CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-560 /S028

Trade Name: Fosamax Tablets

Generic Name: alendronate sodium

Sponsor: Merck & Co., Inc

Approval Date: September 16, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-560 /S028

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-560 /S028

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-560/S-028

Merck & Co., Inc.
Attention: Michele Flicker, M.D., Ph.D.
Director, Regulatory Affairs
P.O. Box 2000
Mail Drop: Ry 33-720
Rahway, NJ 07065

Dear Dr. Flicker:

Please refer to your supplemental new drug application dated January 18, 2001, received January 19, 2001, 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 July 9, and August 30, 2001.

This supplemental new drug application proposes revised physician sample package labeling text for the 10 mg daily dose, and 35 and 70 mg weekly doses.

We have completed the review of this supplemental application, 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 submitted draft labeling (text for the 10 mg daily dose, 35 and 70 mg weekly doses physician sample packages) with the minor revision listed below for the 10 mg daily dose text. Accordingly, the supplemental application is approved effective on the date of this letter.

The first bullet in the panel for the 10 mg daily dose text which reads, "Some Facts About FOSAMAX" should be changed from, (b)---------- . . ." to "FOSAMAX increased bone mass, and reduced the number of . . ."

The final printed labeling (FPL) must be identical to the submitted draft labeling (text for the 10 mg daily dose, and 35 and 70 mg weekly doses physician sample packages) with the minor revision listed above. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-318." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff
9/16/02 06:22:39 PM

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/s/

David Orloff
9/16/02 06:22:39 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-560 /S028

LABELING

Component Number Bar Code Verification: Code 128 Subset C, 13 mil, Height 1/4"

ONCE WEEKLY

FOSAMAX®
(alendronate sodium tablets)

USUAL ADULT DOSAGE: ONE 35 mg TABLET ONCE WEEKLY.
See accompanying circular for complete dosage information.

Package not child-resistant. Keep this and all drugs out of the reach of children. Store at room temperature, 15–30°C (59–86°F).

N
3 0006-0077-01 6

Patient instructions

Physician

Patient Date dispensed

Side effects in studies have usually been mild and generally have not caused patients to stop taking FOSAMAX. The most commonly reported side effect was abdominal (stomach) pain.

Please read the enclosed Patient Information leaflet for further details.

COMPLIMENTARY SRN 6292

MERCK

Printed in USA

F P O
1234567

Once Weekly FOSAMAX® (Alendronate Sodium Tablets) 35 mg Patient Starter Kit

For the prevention of osteoporosis in postmenopausal women

ONCE WEEKLY

FOSAMAX® 35 mg

(Alendronate Sodium Tablets)

Patient Starter Kit

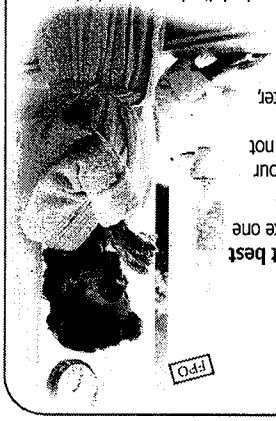
Each tablet contains
45.68 mg Alendronate Sodium
(35 mg free acid equivalent)

1 tablet
NO. 3813
COMPLIMENTARY

Rx only

MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

How to take
Once Weekly
FOSAMAX® 35 mg
(Alendronate Sodium Tablets)



Choose the day of the week that best fits your schedule. Every week, take one FOSAMAX tablet on your chosen day.

After getting up for the day on your chosen day of the week, swallow (do not chew or suck) one FOSAMAX tablet with a full glass (6–8 oz.) of plain water, on an empty stomach. Do not take FOSAMAX at bedtime or before arising for the day.

Begin your morning activities... but don't lie down, eat, drink, or take other medication for at least 30 minutes. If you want to lie down after 30 minutes, you must eat breakfast first.

Remember to take one FOSAMAX tablet once each week on that same day for as long as your doctor prescribes it.

If you miss a dose, take only one FOSAMAX tablet on the morning after you remember. *Do not take two tablets on the same day.* Return to taking one tablet once a week, as originally scheduled on your chosen day.

There is important additional information about how to take *Once Weekly* FOSAMAX in the enclosed Patient Information leaflet. Please read it carefully.

ONCE WEEKLY

FOSAMAX®
(alendronate sodium tablets)

Choose your day for taking *Once Weekly* FOSAMAX® 35 mg

WEEK 1

Push tablet through back of package

Sunday
Monday
Tuesday
Wednesday
Thursday
Friday
Saturday

To help you remember to take your FOSAMAX, choose a day of the week that will be best for you to remember. Write in the best date for you to start FOSAMAX.

Component Number Bar Code Verification: Code 128 Subset C, 13 mil, Height 1/4"

ONCE WEEKLY

FOSAMAX®

(alendronate sodium tablets)

USUAL ADULT DOSAGE: ONE 70 mg TABLET ONCE WEEKLY.
See accompanying circular for complete dosage information.

Package not child-resistant. Keep this and all drugs out of the reach of children. Store at room temperature, 15–30°C (59–86°F).

N
3 0006-0031-01 4

Patient instructions

Physician

Patient Date dispensed

Side effects in studies have usually been mild and generally have not caused patients to stop taking FOSAMAX. The most commonly reported side effect was abdominal (stomach) pain.

Please read the enclosed Patient Information leaflet for further details.

COMPLIMENTARY SRN 6303

MERCK

F P O
1234567

Once Weekly FOSAMAX® (Alendronate Sodium Tablets) 70 mg Patient Starter Kit

For the treatment of osteoporosis in postmenopausal women

ONCE WEEKLY

FOSAMAX®

(Alendronate Sodium Tablets)

70 mg

Patient Starter Kit

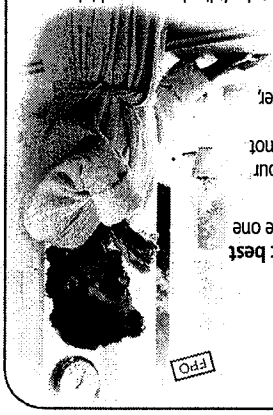
Each tablet contains
91.37 mg Alendronate Sodium
(70 mg free acid equivalent)

1 tablet
NO. 3814
COMPLIMENTARY

Rx only

MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

How to take
Once Weekly
FOSAMAX® 70 mg
(Alendronate Sodium Tablets)



Choose the day of the week that best fits your schedule. Every week, take one FOSAMAX tablet on your chosen day.

After getting up for the day on your chosen day of the week, swallow (do not chew or suck) one FOSAMAX tablet with a full glass (6–8 oz.) of plain water, on an empty stomach. Do not take FOSAMAX at bedtime or before arising for the day.

Begin your morning activities... but don't lie down, eat, drink, or take other medication for at least 30 minutes. If you want to lie down after 30 minutes, you must eat breakfast first.

Remember to take one FOSAMAX tablet once each week on that same day for as long as your doctor prescribes it.

If you miss a dose, take only one FOSAMAX tablet on the morning after you remember. *Do not take two tablets on the same day.* Return to taking one tablet once a week, as originally scheduled on your chosen day.

There is important additional information about how to take *Once Weekly* FOSAMAX in the enclosed Patient Information leaflet. Please read it carefully.

ONCE WEEKLY

FOSAMAX®

(alendronate sodium tablets)

Choose your day for taking *Once Weekly* FOSAMAX® 70 mg

WEEK 1

Push tablet through back of package

Sunday
Monday
Tuesday
Wednesday
Thursday
Friday
Saturday

To help you remember to take your FOSAMAX, choose a day of the week that will be best for you to remember. Write in the best date for you to start FOSAMAX.

How to Take FOSAMAX® (Alendronate Sodium Tablets)

1. After getting up for the day, swallow (do not chew or suck) one FOSAMAX tablet with a full glass (6–8 oz.) of plain water only. Do not take FOSAMAX at bedtime, or before arising for the day.

2. Begin the day's activities…but DON'T LIE DOWN, eat, drink, or take other medication for at least 30 minutes. (If you want to lie down after 30 minutes, you must eat breakfast first.)

What Else Should I Know?

- Follow dosing instructions exactly to obtain benefit from FOSAMAX and reduce the potential for esophageal irritation. Stop taking FOSAMAX and tell your doctor if you develop new or worsening heartburn, difficult or painful swallowing, or chest pain because these may be signs of serious upper digestive problems which can include irritation, inflammation, or ulceration of the esophagus.

Day 1

Day 2

Day 3

Day 4

Day 5

Day 6

Day 7

PUSH TO RELEASE TABLETS

QUESTIONS & ANSWERS

DO I HAVE TO DRINK A FULL GLASS OF PLAIN WATER?
YES. Drinking a full glass of plain water (6–8 oz.) delivers FOSAMAX® (Alendronate Sodium Tablets) to your stomach and helps dissolve the medication.

CAN I TAKE OTHER MEDICATIONS OR DRINK COFFEE WITH FOSAMAX?
NO. Anything other than plain water may interfere with how well FOSAMAX works.

WHY MUST I WAIT AT LEAST 30 MINUTES BEFORE EATING BREAKFAST?
FOSAMAX is effective only when taken on an empty stomach.

WHY CAN'T I LIE DOWN AFTER TAKING FOSAMAX?
Remaining upright lets the tablet settle quickly in your stomach and may help you avoid certain side effects like heartburn, chest pain, or difficulty or pain upon swallowing. If you must lie down, wait 30 minutes, eat breakfast, then lie down.

WHO SHOULD NOT TAKE FOSAMAX?
FOSAMAX should not be used if you have certain disorders of the esophagus (the tube that connects your mouth with your stomach), are unable to stand or sit upright for at least 30 minutes, or have severe kidney disease, low levels of calcium in your blood, are allergic to FOSAMAX, or are pregnant or nursing.

FOSAMAX® (Alendronate Sodium Tablets) 10 mg

FOSAMAX®
(alendronate sodium tablets)

USUAL ADULT DOSAGE: ONE 10 mg TABLET DAILY.
See accompanying circular for complete dosage information.
Package not child-resistant.
Keep this and all drugs out of the reach of children.
Store at room temperature, 15–30°C (59–86°F).

Side effects in studies have usually been mild and generally have not caused patients to stop taking FOSAMAX. The most commonly reported side effect was abdominal (stomach) pain.

Please read the enclosed Prescribing Information and Patient Information leaflet for further details.

Patient instructions

Physician

Patient

Date dispensed

COMPLIMENTARY SRN 6160

MERCK

Printed in USA

0006-0936-07

6254602

FOSAMAX® (Alendronate Sodium Tablets) 10 mg

For the Treatment of Postmenopausal Osteoporosis and for the Treatment to Increase Bone Mass in Men with Osteoporosis

FOSAMAX® 10 mg
(Alendronate Sodium Tablets)
Patient Starter Kit

Rx only
7 Tablets
No. 3797
Complimentary
Each tablet contains 10 mg Alendronate Sodium (Hydrous free acid equivalent).

Merck Sharp & Dohme
West Point, PA 19486

Please see the enclosed Prescribing Information and Patient Information leaflet.

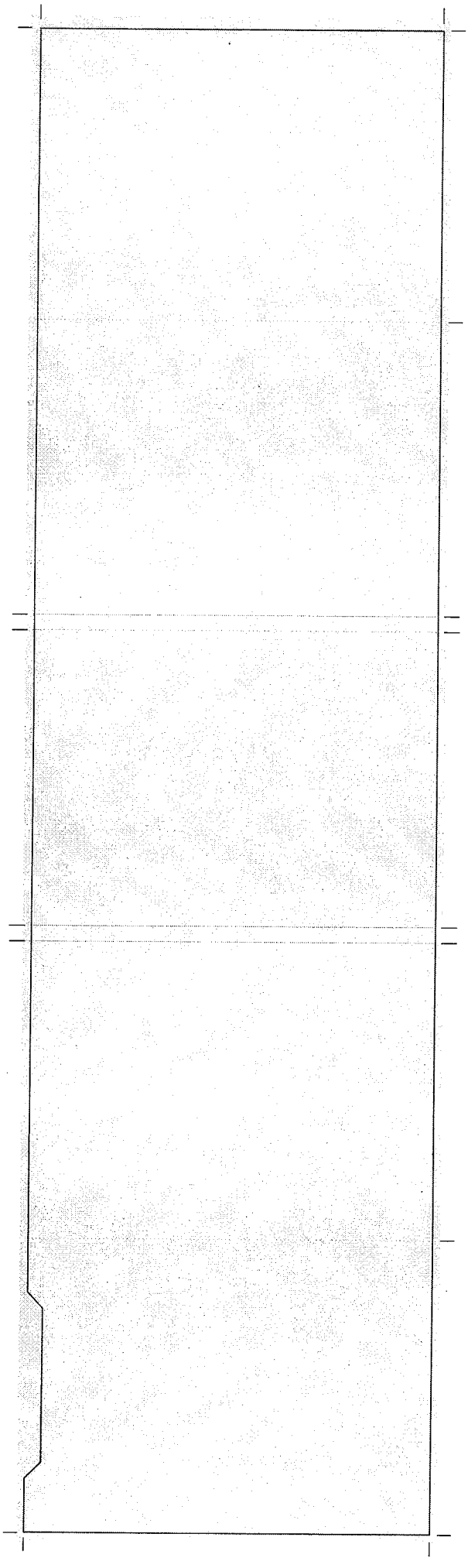
What Should I Know About Osteoporosis?

- Osteoporosis is a disease that causes bones to become thin, weak, and easy to break or fracture.
- Osteoporosis may cause pain, height loss, and humped back, limiting your mobility.
- Broken bones of the hip, spine, and wrist may cause pain, severe disability, or loss of mobility.

Some Facts About FOSAMAX® (Alendronate Sodium Tablets)

In clinical studies...

- FOSAMAX helped build bone, and reduced the number of fractures, including those at the hip and spine, in postmenopausal women.
- FOSAMAX increased bone mass in men with osteoporosis.
- FOSAMAX increased the amount of bone as early as 3 months after therapy was begun.



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-560 /S028

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Division of Metabolic and Endocrine Drug Products

PROJECT MANAGER LABELING REVIEW

Application Number: 20-560/S-028

Name of Drug: Fosamax (alendronate sodium) Tablets

Sponsor: Merck Research Laboratories

Material Reviewed

Submission Dates:

- January 18, 2001, containing draft text for the 10, 35, and 70 mg strength physician sample packaging.
- July 9, 2001, containing revised draft text for the 10, 35, and 70 mg strength physician sample packaging.
- August 30, 2001, containing an electronic version of the revised text for the 10, 35, and 70 mg strength physician sample packaging submitted on July 9, 2001.

Background and Summary Description:

This prior approval supplemental new drug application was submitted on January 18, 2001, and proposes revised physician sample package labeling for the 10 mg daily dose, and 35 and 70 mg weekly doses. An information request letter was sent on May 15, 2001, requesting revisions to the 10 mg physician sample package labeling. Merck responded on July 9, 2001 with revised labeling for the 10 mg daily dose, and 35 and 70 mg weekly doses. Merck submitted the revised labeling electronically on August 30, 2001.

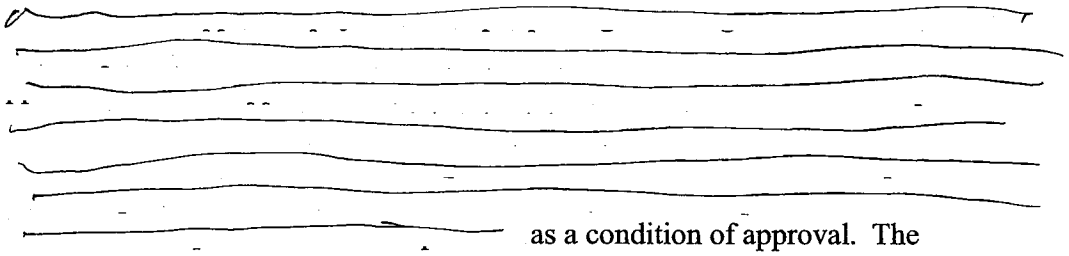
Review

10 Mg Daily Dose

The submitted final printed labeling (FPL) of text for the 10 mg daily dose (Identifier Number SRN Issued 2001), was compared to the currently approved FPL of the text for the 10 mg daily dose (Identifier Number Issued 2000.) I telephoned Merck concerning the (SRN) for supplement 028 which is This SRN

Merck further stated that the currently

approved FPL is differentiated from the pending FPL by the issue date, 2000 vs. 2001. In addition, the last approved physician sample package labeling for supplement 016 has an SRN number of 5764.



as a condition of approval. The physician sample package labeling dated 2000 incorporated this change. This is the only change from the approved sample package labeling text (SRN 5764).

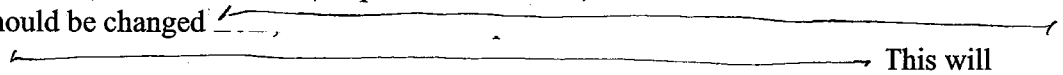
70 Mg Weekly Dose

The submitted physician sample package labeling FPL text for the 70 mg weekly dose (Identifier Number SRN6303, Issued 2001), was compared to the currently approved FPL of the text for the 70 mg daily dose physician sample package labeling FPL (Identifier Number SRN 6303, Issued 2000).

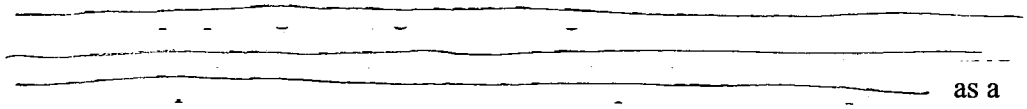
35 Mg Weekly Dose

The submitted physician sample package labeling FPL text for the 35 mg weekly dose (Identifier Number SRN6292, Issued 2001), was not compared to an approved 35 mg weekly dose physician sample package labeling text. A 35 mg physician sample package labeling text was never approved. However, the physician sample package labeling FPL text for the 35 mg weekly dose was compared to the 70 mg text and is identical except for the dose.

The physician sample package labeling FPL text for the 10 mg daily dose contains the revisions requested in our information request letter dated on May 15, 2001. However, the first bullet in the panel which reads, "Some Facts About FOSAMAX" should be changed



This will more closely reflect the results of the trials, and comply with our request in our approval letter for supplement 016 dated October 9, 1999, which requested the



as a condition of approval. Fosamax , it increases bone mass, or bone mineral density. This was originally in the approval letter for supplement-016 dated October 19, 1999.

Conclusions

The labels are acceptable with the minor revision noted for the 10 mg daily dose text, and an approval letter should be issued.

Reviewed by: Randy Hedin, R.Ph., Senior Regulatory Management Officer

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/s/

Randy Hedin
9/12/02 08:58:44 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-560/S-028

INFORMATION REQUEST LETTER

Merck & Co., Inc.
Attention: Michelle Flicker, M.D., Ph.D.
Director, Regulatory Affairs
P.O. Box 2000
Mail Drop: Ry 33-720
Rahway, NJ 07065

Dear Dr. Flicker:

Please refer to your supplemental new drug application submitted on January 18, 2001, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosamax (alendronate sodium) Tablets.

The supplemental application proposes physician sample package labeling for the 10 mg daily dose, 35 mg weekly dose, and the 70 mg weekly dose.

We are reviewing your submission and have the following labeling comments concerning the 10 mg sample package. We need your prompt written response to continue our evaluation of your supplemental application.

1. The panel headed [redacted]

2. The [redacted] subheading in the "How to Take" panel is [redacted]

3. The claim [redacted] as early as three months . . ."

Please submit revised labeling that addresses the above issues.

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

Sincerely,

{See appended electronic signature page}

Kati Johnson, R.Ph.
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Kati Johnson
5/15/01 10:39:17 AM

DEPARTMENT OF HEALTH & HUMAN SERVICE

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-560/S-028

PRIOR APPROVAL SUPPLEMENT

Merck & Co., Inc.
Attention: Michelle Flicker, M.D., Ph.D.
Director, Regulatory Affairs
P.O. Box 2000
Mail Drop: Ry 33-720
Rahway, NJ 07065

Dear Dr. Flicker:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Fosamax (alendronate sodium) Tablets

NDA Number: 20-560

Supplement Number: S-028

Date of Supplement: January 18, 2001

Date of Receipt: January 19, 2001

This supplemental application proposes physician sample package labeling for the 10 mg daily dose, 35mg weekly dose, and the 70 mg weekly dose.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 20, 2001, in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Randy Hedin, R.Ph.
Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Randy Hedin
4/6/01 10:17:10 AM