CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-560/S014

Trade Name: Fosamax Tablets

Generic Name: alendronate sodium

Sponsor: Merck Research Laboratories

Approval Date: March 19, 1999
**Reviews / Information Included in this NDA Review.**

<table>
<thead>
<tr>
<th>Review Type</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Letter</td>
<td>X</td>
</tr>
<tr>
<td>Approvable Letter</td>
<td></td>
</tr>
<tr>
<td>Labeling</td>
<td>X</td>
</tr>
<tr>
<td>Summary Review</td>
<td></td>
</tr>
<tr>
<td>Officer/Employee List</td>
<td></td>
</tr>
<tr>
<td>Office Director Memo</td>
<td></td>
</tr>
<tr>
<td>Cross Discipline Team Leader Review</td>
<td></td>
</tr>
<tr>
<td>Medical Review(s)</td>
<td></td>
</tr>
<tr>
<td>Chemistry Review(s)</td>
<td></td>
</tr>
<tr>
<td>Environmental Assessment</td>
<td></td>
</tr>
<tr>
<td>Pharmacology Review(s)</td>
<td></td>
</tr>
<tr>
<td>Statistical Review(s)</td>
<td></td>
</tr>
<tr>
<td>Microbiology Review(s)</td>
<td></td>
</tr>
<tr>
<td>Clinical Pharmacology/Biopharmaceutics Review(s)</td>
<td></td>
</tr>
<tr>
<td>Risk Assessment and Risk Mitigation Review(s)</td>
<td></td>
</tr>
<tr>
<td>Proprietary Name Review(s)</td>
<td></td>
</tr>
<tr>
<td>Administrative/Correspondence Document(s)</td>
<td>X</td>
</tr>
</tbody>
</table>
APPLICATION NUMBER:
20-560/S014

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

Dear Dr. Kloss:

Please refer to your supplemental new drug applications dated September 17, 1997, received September 18, 1997 (S-011), and July 23, 1998, received July 24, 1998 (S-014), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fosamax (alendronate sodium) Tablets.

We also acknowledge the receipt of your October 8, 1998, submission containing final printed labeling in response to our May 12, 1998 letter approving your supplemental new drug application (S-011).

We have reviewed the labeling (7957010) for supplement-011 for the prescribing information (PI) that you submitted in accordance with our May 12, 1998, letter, and we find it acceptable.

We note that supplement 014 was submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c). Your submission stated November 1, 1998 as the implementation date for the changes.

This supplemental new drug application (Supplement - 014) provides for revisions to the WARNINGS and ADVERSE REACTIONS sections of the package insert and to the patient package insert (PPI) as follows:

1. Addition of “and rarely followed by esophageal stricture” to types of esophageal adverse experiences in the WARNINGS section.

2. Addition of “rarely, esophageal stricture” and “Skin: rash (occasionally with photosensitivity)” to the ADVERSE REACTIONS, Post-Marketing experience section.

3. In the “What are the possible side effects of FOSAMAX?” section of the Patient Package Insert, addition of a trademark footnote (page 1), an editorial revision to the first paragraph (replacing “and” with “or”), and addition of “(occasionally made worse by sunlight)” after rash.
We have completed the review of this supplemental application (S-014) 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 final printed labeling (package insert [7957009] and patient package insert [7969405] submitted July 23, 1998). Accordingly, the supplemental application is approved effective on the date of this letter.

We note that the final printed labeling (FPL) submitted for supplement 014 dated July 23, 1998, has been superseded by the final printed labeling (FPL) submitted October 8, 1998, for Supplement 011 and includes the PI (7957010) labeling changes in supplement 014.

If a letter communicating important information about this drug product (i.e., a “Dear Health Care Practitioner” 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, contact Randy Hedin, R.Ph., Regulatory Management Officer, at (301) 827-6430.

Sincerely,

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

cc:
Archival NDA 20-560
HFD-510/Div. Files
HFD-510/R.Hedin
HF-2/MedWatch (with labeling)(with CSO labeling review)
HFD-002/ORM (with labeling)
HFD-102/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: RH/December 3, 1998
Initialed by:
final:
filename: N20560AP.L11

APPROVAL (AP) S-014
ACK & RETAIN (ar) S-011

The Patient Package Insert (7969405) in S-014 and the Package Insert (7957010) in S-011 (10-8-98) are the most current approved labels.
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
20-261/S014

LABELING
**FOSAMAX®**
(Alendronate Sodium Tablets)

**DESCRIPTION**
FOSAMAX® (alendronate sodium) is an aminobisphosphonate that acts as a specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

Alendronate sodium is chemically described as (1-amino-1-hydroxyethylidene) bisphosphonic acid sodium salt.

The empirical formula of alendronate sodium is C$_8$H$_{18}$Na$_2$O$_{12}$P$_4$ and its formula weight is 355.12. The structural formula is shown below:

```
  O
 CH$_2$O
 /  \
 Cl  HO
 /   |
Cl  OH
 /   |
O-P-C-P-O-
HO-CH$_2$-CH$_2$-N
```

**Metabolism**
There is no evidence that alendronate is metabolized in animals or humans.

**Excretion**
Following a single IV dose of [14C]alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a single 10 mg IV dose, the renal clearance of alendronate was 71 mL/min, and systemic clearance fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with FOSAMAX (30 mg daily), the amount of alendronate released daily from the skeleton is approximately 2% of that absorbed from the gastrointestinal tract.

**Special Populations**
Pediatric: Alendronate pharmacokinetics have not been investigated in pediatric patients <18 years of age.

Gender: Bioavailability and the fraction of an IV dose excreted in urine were similar in men and women.

Geriatric: Bioavailability and disposition (oral and IV) were similar in elderly (≥65 years of age) and young patients who were normally active and had not received concomitant drugs. No dosing adjustment is necessary in geriatric patients.

Race: Pharmacokinetic differences due to race have not been studied.

**Administration**
- **Oral**: Alendronate is administered as a single daily dose at 7:00 am with 8 ounces (240 mL) of water. Do not take with food or other products. Food decreases absorption of alendronate by 60%.
- **Parenteral**: Parenteral administration is contraindicated. Alendronate is not recommended for parenteral administration.

**Uses**
FOSAMAX is indicated for the treatment of osteoporosis in postmenopausal women and men, and the management of Paget's disease of bone.

**Precautions**
- Patients should be advised to avoid taking alendronate with antacids or other products containing calcium, iron, magnesium, or aluminum.

**Interactions**
- See drug interactions in the full Prescribing Information.
Localization to sites of bone turnover, i.e., under osteoclasts. The osteoclasts adhere normally to the bone surface but lack the ruffled border that is indicative of active resorption. Alendronate does not interfere with osteoclast resorption or attachment, but it does inhibit osteoclast activity. Studies in mice on the localization of radiolabeled (3H)alendronate in bone showed a 10-fold higher uptake on osteoblast surfaces than on osteoclast surfaces. Bones examined 6 and 48 days after (3H)alendronate administration in rats and mice, respectively, showed that normal bone was formed on top of the alendronate, which was incorporated inside the matrix. While incorporated in bone matrix, alendronate is not pharmacologically active. Thus, alendronate must be continuously administered to suppress osteoclasts on newly formed resorption surfaces. Histomorphometry in baboons and rats showed that alendronate treatment reduces bone turnover (i.e., the number of sites at which bone is remodeled). In addition, bone formation exceeds bone resorption at these remodeling sites, leading to progressive gains in bone mass.

**Pharmacokinetics**

**Absorption**

Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.7% for doses ranging from 5 to 40 mg when administered after an overnight fast and 2 hours before a standard breakfast. Oral bioavailability of the 10 mg tablet in men (0.69%) was similar to that in women (0.73%) when administered after an overnight fast and 2 hours before breakfast.

A study examined the effect of timing of a meal on the absorption of alendronate in postmenopausal women. Bioavailability was decreased by approximately 40% when 10 mg alendronate was administered with or up to 2 hours after a standard breakfast when compared to dosing after an overnight fast. Studies treatment of osteoporosis, alendronate was administered with meals or up to 2 hours after a standard breakfast.

Bioavailability is negligible whether alendronate was administered with or up to 2 hours after a standard breakfast. Continuous administration of alendronate with meals reduces bioavailability by approximately 40%.

**Distribution**

Pharmacokinetic studies in male rats show that alendronate is extensively distributed to soft tissues following IV administration, but it is highly concentrated in bone or associated in bone tissue. The mean cumulative volume of distribution in bone is less than 1% of body weight in rats.

**Interactions**

Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increases will occur in patients who take oral H2 antagonists is unknown. No other specific drug interaction studies were performed. Products containing calcium and other divalent cations are likely to interfere with absorption of alendronate.

**Summary of Pharmacokinetic Parameters in the Normal Population**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute bioavailability of 5 mg tablet, taken 2 hours before first meal of the day (females)</td>
<td>0.63% (females)</td>
<td>(0.44, 0.83)</td>
</tr>
<tr>
<td>Absolute bioavailability of 10 mg tablet, taken 2 hours before first meal of the day (females)</td>
<td>0.78% (females)</td>
<td>(0.61, 1.04)</td>
</tr>
<tr>
<td>Absolute bioavailability of 40 mg tablet, taken 2 hours before first meal of the day (females)</td>
<td>0.60% (females)</td>
<td>(0.46, 0.75)</td>
</tr>
</tbody>
</table>

**Pharmacodynamics**

Osteoporosis in postmenopausal women.

Osteoporosis is characterized by low bone mass that leads to an increased risk of fracture. The incidence of osteoporosis can be determined by the measurement of osteocalcin, which is a marker for bone turnover. Osteocalcin levels are increased in postmenopausal women, indicating a higher risk of fracture. The risk of fracture in postmenopausal women is approximately 40% lower than that in age-matched men.

**References**

Highly significant increases in BMD, relative to baseline and placebo, were seen at each measurement site in each study in patients who received 

FOSAMAX® (Aminodronate Sodium Tablets)

The cumulative incidence of hip and wrist fractures was significantly less in patients treated with FOSAMAX® than in those receiving placebo. Overall, these results demonstrate the efficacy of FOSAMAX® to reduce the incidence of fractures at the spine, hip, and wrist, which are the three most common sites of osteoporotic fracture.

Bone histology

Bone histology in 278 postmenopausal patients with osteoporosis treated with FOSAMAX® showed a decrease in bone turnover, as evidenced by a decrease in osteoclast activity. The bone density observed in these patients was similar to that observed in osteoporotic patients treated with placebo.

Prevention of osteoporosis is achieved with FOSAMAX®

Prevention of bone loss was demonstrated in two double-blind, placebo-controlled studies of postmenopausal patients 50 years of age or older. In these studies, patients received FOSAMAX® daily for three years, followed by placebo for an additional three years. A significant decrease in bone density was observed in patients treated with FOSAMAX® compared to those treated with placebo. Overall, these results demonstrate the efficacy of FOSAMAX® in reducing the incidence of fractures and improving bone density in postmenopausal women.
The Vertebral Fracture Study of the Fracture Intervention Trial (FITT) included results from 2027 patients who had at least one baseline vertebral (compression) fracture. The results of this study demonstrated the reduction in fracture incidence due to FOSAMAX. In this three-year, randomized, double-blind, placebo-controlled study, 1027 patients received FOSAMAX and 1000 patients received placebo. Treatment with FOSAMAX resulted in statistically significant and clinically meaningful reductions in the proportion of patients experiencing fractures as shown in the table below:

<table>
<thead>
<tr>
<th>Effect of FOSAMAX on Fracture Incidence after Three Years in the Vertebral Fracture Study of FITT</th>
<th>N (Patients)</th>
<th>FOSAMAX</th>
<th>Placebo</th>
<th>Reduction (%) in Fracture Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with 1 or more vertebral fractures</td>
<td>870</td>
<td>60.0</td>
<td>65.9</td>
<td>9.9</td>
</tr>
<tr>
<td>New vertebral fractures</td>
<td>258</td>
<td>14.4</td>
<td>23.9</td>
<td>40.3</td>
</tr>
<tr>
<td>1 or more vertebral fractures</td>
<td>210</td>
<td>7.8</td>
<td>11.2</td>
<td>30.2</td>
</tr>
<tr>
<td>New non-vertebral fracture</td>
<td>44</td>
<td>2.2</td>
<td>5.5</td>
<td>60.9</td>
</tr>
</tbody>
</table>

Furthermore, treatment with FOSAMAX significantly reduced the incidence of total hospitalizations (12.4% vs. 20.1%).

The reductions in the incidence of vertebral fractures (FOSAMAX vs. placebo) in the Vertebral Fracture Study of FITT were consistent with that in the Controlled Osteoporosis Multinational Study (COMOS) Multinational Study (shown above) and in a large proportion of the women did not have a vertebral fracture at baseline. The incidence of new fractures was lower with FOSAMAX than with placebo in both study populations by 23.7% (95% CI: 13.0, 34.5, p < 0.001). Similarly, FOSAMAX reduced the proportion of women experiencing multiple (two or more) new vertebral fractures by 31.7% (95% CI: 23.1, 40.4, p < 0.001).

Bone histology was normal in the 28 patients biopsied at the end of three years who received FOSAMAX at doses of up to 10 mg/day.

Falci’s disease of bone:

The efficacy of FOSAMAX 40 mg once daily for six months was demonstrated in two double-blind, placebo-controlled studies of male and female patients with moderate to severe Falci’s disease (alkaline phosphatase at least twice the upper limit of normal). A placebo-controlled, randomized study and a U.S. nonrandomized study with edrophosphate disodium 400 mg/day.

The following figures show the mean percent change from baseline to serum alkaline phosphatase for up to six months of randomized treatment:

At six months, suppression in alkaline phosphatase in patients treated with FOSAMAX was significantly greater than suppression in alkaline phosphatase in placebo-treated patients.
FOSAMAX®
(Afendronate Sodium Tablets)

Response (defined as either normalization of serum alkaline phosphatase or decrease from baseline 33%) occurred in approximately 50% of patients treated with FOSAMAX in the combined studies vs. 30% in the etidronate group and 0% in the placebo group. FOSAMAX was similarly effective irrespective of age, gender, race, prior use of other bisphosphonates, or baseline alkaline phosphatase within the range studied (at least twice the upper limit of normal).

Bone histology was evaluated in 33 patients with Paget's disease treated with FOSAMAX 40 mg/day for 6 months. As in patients treated for osteoporosis (see CLINICAL STUDIES. Treatment of osteoporosis in postmenopausal women. Bone histology), FOSAMAX did not improve mineralization, and the expected decrease in the rate of bone turnover was observed. Normal lamellar bone was produced during treatment with FOSAMAX, even where preexisting bone was woven and disorganized. Overall, bone histology data support the conclusion that bone formed during treatment with FOSAMAX is of normal quality.

ANIMAL PHARMACOLOGY

The relative inhibitory activities on bone resorption and mineralization of afendronate and etidronate were compared in the Sorenson assay, which is based on histological examination of the epiphyses of growing rats. In this assay, the lowest dose of etidronate that interfered with bone mineralization (leading to osteomalacia) was 600-fold the antiresorptive dose, the corresponding ratio for afendronate was only 3.2. Administered in therapeutic doses, afendronate is highly unlikely to reduce osteomalacia.

INDICATIONS AND USAGE

FOSAMAX® is indicated for the treatment and prevention of osteoporosis in postmenopausal women and for the treatment of Paget's disease of bone.

For the treatment of osteoporosis, FOSAMAX® decreases bone turnover and prevents fractures, including those of the hip, wrist, and spine. Vertebroplasty fracture healing is reported to be enhanced when an anti-resorptive drug is administered concurrently. The incidence of new vertebral fractures in patients taking FOSAMAX® has been approximately 3%.

For the treatment of Paget's disease of bone, in addition to the skeletal changes associated with Paget's disease, bone turnover is increased, with increased bone necrosis and a high rate of bone remodeling. FOSAMAX significantly reduces bone turnover and the remodeling process, leading to a reduction in bone pain and a stabilization of bone mass.

FOSAMAX® is not recommended for patients with renal insufficiency (creatinine clearance <35 mL/min). (See DOSAGE AND ADMINISTRATION.)

Causes of osteoporosis other than estrogen deficiency and aging should be considered.

Hypocalcemia must be corrected before initiating therapy with FOSAMAX (see CONTRAINDICATIONS). Other disturbances of mineral metabolism (such as vitamin D deficiency), should also be effectively treated. Pre-analytically, due to the effects of FOSAMAX on increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated. Adequate calcium and vitamin D intake should be ensured to provide for these enhanced needs.

Information for Patients

Patients should be instructed that the expected benefits of FOSAMAX may only be obtained when each tablet is swallowed with plain water just before or shortly after the last bite of food, and then not to eat or drink for at least 30 minutes after the last bite of food. Patients should be informed to avoid taking any other medication, including aspirin, that may interact with FOSAMAX. Patients should be informed to take FOSAMAX at bedtime, 2 hours after any oral or parenteral medication, and to avoid taking it with any other medication that may interact with FOSAMAX.

Patients should be instructed to take supplemental calcium and vitamin D daily as recommended by their physician. Patients should be instructed to take FOSAMAX at bedtime in order to ensure optimal calcium absorption. Patients should be informed that a low-fat diet high in calcium and vitamin D is recommended for all patients, regardless of whether they are taking FOSAMAX. Patients should be instructed to avoid concurrent use of any other medications that may interact with FOSAMAX. Patients should be informed that FOSAMAX is not recommended for patients with renal insufficiency (creatinine clearance <35 mL/min). (See DOSAGE AND ADMINISTRATION.)

Information for Physicians

FOSAMAX is not recommended for patients with renal insufficiency (creatinine clearance <35 mL/min). (See DOSAGE AND ADMINISTRATION.)

Causes of osteoporosis other than estrogen deficiency and aging should be considered.

Hypocalcemia must be corrected before initiating therapy with FOSAMAX (see CONTRAINDICATIONS). Other disturbances of mineral metabolism (such as vitamin D deficiency), should also be effectively treated. Pre-analytically, due to the effects of FOSAMAX on increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated. Adequate calcium and vitamin D intake should be ensured to provide for these enhanced needs.

Information for Patients

Patients should be instructed that the expected benefits of FOSAMAX may only be obtained when each tablet is swallowed with plain water just before or shortly after the last bite of food, and then not to eat or drink for at least 30 minutes after the last bite of food. Patients should be informed to avoid taking any other medication, including aspirin, that may interact with FOSAMAX. Patients should be informed to take FOSAMAX at bedtime, 2 hours after any oral or parenteral medication, and to avoid taking it with any other medication that may interact with FOSAMAX. Patients should be instructed to take supplemental calcium and vitamin D daily as recommended by their physician. Patients should be instructed to take FOSAMAX at bedtime in order to ensure optimal calcium absorption. Patients should be informed that a low-fat diet high in calcium and vitamin D is recommended for all patients, regardless of whether they are taking FOSAMAX. Patients should be instructed to avoid concurrent use of any other medications that may interact with FOSAMAX. Patients should be informed that FOSAMAX is not recommended for patients with renal insufficiency (creatinine clearance <35 mL/min). (See DOSAGE AND ADMINISTRATION.)

Information for Physicians
below the mean for healthy young adult women); thin,
body build; Caucasian or Asian race; and family history
of osteoporosis. The presence of such risk factors may
be important when considering the use of FOSAMAX
for prevention of osteoporosis.

FOSAMAX is indicated for the treatment of Paget's disease
of bone.

- Treatment is indicated in patients with Paget's disease
  of bone having alkaline phosphatase at least two times
  the upper limit of normal, or those who are symptomatic,
  or those at risk for future complications from their
disease.

CONTRAINDICATIONS
- Abnormalities of the esophagus which delay esophageal
  emptying such as stricture or achalasia
- Hypersensitivity to any component of this product
- Hypocalcemia (see PRECAUTIONS, General)

WARNINGS

FOSAMAX, like other bisphosphonates, may cause local
irritation of the upper gastrointestinal tract. Esophagitis,
ulcers, and esophageal injuries, occasionally with
bleeding and rarely, perforation by esophageal stricture
have been reported in patients receiving treatment with
FOSAMAX. In some cases, esophagitis has been
reported even when the medication was taken with
food. Upper gastrointestinal symptoms should be
monitored closely in patients taking FOSAMAX and
patients should be advised to seek medical attention
immediately if any symptoms occur, before taking any
more FOSAMAX and stopping the dose. Because of the
development of symptomatic esophagitis in patients
taking FOSAMAX, the dose should be taken with
food. The upper gastrointestinal symptoms in patients
who continue to take FOSAMAX should be monitored
for at least 72 hours after taking the first dose of the
medication. Symptomatic esophagitis should be
monitored closely in patients taking FOSAMAX and
patients should be advised to seek medical attention
immediately if any symptoms occur, before taking any
more FOSAMAX and stopping the dose. Because of the
development of symptomatic esophagitis in patients
taking FOSAMAX, the dose should be taken with
food. The upper gastrointestinal symptoms in patients
who continue to take FOSAMAX should be monitored
for at least 72 hours after taking the first dose of the
medication. Symptomatic esophagitis should be
monitored closely in patients taking FOSAMAX and
patients should be advised to seek medical attention
immediately if any symptoms occur, before taking any
more FOSAMAX and stopping the dose. Because of the
development of symptomatic esophagitis in patients
taking FOSAMAX, the dose should be taken with
food. The upper gastrointestinal symptoms in patients
who continue to take FOSAMAX should be monitored
for at least 72 hours after taking the first dose of the
medication. Symptomatic esophagitis should be
monitored closely in patients taking FOSAMAX and
patients should be advised to seek medical attention
immediately if any symptoms occur, before taking any
more FOSAMAX and stopping the dose. Because of the
development of symptomatic esophagitis in patients
taking FOSAMAX, the dose should be taken with
food. The upper gastrointestinal symptoms in patients
who continue to take FOSAMAX should be monitored
for at least 72 hours after taking the first dose of the
medication. Symptomatic esophagitis should be
monitored closely in patients taking FOSAMAX and
patients should be advised to seek medical attention
immediately if any symptoms occur, before taking any
more FOSAMAX and stopping the dose. Because of the
development of symptomatic esophagitis in patients
taking FOSAMAX, the dose should be taken with
food. The upper gastrointestinal symptoms in patients
who continue to take FOSAMAX should be monitored
for at least 72 hours after taking the first dose of the
medication. Symptomatic esophagitis should be
monitored closely in patients taking FOSAMAX and
patients should be advised to seek medical attention
immediately if any symptoms occur, before taking any
more FOSAMAX and stopping the dose. Because of the
development of symptomatic esophagitis in patients
taking FOSAMAX, the dose should be taken with
food. The upper gastrointestinal symptoms in patients
who continue to take FOSAMAX should be monitored
for at least 72 hours after taking the first dose of the
medication. Symptomatic esophagitis should be
monitored closely in patients taking FOSAMAX and
patients should be advised to seek medical attention
immediately if any symptoms occur, before taking any
more FOSAMAX and stopping the dose. Because of the
development of symptomatic esophagitis in patients
Taking FOSAMAX, the dose should be taken with
food. The upper gastrointestinal symptoms in patients
who continue to take FOSAMAX should be monitored
for at least 72 hours after taking the first dose of the
medication. Symptomatic esophagitis should be
monitored closely in patients taking FOSAMAX and
patients should be advised to seek medical attention
immediately if any symptoms occur, before taking any
more FOSAMAX and stopping the dose. Because of the
development of symptomatic esophagitis in patients

The safety and effectiveness of the concomitant use of hor-
mone replacement therapy and FOSAMAX in postmen-
opausal women has not been established.

Calcium Supplements/Antacids
- It is likely that calcium supplements, antacids, and some
oral medications will interfere with absorption of FOSAMAX.
Therefore, patients must wait at least one-half hour after tak-
ing FOSAMAX before taking any other drugs.

Aspirin
- In clinical studies, the incidence of upper gastrointestinal
adverse events was increased in patients receiving concom-
unt therapy with doses of FOSAMAX greater than 10 mg/day
and aspirin-containing compounds.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
- FOSAMAX may be administered to patients taking NSAIDs.
- A 3-year, controlled clinical study (N=279) during which a
majority of patients received concomitant NSAIDs, the inci-
dence of upper gastrointestinal adverse events was similar in
patients taking FOSAMAX or 10 mg compared to those tak-
ing placebo. However, since NSAID use is associated with
gastrointestinal irritation, caution should be used during con-
comitant use with FOSAMAX.

Coexistence, Mutagenesis, Impairment of Fertility
- Harderian gland (a retro-orbital gland) not present in
humans administered were increased in high-dose female mice
(30x) in an 18-month carcinogenicity study at doses of alka-
lunate of 1.3, 10, and 100 mg/kg/day (calcium, 0.1, 0.5, and 5 mg/
day (females). These doses are equivalent to 0.5 to 3 times
the human dose based on surface area.
- Pericardial effusions were increased in high-dose,
(100 mg/kg/day). The median effective dose of 5 to 17.5 mg/kg/day,
which is the human equivalent dose, was equivalent to 7 to 50
times the human dose.
- Germ cell abnormalities were increased in high-dose,
(100 mg/kg/day). The median effective dose of 5 to 17.5 mg/kg/day,
which is the human equivalent dose, was equivalent to 7 to 50
times the human dose.
- Maternal toxicity was not greater in the pregnant
cynomolgus monkeys at a dose of 0.5 mg/kg/day.
- The intramuscular injection of rabbit mammary adenocar-
cinoma ascites line xenografts in immunodeficient mice,
inhaled albuterol-saline, and 100 mg/kg/day, which is the human
equivalent dose, was equivalent to 7 to 50 times the human dose.
- No teratogenic effects were observed in mice with doses up to 50
mg/kg/day.

The above studies are not necessarily predictive of effects seen in humans.
(10 mg/kg) the 10 mg human dose based on surface area. No similar effects were seen when pregnant rabbits were treated at doses up to 30 mg/kg/day (5 times the 10 mg human dose based on surface area, mg/m²).

Both total and ionized calcium concentrations in pregnant rats at 15 mg/kg/day (13 times the 10 mg human dose based on surface area) resulted in delays and failure of delivery. Protracted parturition due to maternal hypocalcemia occurred in rats at doses as low as 1.5 mg/kg/day (0.5 times the recommended human dose) when rats were treated from before mating through gestation. Maternal toxicity (late pregnancy deaths) occurred in the female rats treated with 15 mg/kg/day for varying periods of time ranging from treatment only during pre-mating to treatment only during early, middle, or late gestation; these deaths were not caused by cessation of treatment. Calcium supplementation (either in the drinking water or by minipump) could not ameliorate the hypocalcemia or prevent maternal and neonatal deaths due to delays in delivery; calcium supplementation IV prevented maternal, but not fetal deaths.

There are no studies in pregnant women. FOSAMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers

It is not known whether alendronate is excreted in human milk. It is also not known whether it is excreted in human milk. Caution should be exercised when FOSAMAX is administered to nursing women.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The incidence of adverse experiences associated with FOSAMAX was assessed in clinical trials and generated data. A summary of experience in over 900 patients enrolled in the 2-year placebo-controlled trials of FOSAMAX 5 and 15 mg/day in patients with osteoporosis is shown in the table below.

Table: Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n=118)</th>
<th>FOSAMAX 5 mg/day (n=119)</th>
<th>FOSAMAX 15 mg/day (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>3.7%</td>
<td>1.7%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.5%</td>
<td>1.7%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Headache</td>
<td>2.5%</td>
<td>3.4%</td>
<td>5.0%</td>
</tr>
</tbody>
</table>

ADVERSE REACTIONS

The most common adverse reaction associated with FOSAMAX was abdominal pain. The incidence of adverse reactions was dose-dependent. The majority of adverse reactions occurred within the first 2 weeks of treatment and resolved upon discontinuation of the drug.
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Fosamax</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>0.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Headache</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Mucositis</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Urticaria</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*N with possible, probably, or definitely drug related as assessed by the investigator.

Nausea, rash, and urticaria have occurred.

One patient treated with FOSAMAX (10 mg/day) who had a history of peptic ulcer disease and gastrinoma and who was taking concomitant aspirin developed an anastomotic ulcer with mild hemorrhage which was considered drug related. Aspirin and FOSAMAX were discontinued and the patient recovered.

The adverse experience profile was similar for the 401 patients treated with either 6 or 30 mg doses of FOSAMAX in the United States and Multinational studies.

In the Vertebral Fracture Study of the Fracture Intervention Trial, discontinuation of therapy due to any clinical adverse experience occurred in 7.6% of 1,022 patients treated with FOSAMAX 5 mg/day for 7 years and 18 mg/day for the first year and 4.8% of 1,009 patients treated with placebo. Some
FOSAMAX®
(Alen doprate Sodium Tablets)

FOSAMAX should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal adverse experiences (see WARNINGS).

Patients should receive supplemental calcium and vitamin D, if dietary intake is inadequate (see PRECAUTIONS, General).

- No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). FOSAMAX is not recommended for patients with more severe renal insufficiency (creatinine clearance <35 mL/min) due to lack of experience.

Treatment of osteoporosis in postmenopausal women (see INDICATIONS AND USAGE):

- The recommended dosage is 10 mg once a day.

Prevention of osteoporosis in postmenopausal women (see INDICATIONS AND USAGE):

- The recommended dosage is 5 mg once a day.

Safety of treatment of patients with FOSAMAX for longer than four years has not been studied; extension studies are ongoing.

Paget's disease of bone

The recommended treatment regimen is 40 mg once a day for six months.

Retreatment of Paget's disease

In clinical studies in which patients were followed every six months, relapse during the 36 months following treatment occurred in 3% (11 out of 321) of patients who received the treatment with FOSAMAX. Severe recurrent Paget's disease occurred in 3% of patients who had received prior phosphatonin therapy to those who had not. Relapse may occur following a six-month period of treatment in patients who have been treated with long-term phospho phosphate therapy. Retreatment may be considered in patients who fail to normalize their serum alkaline phosphatase.

HOW SUPPLIED

A white or off-white, oval-shaped tablet FOSAMAX, 5 mg or 10 mg, coated with a film-coated tablet with an orange core. Each FOSAMAX 5 mg tablet contains 100 mg of aluminum hydroxide, 13.2 mg of aluminum oxide, 42.1 mg of calcium carbonate, 3.7 mg of magnesium carbonate, 51.6 mg of magnesium oxide, 49.5 mg of zirconium silicate and 10 mg of aluminum phosphate. Each tablet contains 3.6 mg of aluminum hydroxide, 13.2 mg of aluminum oxide, 50 mg of calcium carbonate, 3.7 mg of magnesium carbonate, 51.6 mg of magnesium oxide, 49.5 mg of zirconium silicate and 10 mg of aluminum phosphate. Each 10 mg tablet contains 3.6 mg of aluminum hydroxide, 13.2 mg of aluminum oxide, 100 mg of calcium carbonate, 3.7 mg of magnesium carbonate, 51.6 mg of magnesium oxide, 49.5 mg of zirconium silicate and 20 mg of aluminum phosphate.
incidences of decreases in serum calcium to <3.0 mg/dL (2.0 mM) and serum phosphate to <2.0 mg/dL (0.65 mM) were similar in both treatment groups.

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing use:

Body as a Whole: hypersensitivity reactions including urticaria and rarely angioedema;

Gastrointestinal: esophagitis, esophageal erosions, esophageal ulcer, rarely esophageal stricture, and oropharyngeal ulceration. Rarely, gastric or duodenal ulcers, some severe and with complications have been reported (see WARNINGS, PRECAUTIONS, General product information for Patients, and DOSAGE AND ADMINISTRATION).

Skin: rash (occasionally with photosensitivity).

OVERDOSAGE

Significant lethality after single oral doses was seen in female rats and mice at 552 mg/kg (1256 mg/m²) and 956 mg/kg (2085 mg/m²), respectively. In males, these values were slightly higher, 626 and 1280 mg/kg, respectively. There was no lethality in dogs at oral doses up to 2000 mg/kg (4000 mg/m²).

No specific information is available on the treatment of overdosage with FOSAMAX, Hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcers, may result from oral overdosage. Milk or antacids should be given to bind alendronate. Due to the risk of esophageal irritation, vomiting should not be induced and the patient should remain fully upright.

Dialysis would not be beneficial.

DOSAGE AND ADMINISTRATION

FOSAMAX must be taken at least one half hour before the first food, beverage or medication of the day with plain water only (see PRECAUTIONS, Information for Patients). Other beverages (including mineral water, food, and some medications) are likely to reduce the absorption of FOSAMAX (see PRECAUTIONS, Drug Interactions). Waiting less than 30 minutes, or taking FOSAMAX with food, beverages, or other medications, will lessen the effect of FOSAMAX by decreasing the bioavailability of alendronate.

To facilitate delivery to the stomach, and thus reduce the potential for esophageal irritation, FOSAMAX should only be swallowed upon arising on the day with a full glass of water. 16.3 oz and patients should remain down for at least 30 min.

15-30°C (59-86°F).
Please read this information before you start taking FOSAMAX®. Also, read the leaflet each time you renew your prescription, just in case anything has changed. Remember, this leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss FOSAMAX when you start taking your medication and at regular checkups.

How should I take FOSAMAX?

These are the important things you must do to help make sure you will benefit from FOSAMAX:

1. After getting up for the day, swallow your FOSAMAX tablet with a full glass (6-8 oz) of plain water only.
   - Not mineral water
   - Not coffee or tea
   - Not juice

2. After swallowing your FOSAMAX tablet do not lie down - stay fully upright (sitting or standing) for at least 30 minutes and until after your first food of the day. Do not chew or suck on a tablet of FOSAMAX. This will help the FOSAMAX tablet reach your stomach quickly and help avoid irritation of your esophagus (the tube that connects your mouth with your stomach).

3. After swallowing your FOSAMAX tablet, wait at least 30 minutes before taking your first food, beverage, or other medication of the day, including antacids, calcium supplements and vitamins. FOSAMAX is effective only if taken when your stomach is empty.

4. Do not take FOSAMAX at bedtime or before getting up for the day.

You will find more information about osteoporosis at the end of this leaflet.

How does FOSAMAX work?

FOSAMAX works by:

- Reducing the activity of the cells that cause bone loss
- Decreasing the faster rate of bone loss that occurs after menopause
- Increasing the amount of bone in most patients

These effects are seen as soon as three months after therapy with FOSAMAX has begun. These effects continue as long as you keep taking FOSAMAX. The density of bone is maintained or increased and the bone is less likely to fracture. Thus, FOSAMAX prevents or reverses the progression of osteoporosis.

Who should not take FOSAMAX?

Patients with:

- Certain disorders of the esophagus (the tube that connects your mouth with your stomach)
- Inability to stand or sit upright for at least 30 minutes
- Low levels of calcium in their blood
- Severe kidney disease
- Allergy to FOSAMAX

Patients who are:

- Pregnant or Nursing
  FOSAMAX is for use by women after menopause. If you are pregnant or nursing, you should not be taking FOSAMAX. Talk to your doctor.

What other medical problems should I discuss with my doctor?
other medication of the day, including antacids, calcium supplements and vitamins. FOSAMAX is effective only if taken when your stomach is empty.

4. Do not take FOSAMAX at bedtime or before getting up for the day.

5. If you have difficulty or pain upon swallowing, chest pain, or new or worsening heartburn, stop taking FOSAMAX and call your doctor.

6. Take FOSAMAX once a day, every day.

7. It is important that you continue taking FOSAMAX for as long as your doctor prescribes it. FOSAMAX can treat your osteoporosis or help you from getting osteoporosis only if you continue to take it.

8. If you miss a dose do not take it later in the day. Continue your usual schedule of 1 tablet once a day the next morning.

What is FOSAMAX?

FOSAMAX is for the treatment or prevention of osteoporosis (thinning of bone) in women after menopause. It reduces the chance of having a hip, wrist or spinal fracture.

FOSAMAX is for use by women after menopause. If you are pregnant or nursing, you should not be taking FOSAMAX. Talk to your doctor.

What other medical problems should I discuss with my doctor?

Talk to your doctor about any:
- Problems with swallowing
- Stomach or digestive problems
- Other medical problems you have or have had in the past

What are the possible side effects of FOSAMAX?

Some patients may develop severe digestive reactions including irritation, inflammation or ulceration (occasionally with bleeding) of the esophagus (the tube that connects your mouth with your stomach). These reactions can cause chest pain, heartburn or difficulty or pain upon swallowing. This may occur especially if patients do not drink a full glass of water with FOSAMAX and/or if they lie down in less than 30 minutes or before their first food of the day. Esophageal reactions may worsen if patients continue to take FOSAMAX after developing symptoms suggesting irritation of the esophagus.

Like all prescription drugs, FOSAMAX may cause side effects. Side effects usually have been mild. They generally have not caused
FOSAMAX® (Alendronate Sodium Tablets)

patients to stop taking FOSAMAX. Some patients treated with FOSAMAX experienced abdominal (stomach) pain. This is the most commonly reported side effect. Less frequently reported side effects are:

Nausea, heartburn, irritation or pain of the esophagus (the tube that connects your mouth with your stomach), vomiting, difficulty swallowing, a full or bloated feeling in the stomach, constipation, diarrhea and gas.

Rarely stomach or other peptic ulcers (some severe) have occurred.

Bone, muscle or joint pain, headache, or an altered sense of taste were also experienced by some patients. Rarely, a rash (occasionally made worse by sunlight) has occurred. Allergic reactions such as hives or rarely swelling of the face, lips, tongue and/or throat which may cause difficulty in breathing or swallowing have also been reported. Mouth ulcers have occurred when the tablet was chewed or dissolved in the mouth.

Anytime you have a medical problem you think may be related to FOSAMAX, talk to your doctor.

What should I know about osteoporosis?
 Normally your bones are being rebuilt all the time. First, old bone is removed (resorbed). Then a similar amount of new bone is formed. This balanced process keeps your skeleton healthy and strong.

Osteoporosis is a thinning and weakening of the bones. It is common in women after menopause. Menopause happens when the ovaries stop producing the female hormone, estrogen, or are removed (which may occur.

FOSAMAX® (Alendronate Sodium Tablets) bone to break. Fractures most often occur at the hip, spine, or wrist. This can lead to pain, severe disability, or loss of mobility.

How can osteoporosis in postmenopausal women be treated or prevented?

- **Medication.**
  Your doctor has prescribed FOSAMAX. FOSAMAX acts specifically on your bones. FOSAMAX is not a hormone and does not have the benefits and risks of estrogen (hormone replacement therapy) elsewhere in your body. Either FOSAMAX or estrogen may be used to treat or prevent osteoporosis. You may want to talk to your doctor about these options.

- **Lifestyle changes.**
  In addition to FOSAMAX, your doctor may recommend one or more of the following lifestyle changes:

  - **Stop smoking.** Smoking appears to increase the risk of osteoporosis.
  
  - **Reduce the use of alcohol.** Too much alcohol appears to increase the risk of osteoporosis and injuries that may cause fractures.
  
  - **Exercise regularly.** Like muscles, bones need exercise to stay strong and healthy. Exercise must be safe to prevent injuries including fractures. You should consult your doctor before you begin any exercise program.
  
  - **Eat a balanced diet.** Adequate dietary calcium is important. Your doctor can advise you whether you need to change your diet or take any dietary supplements such as calcium or vitamin D.
osteoporosis is a disease causing the weakening of the bones. It is common in women after menopause. Menopause happens when the ovaries stop producing the female hormone, estrogen, or are removed (which may occur, for example, at the time of a hysterectomy). After menopause, bone is removed faster than it is formed, so bone loss occurs and bones become weaker. Therefore, maintaining bone mass is important to keep your bones healthy.

At the start osteoporosis usually has no symptoms, but it can result in fractures (broken bones). Fractures usually cause pain. Fractures of the bones of the spine may not be painful, but over time they cause height loss. Eventually the spine becomes curved and the body becomes bent over. Fractures may happen during normal, everyday activity, such as lifting, or from minor injury that would normally not cause

advise you whether you need to change your diet or take any dietary supplements such as calcium or vitamin D.

This medication was prescribed for your particular condition. Do not use it for another condition or give the drug to others. Keep FOSAMAX and all medicines out of the reach of children. If you suspect that more than the prescribed dose of this medicine has been taken, drink a full glass of milk and contact your local poison control center or emergency room immediately. Do not induce vomiting. Do not lie down.

This leaflet provides a summary of information about FOSAMAX. If you have any questions or concerns about either FOSAMAX or osteoporosis, talk to your doctor. In addition, talk to your pharmacist or other health care provider.

MERCK & CO., INC.
West Point, PA 19486, USA

Issued March 1998
APPLICATION NUMBER:
20-560/S014

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
NDA 20-560/S-014

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 Dr. Kloss:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Fosamax (Alendronate Sodium Tablets)
NDA Number: 20-560
Supplement Number: S-014
Date of Supplement: July 23, 1998
Date of Receipt: July 24, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on September 22, 1998, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

[Signature]

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
cc:
  Original NDA 20-560/S-014
  HFD-510/Div. Files
  HFD-510/CSO/R. Hedin

filename: C:\DATA\WPFILES\20560ACK

SUPPLEMENT ACKNOWLEDGEMENT
July 23, 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

SPECIAL SUPPLEMENT – CHANGES BEING EFFECTED

Dear Dr. Sobel:

Pursuant to Section 505(b) of the Food Drug and Cosmetic Act and in accordance with 21 CFR
314.70 (c), we submit a supplement to NDA 20-560.

As indicated on the attached Form FDA 356h, the supplemental application provides for changes
in the Labeling of the approved New Drug Application for FOSAMAX™.

This supplemental application provides for labeling revisions to the WARNINGS and
ADVERSE REACTIONS, Post-Marketing Experience sections of the Physicians Package
Circular, and also provides for revisions under “What are the possible side effects of
FOSAMAX?” in the Patient Package Insert. Specifically, the text “and rarely followed by
esophageal stricture” has been added to the WARNINGS section, and the text “rarely,
esophageal stricture” and “Skin: rash (occasionally with photosensitivity)” have been added to the
ADVERSE REACTIONS, Post-Marketing Experience section of the Package Circular. In the
Patient Package Insert, the text “(occasionally made worse by sunlight)” has been added after
“rash”, along with an editorial revision, to the first paragraph. In addition, a trademark footnote
has been added to the Patient Package Insert for consistency with the Package Circular.

Attached for submission are the following:

- Summary of Revisions
- Printed Package Circular #7957009 (15 mounted copies)
- Printed Patient Package Insert #7969405 (15 mounted copies)
- Annotated Package Circular (1 copy)
- Annotated Patient Package Insert (1 copy)
The changes will become effective on or about November 1, 1998 and will apply to all packages of FOSAMAX™ distributed from the company’s manufacturing facilities at West Point, PA.

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.

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,

[Signature]

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

Attachment
q\carna\tmk217\cbe7_98.doc

Federal Express #1

Desk copy: Mr. Randy Hedin, CSO, HFD-510, Room 14B-19
            Federal Express #1
1. **APPLICANT'S NAME AND ADDRESS**
   Merck Research Laboratories  
   P.O. Box 4, BLA-20  
   West Point, PA 19486-0004

2. **USER FEE BILLING NAME, ADDRESS, AND CONTACT**
   Merck Research Laboratories  
   P.O. Box 4, BLA-20  
   West Point, PA 19486-0004  
   ATTN: Bonnie J. Goldmann, M.D.  
   Vice President  
   Regulatory Affairs

3. **TELEPHONE NUMBER (Include Area Code)**
   (610) 397-2383

4. **PRODUCT NAME**
   Alendronate Sodium Tablets; FOSAMAX

5. **DOES THIS APPLICATION CONTAIN CLINICAL DATA?**
   - [ ] YES
   - [X] NO
   **IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.**

6. **USER FEE I.D. NUMBER**

7. **LICENSE NUMBER AND/or NUMBER**

8. **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 BEFORE 9/1/92
   - [ ] AN INSULIN PRODUCT SUBMITTED UNDER 506
   - [ ] THE APPLICATION IS SUBMITTED UNDER 505(b)(2) (See reverse before checking box.)
   - [ ] FOR BIOLOGICAL PRODUCTS ONLY
   - [ ] WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION
   - [ ] BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92
   - [ ] A CRUDE ALLERGENIC EXTRACT PRODUCT
   - [ ] AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9. a. **HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION?**
   - [ ] YES
   - [ ] NO
   **(See reverse if answered YES)**

   b. **HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?**
   - [ ] YES
   - [ ] NO
   **(See reverse if answered YES)**

---

**SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE**

**TITLE**
Vice President  
Regulatory Affairs

**DATE**
7/23/98
USER FEE DATA ENTRY/VALIDATION FORM

NDA # 20560

DOCUMENT AD/LETTER DATE SUR-014 July 23, 1998

APPLICANT NAME Midine Research Inc.

PRODUCT NAME Faxmax (Hemorrhage Solution)

FORM MUST BE COMPLETED ASAP

1. O ] User Fee Cover Sheet Validated?

NOTE TO DOCUMENT ROOM:
PLEASE MAKE THE FOLLOWING CHANGES TO THE COURTS DATA ELEMENTS

2. [ ] CLINICAL DATA?
[Check YES if contains study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials. *Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).]

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION?

3. O ] NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (OTHER THAN BUNDLING)? IF YES, list ALL NDA numbers, review divisions & indicate those for which application fees apply.

NDA #  
DIVISION  
N FEE NO FEE
N NO FEE  

4. [ ] BUNDLING POLICY APPLIED CORRECTLY? NO DATA ENTRY REQUIRED FOR ELEMENT
[Check YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Check NO if application should be split into more than one application or submitted as an original instead of a supplement. IF NO, list resulting NDA numbers, and review divisions.]

NDA #  
DIVISION  
N  

5. P ] PRIORITY OR STANDARD?

6. CSO SIGNATURE/DATE

SCSO CONCURRENCE SIGNATURE/DATE

COPY DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY EACH TO DIVISION FILE AND CDBR, ASSOCIATE DIRECTOR FOR POLICY HDF-5