REVIEWS COMPLETED	
CSO ACTION:	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
<i>JK</i>	<i>3/2/99</i>
CSO INITIALS	DATE

**AMENDMENT TO PENDING SUPPLEMENTAL APPLICATION**

Dear Dr. Sobel:

Reference is made to the Supplemental New Drug Application cited above submitted on October 30, 1998 which provides for the addition of a physicians' sample blister package for the 10 mg strength of FOSAMAX™. Reference is also made to a December 8, 1998 telephone conversation between Dr. Shelly Markofsky (FDA) and Dr. Michelle Kloss (MRL, a Division of Merck & Co., Inc.) in which Dr. Markofsky requested that Merck provide a commitment to place the first lot packaged \_\_\_\_\_ and \_\_\_\_\_ on stability and to report the data in the Annual Report; further reference is made to a December 28, 1998 amendment to this supplemental application which provided this commitment. Additional reference is made to a January 29, 1999 telephone conversation between Dr. Markofsky and Dr. Kloss in which Dr. Markofsky requested that Merck also provide a commitment to place the first lot blistered at the Wilson facility on stability and to report the data in the Annual Report.

With this submission, as requested, Merck provides the commitment that the first lot blistered at Wilson will be placed on stability under the current protocol \_\_\_\_\_ and that the data will be reported in the Annual Report.

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,

*Michelle W. Kloss*

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

q/camal/mk0217/s016amnd

Federal Express #1

Desk copy: Mr. Randy Hedin, CSO, HFD-510, Room 14B-04 Fed. Ex. #1  
Dr. Shelly Markofsky, HFD-510, Room 14B-04 FAX/Fed. Ex. #1

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

These copies are OFFICIAL FDA Copies  
not desk copies.

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

ORIGINAL

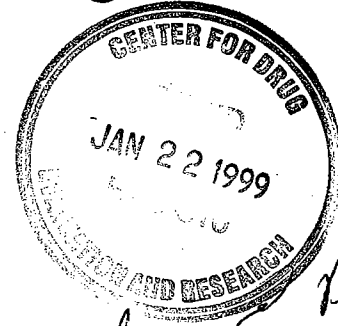
January 20, 1999

NDA SUPP AMEND

SCP-016 BC



Solomon Sobel, M. D., Director  
Division of Metabolism and Endocrine Drug Products  
HFD-510, Room 14B-04  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857



*Review 1/19/99  
Comments enclosed*

NDA 20-560/S-016: FOSAMAX™  
(Alendronate Sodium Tablets)

Response to FDA Request for Information

Dear Dr. Sobel:

Reference is made to the Supplemental New Drug Application cited above submitted on October 30, 1998 which provides for the addition of a physicians' sample blister package for the 10 mg strength of FOSAMAX™. Reference is also made to a December 8, 1998 telephone conversation between Dr. Shelly Markofsky (FDA) and Dr. Michelle Kloss (MRL.) in which Dr. Markofsky requested that Merck Research Laboratories (MRL; a division of Merck & Co., Inc) provide a commitment to place the first lot packaged at / and / on stability and to report the data in the Annual Report. During the same conversation, Dr. Markofsky also requested that MRL provide a complete physicians' sample blister package, including all components, for his review. Further reference is made to a December 28, 1998 submission which provided a response to the first Agency request cited above (i.e., in which MRL provided a commitment that the first lot packaged entirely at each site will be placed on stability and that the data will be reported in the Annual Report). With this submission, we are providing a complete physicians' sample blister package, including all components, in response to the second Agency request cited above.

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).

*Review completed  
2-12-99  
SAM*

Sincerely,

*Michelle W. Kloss*

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

q/carnal/mk0217/s016amr2

Attachment

Federal Express #1

Desk copy: Mr. Randy Hedin, CSO, HFD-510, Room 14B-04 Fed. Ex. #1  
Dr. Shelly Markofsky, HFD-510, Room 14B-04 Fed. Ex. #1

REVIEWS COMPLETED	
CSO ACTION:	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE
<i>[Signature]</i>	<i>3/12/99</i>

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

**ORIGINAL**

These copies are  
**OFFICIAL FDA Copies**  
not desk copies.

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

December 28, 1998

Solomon Sobel, M. D., Director  
Division of Metabolism and Endocrine Drug Products  
HFD-510, Room 14B-04  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857



**NDA SUPP AMEND**

*508-016 BL*

*SRM  
5-10-99*

**NDA 20-560/S-016: FOSAMAX™  
(Alendronate Sodium Tablets)**

**AMENDMENT TO PENDING SUPPLEMENTAL APPLICATION**



Dear Dr. Sobel:

Reference is made to the Supplemental New Drug Application cited above submitted on October 30, 1998 which provides for the addition of a physicians' sample blister package for the 10 mg strength of FOSAMAX™. Reference is also made to a December 8, 1998 telephone conversation between Dr. Shelly Markofsky (FDA) and Dr. Michelle Kloss (MRL) in which Dr. Markofsky requested that MRL provide a commitment to place the first lot packaged at \_\_\_\_\_ and \_\_\_\_\_ stability and to report the data in the Annual Report. During the same conversation, Dr. Markofsky also requested that MRL provide a complete physicians' sample blister package, including all components, for his review. With this submission, we are providing a response to the Agency's request for commitment for stability testing cited above; we are currently assembling the complete physicians' sample blister package in response to the second Agency request cited above and this response will be submitted shortly under separate cover.

With this submission, as requested, Merck provides the commitment that the first lot packaged entirely (blistering and final assembly) at each site, \_\_\_\_\_ and \_\_\_\_\_ will be placed on stability under the current protocol \_\_\_\_\_ and that the data will be reported in the Annual Report.

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).

<b>REVIEWS COMPLETED</b>	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I.
<input type="checkbox"/> MEMO	
<i>WK</i>	<i>5/11/99</i>
CSO INITIALS	DATE

Sincerely,

*Larry P. Bell*  
for Michelle W. Kloss, Ph.D.  
Director, Regulatory Affairs

*no RW statement  
5/10/99*

q/carnal/mk0217/s016amnd

Federal Express #1

Desk copy: Mr. Randy Hedin, CSO, HFD-510, Room 14B-04 Fed. Ex. #1  
Dr. Shelly Markofsky, HFD-510, Room 14B-04 Fed. Ex. #1

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

October 30, 1998

**These copies are OFFICIAL FDA Copies  
not desk copies.**

NDA NO. 20-560 REF NO. 016  
NDA SUPPL FOR SCP



Solomon Sobel, M.D., Director  
Division of Metabolism and Endocrine Drug Products  
HFD-510, Room 14B-04  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
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 Food Drug and Cosmetic Act and in accordance with 21 CFR 314.70 (b), we submit a supplement to NDA 20-560.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in the Labeling and Chemistry Section(s) of the approved New Drug Application for FOSAMAX™.

This supplemental application provides for the addition of a physicians' sample blister package for the 10 mg strength of FOSAMAX™. Merck & Co., Inc. currently markets a FOSAMAX™ individualized blister card (UNIBLISTER™) with 31 tablets (10 mg strength) for institutional use; this supplemental application provides for a blister package with 7 tablets for use as physicians' samples. Proposed labeling for this physicians' sample blister package is included in this application.

The packaging components in contact with FOSAMAX™ tablets in the proposed physicians' sample blister are identical to the currently marketed UNIBLISTER™ packaging components and are obtained from the same suppliers) as for the currently marketed UNIBLISTER™. The cavity dimensions are also identical. Both the proposed physicians' sample blister and the UNIBLISTER™ are "push-through", non-child-resistant configurations supported by a paperboard card. Proposed packaging sites for the physicians' sample blister package, one of which is currently approved for the packaging of the UNIBLISTER™, are included in the Chemistry, Manufacturing and Controls (CMC) section of this supplemental application.

In accordance with the Food and Drug Administration Modernization Act of 1997, as indicated in the attached Form 3397, no user fee is required for this supplemental application.

Attached in Draft for Approval are the following:

- CMC documentation for the physicians' sample blister package.
- 20 mounted copies of front and back panels of physicians' sample blister package labeling.



Solomon Sobel, M.D., Director  
NDA 20-560: FOSAMAX™ (Alendronate Sodium Tablets)  
Page 2

Pursuant to 21 CFR 314.70(a), a complete field copy of this supplement has been submitted to the FDA Philadelphia District Office.

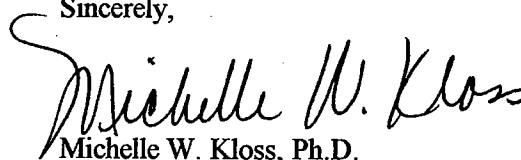
Merck is requesting a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR 25.31(a) for this supplemental application.

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [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.

We consider the filing of this Supplemental New Drug Application to be a confidential matter, and request 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,



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

q/carnal/mk217/blister

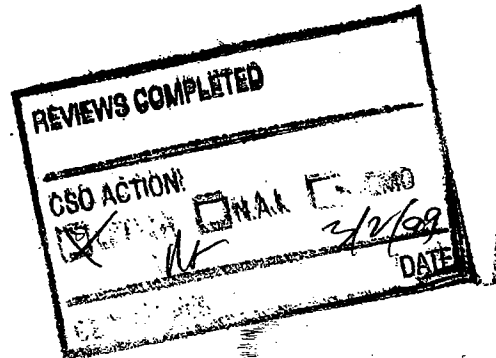
Attachments

Federal Express #1

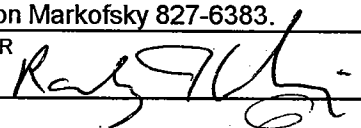
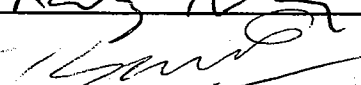
Desk copy:

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

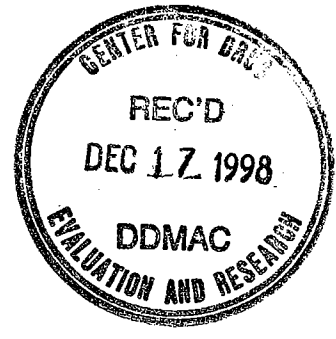
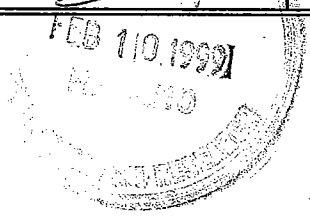
Ms. Debra Pagano  
Philadelphia District Office  
Food & Drug Administration  
U.S. Custom House Room 900  
2nd and Chestnut Street  
Philadelphia, Pennsylvania 19106-2973 - Federal Express #2



12/10/98

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>			
TO (Division/Office) HFD-44 Attn Jane Peterson			FROM: HFD-510		
DATE OF DOCUMENT September 9, 1998	IND NO.	NDA NO. NDA 20-560	TYPE OF DOCUMENT Physicians' Sample Pak	DATE OF DOCUMENT October 30, 1998	
NAME OF DRUG Fosamax (alendronate sodium)		PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG S	DESIRED COMPLETION DATE January 9, 1999	
NAME OF FIRM Merck Research Laboratories					
<b>REASON FOR REQUEST</b>					
<b>I. GENERAL</b>					
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY		<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW)	
<b>II. BIOMETRICS</b>					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER		
<b>III. BIOPHARMACEUTICS</b>					
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input checked="" type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>					
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Please review the attached supplement containing a new physicians' sample blister package. If you have any questions please contact Randy Hedin at 827-6392. The medical officer is Dr. Bruce Schneider 827-6425, and the chemist is Dr. Sheldon Markofsky 827-6383.					
SIGNATURE OF REQUESTER 			METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND		
SIGNATURE OF RECEIVER 			SIGNATURE OF DELIVERER		

Consult.070





Food and Drug Administration  
Rockville MD 20857

NDA 20-560/S-016

NOV 17 1998  
NOV 17 1998

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 Ms. Kloss:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Fosamax<sup>®</sup> (Alendronate Sodium Tablets)  
NDA Number: 20-560  
Supplement Number: S-016  
Date of Supplement: October 30, 1998  
Date of Receipt: November 2, 1998

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

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

NDA 20-560/S-016

Page 2

cc:

Original NDA 20-560/S-016

HFD-510/Div. Files

HFD-510/CSO/R. Hedin

filename: C:\DATA\WPFILES\20560ACK.

**SUPPLEMENT ACKNOWLEDGEMENT**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297  
Expiration Date: 04-30-01

# USER FEE COVER SHEET

**See Instructions on Reverse Side Before Completing This Form**

1. APPLICANT'S NAME AND ADDRESS

Merck & Co., Inc.  
Sumneytown Pike, BLA-10  
P. O. Box 4  
West Point, PA 19486

3. PRODUCT NAME

*Fosamax*

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?  
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE  
AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

- THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.  
 THE REQUIRED CLINICAL DATA ARE SUBMITTED BY  
REFERENCE TO \_\_\_\_\_  
(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

( 610 ) 397-2383

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

- A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92  
(Self Explanatory)
- A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE  
(See item 7, reverse side before checking box.)
- THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act  
(See item 7, reverse side before checking box.)
- THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act  
(See item 7, reverse side before checking box.)
- THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY  
(Self Explanatory)

### FOR BIOLOGICAL PRODUCTS ONLY

- WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION
- A CRUDE ALLERGENIC EXTRACT PRODUCT
- AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY
- AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
- BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES  NO

(See reverse side if answered YES)

**A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.**

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer  
Paperwork Reduction Project (0910-0297)  
Hubert H. Humphrey Building, Room 531-H  
200 Independence Avenue, S.W.  
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

*Bonnie J. Goldmann*

TITLE **Bonnie J. Goldmann, M.D.**  
**Vice President, Domestic Liaison**  
**Regulatory Affairs**

DATE