1. General Information

1.1 NDA 20560/S-012

Medical Officer's Review

Submission dated:	11-26-97
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Advisory Committee:	No
Action Goal Date (PDUFA):	6-26-98
Review Completed:	3-12-98
Standard/Priority Review:	Priority
Pediatric Studies:	Required

1.2 **Drug name:** Alendronate
Trade name: Fosamax

Chemical name: 4-amino,1-hydroxybutylidene

1.3 **Sponsor:** Merck Research Laboratories
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1.4 **Pharmacologic Category:** Bisphosphonate

1.5 **Indication:** Osteoporosis
The proposed Indication is: "Treatment and prevention of glucocorticoid-induced osteoporosis in men and women."

No change in the Precautions, Pediatric Use Subsection is proposed. It would remain: "Safety and effectiveness in pediatric patients have not been established." This is not acceptable, if the drug is eventually approved. Studies should be done in children, and at least there should be a committment from the sponsor to do the studies. Preferably, they should be completed or under way.

1.6 **Dosage and Route of Administration**
The proposed dose for CIOP is "5 mg once a day except for postmenopausal women not receiving estrogen for whom the recommended dosage is 10 mg once a day." The

currently marketed Fosamax is available in tablets of 5, 10 or 40 mg. 5 mg once a day is recommended for prevention of osteoporosis; 10 mg once a day is recommended for treatment of osteoporosis; and 40 mg once a day for six months is recommended for Paget's Disease.

1.7 **NDA Classification SE1**

1.8 **Related Drugs:** Several **bisphosphonates** have been studied for Paget's Disease. **Etidronate, pamidronate, and alendronate** are approved for Paget's Disease.

1.9 **Related reviews:** Reviews on the above bisphosphonates are related. **Pharmacology, Chemistry, Statistics, Biopharm** reviews should all be considered in conjunction with this review.

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3 **Material Reviewed:** CANDA, summary of GIOP efficacy, References 1, 2 and 3.

Volume 2 Summary of Application

4 **Chemistry/Manufacturing:** No clinical implications of chemistry. Alendronate is soluble in water. The formulation also contains microcrystaline cellulose, anhydrous lactose, croscarmellose sodium and magnesium stearate.

5 **Animal Pharmacology/Toxicology:** See approved NDA and pharmacology review.

6. **Clinical Background**

6.1 **NDAs and INDs** Alendronate is approved for treatment of postmenopausal osteoporosis and Paget's Disease. The NDA contains data on which it was approved for both prevention and treatment of these conditions and for reducing the risk of fractures. The most serious problems have been GI, particularly esophageal erosions with bleeding and perforations.

6.2 **Human Pharmacology:** Pharmacokinetics, pharmacodynamics. See Biopharmaceutical Review. Absorption of this drug is very small, and is further reduced by concomitant intake of food or drink of any kind except water. This is the basis of the requirement that patient have no food or drink other than water until 30 minutes after the ingestion of alendronate on arising in the morning.

One **clinical biopharm study** (Ref 1) was done for this NDA supplement. In this study, drug and radioactivity were measured in blood and urine of 15 subjects after simultaneous dosing with both 20 mg oral alendronate and intravenous C^{14} labeled alendronate. After a 10-18 day wash-out period and 5 days of treatment with prednisone 20 mg tid, the oral and intravenous dosing and measurements were repeated. After prednisone, **availability of alendronate was increased** by 20-44%. Subject AN 4 had poor urine collection in this second period, yielding questionable results. When subject AN 4's results were included in the analysis, this difference was not statistically significant. When his

results were not included, the absorption was 0.73 before and 1.05% of dose after prednisone, a significant difference, p=0.007. The clinical significance of this increase in availability is not clear. However, the recommended dose for CIOP (5mg) is half that for postmenopausal osteoporosis (10mg), and the only group for whom 10 mg is recommended for prevention of CIOP is postmenopausal women, so the recommended doses are well studied in the post-menopausal population, and it is not likely that the small increase in absorbed drug will result in unexpected toxicity.

7. **Clinical Data Sources:** Two well-controlled studies were conducted for determining the efficacy of alendronate for glucocorticoid-induced osteoporosis. One of the studies was conducted in the United States (US Study 083, ref 3) and the other was conducted multinationally (MN Study 082, ref 2). The two references are structured to be very similar. The result is that tables with the same number generally contain corresponding information. I have, therefore given the references to the two corresponding tables this way: "Illnesses that **required glucocorticoid therapy** (Tables 12 in Ref 2 & 3)" means that information on the illnesses for which glucocorticoid therapy was required is in table 12 in reference 2 and table 12 in reference 3.

8. **Clinical Studies:** Both efficacy studies are reviewed together because of almost identical methods.

8.1 **Rationale and Objective:**

The rationale is: Alendronate increases BMD and vertebral trabecular thickness and decreases the risk of vertebral fractures in post-menopausal osteoporosis.

The objective is: To determine the effects of alendronate on lumbar spine BMD in patients who are taking glucopcorticoids in amounts at least equivalent to 7.5 mg prednisone.

8.2 **Study Design:** randomized, double-blind, placebo controlled.

8.3 Protocol.

8.3.1 Population: Patients (men and women 18 to 80 years old) were included if they had 1) an illness that was anticipated to require treatment with glucocorticoids equivalent to at least 7.5 mg prednisone for at least 1 year and 2) at least 3 evaluable lumbar vertebrae L1-L4. Exclusions included other metabolic bone disease, concomitant medications known to affect bone turnover, history of upper GI disease related to NSAIDS (unless the patient agreed not to take NSAIDs during the trial), pregnant or lactating women, history of major GI disease or kidney or heart disease or cancer. HRT was allowed if dose was stable, as was thyroid disease if the patient was clinically euthyroid.

There were modest differences in distribution to the treatment groups of illnesses that required glucocorticoid therapy (Tables 12 in Ref 2 & 3).

The following table (Table A) shows the number of patients who entered MN and US with glucocorticoid use for the listed illnesses. MN + US = T means that for each illness, the number in MN is followed by +, the number in US, =, and the total number studied with that illness.

Table A: Numbers randomized to PBO, 5, and 10 mg groups by glucocorticoid-requiring illness

	PBO	5mg	10mg
Illness	MN + US = T	MN + US = T	MN + US = T
Rheumatologic	51 + 51 =102	59 + 57 =116	55 + 51 =106
Pulmonary	5 + 18 = 23	2 + 16 = 18	6 + 17 = 23
Dermatologic	12 + 0 = 12	15 + 0 = 15	10 + 0 = 10
Gastrointest	4 + 4 = 8	3 + 3 = 6	4 + 6 = 10
Renal	1 + 1 = 2	4 + 0 = 4	5 + 2 = 7
Other	8 + 4 = 12	1 + 1 = 2	0 + 1 = 1
Totals	81 + 78 =159	84 + 77 =161	80 + 77 =157

Patients were stratified for their history of glucocorticoid use:

Stratum 1 is for those whose current glucocorticoid regimen began within 4 months of study start with a maximum exposure of 6 months within the 3 years prior to randomization.

Stratum 2 is for those whose current glucocorticoid regimen began 4-12 months prior with a maximum exposure of 18 months within the 3 years, or began within 4 months with maximum exposure of 6-18 months.

Stratum 3 is for those whose regimen began >12 months before the study or the maximum exposure was >18 months in 3 years.

8.3.2 **Procedures:** Procedures were the same for US and MN. All patients **received 800 to 1000 mg of elemental calcium and 250 to 500 units of vitamin D daily.** In the Multinational study, patients were randomized to placebo, 2.5, 5, or 10 mg alendronate daily. The United States study was the same except that randomization was only to placebo, 5 and 10 mg. All doses were to be taken on arising and at least ½ hr before any intake other than water. Patients were also instructed not to lie down during that time.

Bone specific alk phos and N-telopeptides were measured at screening and baseline and at each visit during the study (weeks 4, 12, 24, 36, and 48). **Densitometry** was done at each visit except 4 weeks. **Bone biopsies** were done at the 48 week visit; hand **radiographic absorptiometry** and **spine X-rays** at baseline and 48 weeks. **Height and weight** were measured at screening and at weeks 12, 24, 36 and 48.

8.3.3 **Efficacy Endpoints:**

For both of the studies, endpoints were:

Primary: lumbar spine BMD;

Secondary: femoral neck, trochanter, and total hip BMD, total body BMD, serum alkaline phosphatase, bone specific alkaline phosphatase, calcium and phosphate, and urine NTx.

Analyses were performed on measurements made at the last time that the patient was on 7.5 mg glucocorticoid (Protocol-defined or PD patients), and separately on patients with normal and with low baseline BMD.

The **2.5 mg group** was less efficacious than the 5 mg. The mean percent change from baseline for lumbar spine BMD was 0.7 for the 2.5 mg group compared to 2-3 for the 5 and 10 mg groups. As a result, the 2.5 mg group was not considered in the summary reporting of

combined results. The 10 mg dose was generally slightly and only marginally better than the 5 mg dose. GI adverse events were more common in the 10 mg group. The 2.5 mg group will not regularly be further described in this efficacy review, but only if there is an interesting finding.

8.4 **Results:**

8.4.1 **Patient Disposition (Tables 6, 7 & 8, Ref 2 & 3):** 228 women and 100 men were randomized in MN, 156 women and 76 men in US. In MN, 81 randomized to placebo, 83 to 2.5 mg, 84 to 5 mg, 80 to 10 mg; in US 78 randomized to placebo, 77 to 5 mg and 77 to 10 mg. 6 and 6% (MN and US) were <30 **years of age**, 30 and 27% were 30-50y, 41 and 45% were 50-70y, and 22 and 20% were >70y. 30 and 33% (MN and US) were **men**, 48 and 47% **postmenopausal** women, and 23 and 19% **premenopausal** women. About 90% of patients were caucasian, and most of the others hispanic. A few more postmenopausal women were in the 10 mg group (US but not MN), and the 5 mg group seems to have been slightly older than the other two groups(US): 54% of placebo and 58% of 10 mg patients were under 60 compared to 43% of 5 mg patients. The age differences between treatment groups were not statistically significant. Other characteristics that were not significantly different among the treatment groups were baseline lumbar spine BMD, height, weight, calcium intake, vitamin D, serum creatinine, smokers (slightly fewer smokers in placebo group, US only).

One half of US subjects and 62% of MN subjects had baseline **lumbar spine BMD** (Tables 9, Ref 2 & 3) **more than 1 SD below the sex matched mean peak BMD** of healthy normals. 18 and 13% of MN and US subjects had vertebral fractures at baseline.

Mean and median **glucocorticoid dose and duration of exposure at baseline** did not differ among the treatment groups. The mean daily glucocorticoid dose (Table 10, Refs 2 & 3) in the MN and US studies were initially 21-28 and 15-18 mg prednisone equivalents, but decreased over the study to 10-12 and 7-8 mg. 66-80% of patients were still using the Protocol dose (PD=7.5 mg) at week 48.

8.4.2 **Population analyzed.**

Intention to treat analysis of percent change from baseline at the last time patient was PD user is the primary analysis. Other analyses included:

the per cent change from baseline at each time without regard to glucocorticoid use (results were similar to PD users),
subgroup with low entry lumbar spine bone mineral density (results were comparable to entire population),
the 3 strata (results were similar to total population).
Patients were omitted from the ITT analyses or at a given time point if they did not have a baseline measurement and at least one post-treatment measurement prior to or at that time point.

8.4.3 **Per Protocol Exclusions from Analysis.** Patients' data were omitted from per protocol analyses if they were not using the (protocol dose) PD, changed the dose of estrogen or testosterone, had low 25OH vitamin D, abnormal alk phos or calcium, had low TSH, hyperthyroidism, hypothyroidism, hyperparathyroidism, malabsorption, GH deficiency, acromegaly, renal osteodystrophy, Paget's Disease of bone, hypercalcemia or osteomalacia. Also if they had clinical or laboratory adverse experience (i.e.discontinued), withdrew consent, were lost to follow-up, or violated the off-drug rule (off drug more than 25% of the time in study). **Exclusions** (Tables 21, Ref 2 & 3) **for MN study**, Placebo, 5 and 10 mg groups: 17, 29 and 31 for protocol violations; 5, 3 and 1 discontinued (1, 2, and 1 for AE; 2, 1 and 0 withdrew consent), and 3, 6 and 4 lacked data for the time. **For US**: 34, 31 and 26 had protocol violations, 7, 5, and 5 discontinued (0, 2 and 4 for AE; 6, 0 and 4 withdrew consent), and 7, 5, and 5 lacked data.

8.4.4 **Efficacy. Endpoint analyses. Primary: Lumbar spine** BMD (Tables 26 Refs 2 & 3), ITT, last time PD user, percent change from baseline, for placebo, 5 and 10 mg groups, MN and US studies are included in the table below. I have rounded off the values to tenth of a percent.
The following table (Table B) includes the essential data on mean change in BMD at the various sites measured: lumbar spine, femoral neck, trochanter, total hip, and total body. % chg is percent change from baseline in BMD, at 48 weeks. The # indicates changes that were statistically different from placebo, and the * indicates changes that were statistically different from baseline but not from placebo.

Table B: BMD changes from baseline (at 48 weeks) by dose, by site, and by study

Treatment		Placebo		5 mg		10 mg	
Measurement		N	% chg	N	% chg	N	% chg
Lumbar spine BMD	MN	75	-0.7	78	2.0#	76	3.0#
(Tables 26)	US	67	0.0	68	2.2#	69	2.8#
Femoral Neck BMD	MN	75	-0.7	78	2.2#	79	1.7#
(Tables 28)	US	67	-1.7*	68	0.0#	66	0.2#
Trochanter BMD	MN	75	-0.3	78	2.0#	79	3.3#
(Tables 30)	US	67	-1.3*	68	0.1	66	1.8#
Total Hip BMD	MN	52	0.0	56	1.5#	54	1.7#
(Tables 31)	US	54	-0.9	53	0.3	55	0.7#
Total body BMD	MN	64	-0.1	67	0.2	64	0.5*
(Tables 32)	US	45	0.1	43	0.6	49	1.0#

Most of the changes in BMD in spine and hip were statistically significantly different from placebo with either 5 or 10 mg of alendronate. Overall, mean BMD increases reported in the US study were considerably less than in the MN study. Results for total body were not significant except for the 1% increase in the US study. In the femoral neck US, benefit depends on a significant loss of bone in the placebo group. At the proposed dose, 5 mg daily, results at the 2 hip sites and total hip in MN are mean increases of 1.5 to 2.2%, but in US they are 0.0 to 0.3%. These hip results look a little better when combined with placebo losses: 5 mg group has mean increases in BMD 1.5 to 2.9% MN and 1.2 to 1.7% US.

Table C: Summary BMD changes from baseline (48 weeks) by study, by dose, and by site

Study	MN		US	
Dose	5 mg	10 mg	5 mg	10 mg
Lumb S BMD	2.7	3.7	2.2	2.8
Fem N BMD	2.9	2.4	1.7	1.9
Troch BMD	2.3	3.6	1.4	3.1
Total Hip	1.5	1.7	1.2	1.6
Total Body	0.3	0.6	0.5	0.9

The above table (Table C) is the same data reduced to differences from placebo.

An analysis (Tables 27, Refs 2 & 3) was also done of the **proportion of patients whose lumbar spine BMD increased** by at least set amounts from -6 to 6%.
Table D: percent of patients MN and US that exceeded 0, 2 and 5% increases in BMD.

Table D

BMD	PBO-MN	PBO-US	5MG-MN	5MG-US	10MG-MN	10MG-US
0% Change	40%	49%	74%	81%	80%	78%
2% Change	20%	25%	54%	51%	59%	58%
5% Change	5%	6%	14%	19%	28%	17%

Urine N-Telopeptides/creatinine and **bone specific alkaline phosphatase** decreases (Tables 33 and 34, Refs 2 & 3) were statistically significantly greater than placebo decreases at both doses and in both studies.
Serum **calciums** were not changed.
Mean baseline **serum phosphate** in the MN 5 mg group was slightly higher (3.5 mg/dL) than placebo or 2.5 or 10 mg groups and decreased during the trial to a level (3.2 mg/dL) that was similar to the other groups. No similar differences were observed in the US study.
The combined lumbar spine BMD results (Clinical Documentation, B efficacy 6, p 62, table 27) for MN and US **according to the glucocorticoid-requiring underlying illness** are shown in the following table (Table E). Table contains those randomized who had at least one post-randomization BMD determination. Also randomized were gastrointestinal (pbo 8, 5mg 6, and 10mg 10), renal (2, 4, and 7), and other (12, 2 and 1)

Table E: Lumbar spine BMD changes (at 48 weeks) by glucocorticoid-requiring illness and by dose

	Per cent change from baseline by dose group					
	N	PBO %	N	5mg %	N	10mg %
Asthma	16	-0.57	12	1.90	16	3.66
Dermatologic	10	-3.02	13	2.28	10	1.97
Polymyalgia	27	-2.05	39	1.44	34	2.92
Rheumatoid	40	0.73	47	2.59	47	3.17

When differences between drug and placebo results are used, the changes for 5mg are 2.47 (asthma), 5.30 (dermatologic), 3.49 (polymyalgia rheumatica) and 1.86 (rheumatoid); changes for 10mg are 4.23, 4.99, 4.97, and 2.44. On placebo, deratologic and polymyalgia patients lost more bone than asthma and rheumatoid patients. The more numerous rheumatoid patients seem to have less serious losses on placebo and slightly less gain on drug.

8.4.5 **Safety.** For total adverse events (Tables 38, Refs 2 & 3) thought by investigator to be drug related, there was a statistically significant dose response trend MN. The following table (Table F) displays percent of patients with an AE of the listed category.

Table F: Adverse Events by study and by dose

Adverse Event Summary		Placebo	5 mg	10 mg
Number for analysis	MN/US	81/78	84/77	80/77
Total Reports	MN	72	80	83
	US	87	81	84
"Drug-related"	MN	8.6	11	18
	US	10	5.2	9.1
Serious	MN	14	14	24
	US	30	17	14
Withdrew due to AE	MN	3.7	7.1	2.5
	US	6.4	2.6	5.2
Withdrew due to serious AE	MN	2.5	2.4	2.5
	US	5.1	2.6	2.6

In the US study, in each category in the above table, **placebo exceeded drug patients' rates for AEs.** The MN study had more events and more "drug-related" events and more serious events in the 10 mg group than the 5mg, more withdrawals for AEs from the 5 mg group.

Table G: Adverse Events of interest, combined doses

Adverse event	PBO + 2.5mg MN & US N = 242		5 + 10mg MN + US N = 318	
Gastrointestinal	72	30.0%	95	29.9%
Acidregurgitation	5	2.0%	9	2.8%
Esophagitis	2	0.8%	3	0.9%
Abdominal pain	16	6.6%	24	7.5%
Constipation	12	5.0%	14	4.4%
Diarrhea	11	4.5%	10	3.1%
Nausea	7	2.9%	11	3.5%
Musculoskeletal	99	40.9%	126	39.6%
Spine fractures	27	11.2%	11	3.5%
Non-vertebral Fxs	2	1.3%	12	3.8%
Various pains	10	4.1%	27	8.5%
Back pain	15	6.2%	20	6.3%
Headache	12	5.0%	26	8.2%
Edema, swelling	12	5.0%	16	5.0%

Tables 40, Refs 2, 3.

Gastrointestinal events are not more frequent or severe than expected from the postmenopausal population. Abdominal pain is the most frequently reported GI AE (16 and 24), when Pbo and 2.5mg, both MN and US, are combined, and 5 and 10 mg groups, MN and US, are combined as described below.

Musculoskeletal events: Spinal fractures listed as AEs (and listed separately for each vertebra) are added together for the above table. **Back pain** was reported in 10 and 11% of placebo and 10mg groups MN, 5 and 4% of placebo and 10 mg groups US. Risk of spinal fractures may be decreased, but back pain shows no improvement.

Adding together (the number of patients rather than per cent) the various **pains** listed under Musculoskeletal Disorders (back, hip, foot, knee, leg, neck, shoulder) there are 12, 6, 14, and 14 reports in PBO, 2.5, 5, and 10 mg groups. This pain data may reflect the excess of non-vertebral, non-rib fractures in the treated groups. Number of reports for **[MN and US], [PBO and 2.5 mg]**, and **[5 and 10 mg] are combined**, to prepare the above simple table (Table G). For each AE, four numbers are added to get the number for each cell. Example: MN PBO + MN 2.5mg + US PBO. PBO and 2.5 mg groups are combined because neither showed any substantial efficacy, and 5 and 10 mg groups are combined because they showed efficacy not greatly different from each other. Combining MN and US provides a total inadequately treated and a total treated group. In some cases, events that appeared to be increased in one study or at one dose, are seen not to be increased overall.

In the above table, "Non-vertebral fractures" are actually non-rib fractures also, because ribs, like vertebrae, are mainly trabecular bone and may respond more like vertebrae do (and differently from cortical bone" to glucocorticoids and bisphosphonates. There were 5, 1 and 1 rib fractures in the placebo and treatment groups, possibly reflecting a potential beneficial reduction in rib fractures from alendronate. The number of non-vertebral, non-rib fractures in MN and US combined is seen in Table H.

Table H: Non-vertebral, non-rib fractures by fracture site and dose

Fracture	Dose N	Pbo 159	5 mg 161	10 mg 157
Ankle, lower leg		0	2	1
Foot		0	0	2
Hip, femur		0	0	1
Pelvis, knee		0	1	1
Wrist/arm		2	2	2
Total		2	5	7

The numbers are small, but the fractures are trending in the wrong direction, and are cause for concern.

Not counting fractures or the illnesses and symptoms of illnesses (arthritis, chronic bronchitis, exertional dyspnea, skin disorders, ulcerative colitis) that are indications for long-term glucocorticosteroid therapy, there are 9 events that were **significantly more common in treated than placebo** patients in one or other of the studies (Tables 41, Refs 2,3): contusion, eczema, glaucoma, herpetic infection, laryngitis, melena, memory impairment, nervousness, flank pain. It seems unlikely that these are important findings.

Deaths occurring during the US study were 2 placebo due to myocarditis and myocardial infarction, and 2 drug-treated due to myocardial infarction and cytomegalovirus infection. There was one death in the MN study due to intestinal vascular insufficiency. None of these deaths appear to be drug related, but data are inadequate to know.

9 **Overview of Efficacy**: Results of both efficacy trials at 48 weeks are reviewed together above, and the review will not be repeated here. The efficacy evidenced in these trials is small, but, if BMD is an adequate surogate, alendronate might be useful: If started early in the glucocorticoid treatment, if patient has a great likelihood of developing osteoporosis (e.g. known to lose bone on glucocorticoid therapy), or if bones are modestly osteoporotic at the onset of alendronate therapy, so that the patient is likely to benefit from preventing further bone loss. Bone replacement was in the 1-3% range, and not likely to restore enough bone to prevent fractures if BMD is very low. There is some question about whether benefit from alendronate will **surpass benefit from calcium and vitamin D** if intakes are adequate, and sex hormone deficiencies are