the baseline characteristics of the patients enrolled in the 2-year extension study did not appear to differ from those of the total group of patients initially enrolled in the two randomized, placebo-controlled studies. The completion rates were essentially the same across all four treatment groups.

Thus the patients who were included in the efficacy and safety analyses appear to represent the original trial population adequately. However, it should be noted that the market for this drug is probably four orders of magnitude greater than the size of the study population. The degree to which the trial population represents the intended target population is not known.

It should also be noted that patients were given 500mg of elemental calcium daily, with no added vitamin D (although the mean plasma 1,25-dihydroxy vitamin D levels were found to be normal). This dose of calcium, when added to a normal diet, fails to supply the 1500mg of calcium required daily for normal mineral balance in postmenopausal women. It is entirely possible that the placebo-related efficacy of alendronate would have been somewhat different had the drug been tested against an adequate background of calcium.

The primary efficacy endpoint of this study was lumbar spine BMD, which indicates effects of alendronate on trabecular bone. Secondary endpoints were changes in trochanter, femoral neck, and total body BMD.

Spinal fractures vary greatly in clinical importance. Some can be detected only radiographically, often only by refined computer-assisted analysis of digitized images. Others lead to loss of height and spinal deformity. Many spinal fractures are painful. In contrast, fractures of the proximal femur are clinically and radiographically obvious and always cause serious morbidity (and occasionally, mortality). Other non-vertebral fractures (e.g., wrist, foot) are clinically significant, but not as serious. A low BMD at these skeletal sites is associated with increased fracture risk. Total body BMD is an indicator of overall bone mineral balance.

In addition to BMD, BMC (bone mineral content) was independently measured and analyzed, because vertebral compression fractures of the spine may diminish the denominator in the quotient BMC/area, and thus increase the measured BMD without actually increasing bone mass. In addition, cortical expansion of long bones may occur during normal aging, which would decrease BMD, independent of any changes that may occur in BMC. Thus, changes in BMD and BMC were compared for the forearm and total body sites. The agreement between the two measurements was excellent.

In the lumbar spine, the greatest increases in BMD were observed during the first few years of alendronate treatment. This study clearly showed that, during the additional two years of the extension, the initial gains in lumbar spine BMD were not only maintained in both the 5- and 10-mg groups, but increased modestly in both treatment arms. Compared to the 5-mg group, the mean cumulative increase in spine BMD was greater in the 10-mg group: 9.39 vs 6.36 % over baseline, at 60 months (both within-group changes from baseline were highly statistically significant; the difference between treatment groups was also highly significant). During the extension period (Months 36 to 60) both treatment groups significantly increased BMD, by 0.94 and 0.97% in the 10-mg and 5-mg groups respectively. The between-group difference was not statistically significant. Thus the primary efficacy endpoint was achieved, and a cumulative difference between the 5- and 10-mg dose treatment groups was observed as well.

Although no patients received placebo during this extension phase, the difference between the 10-mg group and a hypothetical continuing placebo would be expected to be somewhat greater, given the small loss of BMD at this site in the placebo group during the first three years. The sponsor estimates this final difference to be about 10% in the 10 mg group, using the –0.44% achieved in placebo during the first 3 years as a comparison baseline. This is reasonable. The sponsor also notes that this 10% is equal to about one SD of the mean baseline BMD of the patients enrolled in the study. Based on this, the sponsor estimates that this gain in 10% should translate into a 50% reduction in vertebral fracture incidence during this period. This conclusion is compatible with the 48% reduction in the incidence of patients with vertebral fractures that was observed during the first 3-year period.

The placebo/10-mg group (these patients started alendronate 10 mg after 3 years of placebo therapy) experienced a mean increase of 6.36% over the 2-year extension, which is similar to the 7.05% increase seen in the first 2 years of treatment with the 10-mg dose during the first 2 years. Thus the responses appear to be consistent, independent of the time at which treatment began.

It is noteworthy that only 2.8% of patients in the alendronate 10-mg group did not increase lumbar spine BMD during 5 years of treatment, and 88% of this treatment group had an increase greater than 3%.

Given these consistent and significant increases in lumbar spine BMD over the entire 5-year period, and given the reduction in fracture incidence noted during the first 3 years, the continued loss of stature in alendronate-treated patients is of concern and requires further explanation. Again, the analysis is hampered by the lack of a placebo group during the extension period.

The sponsor's interpretation is that without alendronate treatment the height loss would have been demonstrably greater over the 5 years. This interpretation is based on the fact that during the first 3 years of the study the placebo groups lost more height than the treated groups, and that this difference disappeared during the last 2 years, when all groups lost about 2mm. The implication is that if there had been a placebo group during the extension period, the differential rates of stature loss between treated and placebo would have been maintained.

This interpretation may be valid, but it leaves open the question why a group of patients who have responded so well (and nearly universally) in terms of spine BMD increase should continue to decline in stature at apparently the same rate throughout a five-year period. In the 10-mg group, the mean increase in BMD had reached over 9% by Year 3 and approached 10% by Year 5. This increase, as the sponsor points out, represents a correction of about 1SD around the baseline mean. This should translate into a decline in incident vertebral fractures of about 50%, according to the sponsor (indeed this was associated with a decline of about that magnitude by 36 weeks).

Despite the lack of a placebo group during the extension period, one can still compare the changes in stature in the 10-mg vs. 5-mg groups. Although both groups responded well to alendronate, in terms of spine BMD, the gains in the 10-mg group were substantially greater throughout the five years, with between-group differences observed as early as 6-12 months after beginning alendronate. Throughout the last 3 years of the 60-month period, the BMD difference between the two treatment groups was at least 3%. This represents about 50% of the gain (over baseline) seen in the 5-mg group and from 30-40% of the gain in the 10-mg group. These between-group differences were highly statistically significant. In addition, the percent of patients achieving a given BMD increase was always less in the 5-mg than in the 10-mg group. Despite these differences, the 10-mg and 5-mg groups lost height at essentially identical rates (if anything, there was a slight tendency toward more rapid height loss in the 10-mg group).

The ability of alendronate treatment to retard height loss becomes more apparent and clinically significant only when comparisons are made within the subgroup of patients that experienced new vertebral fractures within the treatment period. In the analysis at 36 weeks, there was a significant difference in height between alendronate and placebo groups among patients with a new vertebral fracture (about 6% of the population in the placebo arm), but only a small effect of treatment in patients with no new fracture (for all patients at 36 weeks, –3.0mm in treated group vs –4.6mm in placebo, a difference of 1.6mm over 3 years; for those with new fracture, –5.9 mm in treated group vs – 23.3 mm in the placebo, a difference of 17mm

over 3 years). This may mean that the fractures were worse in the placebo patients, or that there were more fractures per patient in that group, or both. In any event, alendronate was associated with a clinically significant effect only in the group of patients that experienced an incident vertebral fracture. This comprised only 5-6% of the population (see Table of vertebral fractures in the 4 treatment arms, above).

In sum, there was a demonstrable reduction in height loss, compared to placebo, of about 1.6 mm after 3 years, in the pooled alendronate vs placebo groups. Among patients with incident fractures, the difference between placebo and alendronate treatment was substantially greater. Loss of stature appeared to continue inexorably in all 4 treatment groups during the extension period, despite ongoing increases in spinal BMD. The 10-mg group appears to lose height at least as rapidly as the 5-mg group, despite substantial differences in BMD responses between these study arms. Since loss of height is probably the most important clinical outcome of spinal osteoporosis, these findings are somewhat disturbing (in terms of assessing the clinical effects of this particular drug and evaluating the overall validity of BMD as a surrogate marker) and should be explained further. It is entirely likely that any clinically meaningful effects on stature are experienced by a small subgroup of the treated population. Additional analysis, based on 5-year (or longer) fracture data, is certainly warranted. Such analysis should attempt to correlate BMD changes with decreases in height, as well as with incident fracture rates.

The femoral neck and trochanter are the most clinically important fracture sites. In this study, the femoral neck BMD increased by 4.7% over the 5 years in the 10mg group and by 2.5% in the 5mg group. Within-group and between-group comparisons were significant. There were no significant changes from Months 36 to 60 in either dose group. Thus the initial gain in BMD was maintained for the 2 additional years. In the 10 mg group, 75% of patients had BMD increases >1% over the 5 years; however, 17% of patients reduced BMD at this site over the 5 years. In the 5mg group only 61% increased BMD at this site by 1% or more over the five years, and about 32% lost bone mineral.

At the trochanter, the 10mg group increased BMD by 9.09% over the five years; the gain in the 5mg group was 5.01%. Between-group and within-group differences were statistically significant. From Months 36-60, the 10 mg group gained 0.88%, while there was no significant change in the 5 mg group (again, comparisons were significant). Over the 5 years, 93.4 and 72.3% of the 10 and 5mg groups, respectively, gained 1% BMD or more at this site, while 5% and 25%, respectively, reduced BMD.

Total body BMD increased over the 5 years, by 2.2 and 1%, respectively in the 10- and 5-mg treatment groups. The gain in total body BMD was attained by 24-36 months, with no further changes between Months 36 and 60.

One-third forearm (radius+ulna) contains over 95% cortical bone. At this site, there was a significant (approximately 2%) loss in the placebo group at 36 months. In this group, the pattern of loss was apparently reversed with alendronate treatment, but the BMD appeared to reach a plateau at around –1.8% from 48-60 months. In contrast, the 10mg group gained about 0.5% by 36 months and maintained this for the 2-year extension period. The 5-mg group showed no change from baseline over the 60 months.

The bone resorption markers deoxypyridinoline and NTx (urinary excretion was expressed as ratios to urine creatinine) decreased over approximately 6 months, reaching a stable level that was maintained over the remainder of the 5 years of treatment with alendronate 10 mg. The reductions from baseline were approximately 50% for deoxypyridinoline and 76.9% for NTx. The final values were within the normal range for premenopausal women. When the placebo group was switched to alendronate 10 mg, the mean deoxypyridinoline and NTx decreased over approximately 6 months to levels that were indistinguishable from those observed in patients treated continuously with 10 mg for 5 years. One implication of these data is that the effects of alendronate on bone resorption are a function of the current, not the cumulative, dose of the drug.

As indices of bone formation, both total serum alkaline phosphatase and bone-specific alkaline phosphatase (BSAP) were measured. Both total and BSAP decreased substantially and reached a new stable plateau over about 9 months of treatment with alendronate. The geometric mean decreases after 5 years of treatment with alendronate 10 mg were 25.6 and 57.3%, respectively. Actually, these results are in agreement, since about 50% of the total alkaline phosphatase in serum is derived from bone. The mean absolute level of BSAP in the 10-mg group was 7.8 ng/mL after 5 years, well within the normal range for premenopausal women.

These data indicate that alendronate treatment is associated with a reduction in bone turnover rates to levels that are similar to those found in normal premenopausal women.

Serum calcium decreased by the end of 1 month of treatment with alendronate 10 mg (2.72% reduction from baseline) and remained below pretreatment levels thereafter. After 5 years of treatment, the geometric mean decrease was 1.56%. These changes were small and are well within the normal range of serum calcium concentrations.

PTH levels increased initially in all alendronate-treated groups, but declined to baseline by Year 3 and remained there for the next 2 years.

Concentrations of 1,25-dihydroxyvitamin D increased by about 20% in all treatment groups and remained so (within the normal reference range) for the duration of the extension study. These changes were thought to be consistent with the changes in serum calcium and PTH.

Following an initial small decrease in mean serum phosphorus (levels remained within normal reference range) during the early phases of treatment, phosphate levels returned to baseline by Month 36 and remained there for the remainder of the study.

Because there was no placebo group during the extension study, the safety analysis was limited to comparisons between the alendronate 5- and 10-mg groups. An additional option, one that is essentially unsatisfactory (as the sponsor states), is to compare the incidence of adverse experiences during the extension with rates found during the first 3 years of double-blind treatment. The major problems with this approach are that patients with adverse experiences may drop out during the first 3 years of the study. In addition, the populations change in other ways as time passes. Furthermore, although patients did not know their dose, they and their physicians know that they were taking alendronate and not placebo, during the last two years.

Despite these limitations, it appears from the data presented that the number, severity, and nature of adverse experiences encountered by this population of patients during the two-year extension are similar to those that have been encountered earlier. Thus, in this study population, the safety profile of alendronate over a five-year period is similar to that which has been encountered during shorter periods of treatment.

Additional safety information can be derived from comparison of AE's encountered in the 5- vs 10-mg treatment groups. In this analysis, there was no evidence that the overall incidence of AE's was greater in the 10-mg group. The only statistically significant dose-related difference in adverse experiences between the 5- and 10-mg groups was in the incidence of abdominal pain reported: 9.3% of patients treated with alendronate 10 mg, compared with 2.8% in the 5-mg group. A statistical comparison of adverse experience incidence in the 5- and 10-mg groups was conducted for all adverse experiences. The only positive result was a trend for sinusitis (2.1% with 5 mg, 7.3% with 10 mg); the rates were intermediate and reversed based on current dose in the placebo/10-mg group (4.2%) and 20-

/5-mg group (5.6%), strongly suggesting that this was a chance observation due to the large number of statistical comparisons.

Serious adverse experiences, including deaths, were observed at similar rates among the treatment groups. There was no pattern of adverse experiences that are rare in this age group.

Upper GI adverse experiences continue to be the major focus of safety evaluations for alendronate. Previous placebo-controlled clinical studies presented by the sponsor have given little indication that significant GI adverse events are associated with alendronate. The sponsor has maintained that if the drug is taken according to directions, there should be very few such experiences. On the other hand, post-marketing experience has yielded significant numbers of spontaneously reported gastrointestinal adverse events, some serious and life-threatening. Since the background incidence of GI signs and symptoms is quite high in this age group, it is extremely difficult to assign a causative role to alendronate with absolute certainty. On the other hand, these concerns cannot be dismissed, especially since the target population ("postmenopausal osteopenic or osteoporotic women") is numerically large and generally healthy. In this population, the introduction of a large number of serious GI adverse events would offset beneficial effects on bone.

During the 2-year extension period, there was a trend toward an increase in GI adverse experiences in the 10-mg treatment groups: 15.9% of patients in the 5-mg group and 22.5% of those in the 10-mg group had at least one upper GI adverse experience. This difference was not statistically significant, but similar differences (i.e., more with 10 mg) were seen in the other 2 treatment groups. In this study, there were very few serious GI adverse events in any treatment group. Of the 727 patients who entered, only 4 patients (0.6%), all receiving 10 mg, were withdrawn from treatment due to an upper GI adverse experience.

Esophageal adverse experiences are a recognized side effect of alendronate. In the first 3 years of the study, 2.0% of patients treated with placebo and 4.6% of those who received alendronate 10mg had symptoms of, and/or diagnosed, esophagitis, esophageal erosions or esophageal ulcer. The incidence in the 5-mg group was the same as that with placebo (2.0%). In the 2-year extension, 2.1% of patients in the 5-mg group and 3.3% in the 10-mg group had esophageal adverse experiences. None of these patients discontinued treatment.

There was no significant increase in the incidence of gastric or duodenal ulcers in alendronate-treated patients (versus placebo) during the first 3 years of this study (during the first 3 years, the incidence for each group was 0.5% in placebo, 0% with 5mg, and 1% with 10mg). During the

extension period, the incidence was 0% in the 5mg group and 1.3% in the 10mg group.

The risk of non-vertebral fracture was assessed during the 2-year extension and over the entire 5-year period. The incidence of non-vertebral fractures in patients who received alendronate continuously from the start of study was slightly lower than in the placebo group during the first 3 years of treatment (placebo, 3.82 events per 100 PYR, vs. alendronate 3.00). The rate during the extension was 2.39 events per 100 PYR).

There was no pattern of adverse laboratory experiences to suggest causal relationship to treatment. No patient was discontinued from treatment due to a laboratory adverse experience. No laboratory adverse experience was serious.

10.1 Significant/potentially significant events: none

10.1.1 Deaths: Seven deaths occurred during the study. None was related to the study drug, by any known mechanism.

10.1.2 Other Significant/Potentially Significant Events: none

10.1.3 Overdose experience: none reported

10.2 Other Safety Findings: none

10.2.2 Laboratory Findings: no significant new findings were reported

10.2.3 Special Studies: none indicated

10.2.4 Drug-Demographic Interactions: not studied in this sNDA

10.2.5 Drug-Disease Interactions: none reported or specifically studied in this sNDA

10.2.6 Drug-Drug Interactions: not studied in this sNDA

10.2.7 Withdrawal Phenomena/Abuse Potential: none reported or known

10.2.8 Human Reproduction Data: Pregnancy Category C

11 Labeling Review:

Proposed labeling revisions are submitted with the sNDA. For convenience, these are detailed below, along with the sponsor's

annotations. The following is a summary of the proposed revisions; page numbers refer to product label pagination:

Pharmacodynamics:
- Fourth paragraph (page 6)
  - Revisions to reflect two year extension marker results
  - Editorial revisions
- Fifth paragraph (pages 6, 7)
  - Revisions to reflect two year extension results

Clinical Studies: Effect on bone mineral density (page 8)
- In the second paragraph, addition of two-year extension BMD results

ADVERSE REACTIONS, Clinical Studies (pages 20-22)
- In the first paragraph, addition of text to reflect that adverse experiences have been studied for up to five years.

Treatment of osteoporosis
- In the fourth paragraph, addition of adverse experience profile/discontinuation results from the two year extension study

DOSAGE AND ADMINISTRATION (page 25)
The statement regarding duration of safety studied has been revised from "four" to "five".


., DRAFT LABELING


DRAFT LABELING


DRAFT LABELING


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DRAFT LABELING

[redacted]

Comments: The proposed changes in the label are adequately supported by the data presented in the sNDA. However, there are modifications that should be made:

1) Clinical Section, page 8 (reproduced above), lines 7-12. The reader is not informed about the design of the extension study, In particular, the proposed text does not give the number of patients who were treated with Fosamax 10 mg. A description of the extension study would be lengthy and is probably not needed. However, since a claim is proposed for Fosamax 10 mg, the label should disclose the number of patients treated with this dose and included in the ITT analysis (n= 147). The text should read: " In the two-year extension of these studies, treatment of 147 patients with FOSAMAX 10 mg/day..."
2) Since all patients in the extension study continued to lose height, this should be stated in the next paragraph, in which loss of stature during the initial 36 months is described. At the conclusion of the paragraph, the following should be added: [redacted]

DRAFT LABELING

[redacted]

3) Clinical Section, page 8, line 12 (reproduced above). "Thus Fosamax appears to reverse the progression of osteoporosis." This sentence is an established part of the label for Fosamax and is not included in the proposed changes. It is the opinion of this reviewer that this statement is misleading. A reversal is a turn in the opposite direction. While it is true that Fosamax, 10 mg, reverses the decline in BMD at several skeletal sites, it is also true that some Fosamax-treated patients continue to experience fractures. Furthermore, the group of Fosamax-treated patients continues to lose stature, as described above. It is only by defining the disease "osteoporosis" *solely* in terms of BMD that this statement is true. A more accurate description of the effects of alendronate would state that the drug reverses the loss of bone mineral density at several anatomical sites and retards the progression of the disease, in terms of fracture incidence and loss of stature.

12 CONCLUSIONS:

The conclusions apply to the safety and efficacy of 5 years of alendronate treatment in a cohort of 727 postmenopausal women who agreed to remain in a clinical trial. This population represents 73% of the original group of patients entering a 3-year, randomized, double-blind, multi-center, safety and efficacy study of alendronate. The patient recruitment rate was excellent, as was the retention rate for the extension period. This may reflect the overall tolerability of the drug, the abilities of the investigators, and/or the motivation of the patients. On the other hand, the responses and behavior of the general population may differ somewhat from those of the study population. The size of the intended treatment population (postmenopausal women with low bone mineral density and no contraindications to use of the drug) is at least four orders of magnitude greater than that of the study population.

It should be noted that the level of calcium supplementation was most likely inadequate for this population. If alendronate had been tested against a background of adequate calcium intake, placebo-related efficacy may have differed somewhat from the present data.

In this study population, daily oral alendronate, 5 or 10 mg for an additional 2 years (total 5 years of treatment), had a very good safety profile and level of tolerability; the safety and tolerability were essentially the same as those which have been previously reported for the 3-year study.

Continuous treatment with alendronate, 10 mg for 5 years, produced a statistically significantly greater increase in lumbar spine, proximal femur, trochanter, and total body BMD from the original pretreatment baseline than achieved following 5mg treatment for 5 years. Both 5 and 10mg alendronate, taken daily for 5 years, prevented BMD loss at the forearm. In this patient population, daily oral administration of alendronate, 10 mg continuously for 5 years, increased or maintained BMD of the spine, proximal femur, forearm, and total body from Months 36 to 60---that is, the gains in BMD that had been achieved by 36 months of treatment were maintained or increased further. The proportion of patients responding to alendronate 10mg was consistently very high.

Studies of biochemical markers of bone formation and resorption in this patient population clearly showed that daily oral alendronate, 5 or 10 mg, substantially decreased biochemical markers of bone turnover to levels found in premenopausal women. This decrease reached a stable plateau that was maintained throughout 5 years of treatment.

Despite substantial gains in spine BMD, all treatment arms lost stature during the five years. Patients treated with 10mg alendronate lost height at a rate that was at least as great as was found in the 5mg group, despite significant differences in gains in BMD between these two groups. Complete interpretation of these data was hindered by the absence of a placebo group during the two-year extension. Data from the first 3 years of the study strongly suggest that alendronate exerts a substantial beneficial effect on height loss in the 6% of patients with an incident vertebral fracture, but that the effects on the remainder of the treatment population, while statistically significant, are very small. Further analysis of the relationships among BMD changes, incident fracture rates, and changes in stature are warranted. This analysis will be important in determining the overall clinical benefits of long-term alendronate therapy.

13 Recommendations

I recommend approval of this supplemental NDA, with the labeling changes that I have suggested above. The data strongly support the proposed five-year indications, based on BMD, biochemical markers, and safety profile. Issues that are raised in this review should be addressed by future analysis of long-term fracture data, as indicated above.

/S/ [redacted]

BRUCE S. SCHNEIDER, MD

/S/ [redacted] 4/29/99

MEDICAL OFFICER, FDA, DMEDP, HFD-510