MEDICAL REVIEW
Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #: 20560-038
Application Type: sNDA
Sponsor: Merck
Proprietary Name: Fosamax (alendronate sodium)
USAN Name:
Pharmaceutical Category: bisphosphonate
Route of Administration: tablets, oral
Indication: Treatment of Osteogenesis Imperfecta
Dosage: 5mg, 10mg
Reviewer: Bruce S. Schneider, MD
Dates of Review: Feb.1, 2003-June 30, 2003

Chemistry Review: NA
Pharmacology Review: NA
Biopharmaceutics Review: J. Lau, PhD
Statistics Review: T. Sahlroot, PhD

REVIEW SUMMARY: Please see Executive Summary

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION: N drive location:

New clinical studies _____ **Clinical Hold** _____ **Study May Proceed**
NDA, Efficacy/Label supplement: _xxx**Approvable** _____ **Not Approvable**
_____ **Approve**

SIGNATURES:
Medical Reviewer: __Bruce S. Schneider, MD
_____ **Date:** June 30, 2003

Medical Team Leader: **Date:** _____
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Executive Summary

A. Recommendations

Recommendation of Approvability: Approvable, pending review of complete set of histomorphometry data and 24-month fracture results.

Recommendation of Phase 4 Studies and Risk Management Steps: none

B. Summary of Clinical Findings

In response to a Written Request, Merck has submitted 12-month safety and efficacy data from an ongoing study of the use of alendronate in children with osteogenesis imperfecta (OI). The study was a randomized, placebo-controlled, multicenter trial that enrolled 139 patients with OI, aged 4-18 years. The patients were randomized 1:3 to receive placebo or alendronate (5 mg or 10 mg, depending on body weight) as double-blind therapy for up to two years, followed by an open-label extension.

Alendronate, 5 mg or 10 mg, produced a substantial increase in lumbar spine BMD (increase of 1 BMD z-score unit, equivalent to a placebo-subtracted increase of 26% in one year). The sponsor obtained hip BMD data on only six patients; consequently, we have no indication of the efficacy of alendronate on peripheral skeletal sites in this population. An analysis of the key secondary efficacy endpoints, radiologically-confirmed and investigator-reported long-bone fractures, found no treatment-group differences. Alendronate treatment was associated with significant suppression of bone turnover markers, consistent with the known pharmacodynamic actions of the drug. There were no other treatment-related benefits of the drug, relative to placebo.

The safety and tolerability profile of alendronate in this population were acceptable, with few serious adverse events (only three of which were possibly related to alendronate) and no deaths. Children treated with alendronate had standing and sitting growth velocities that were essentially equal to those of patients treated with placebo.

C. Current therapeutic options for treating Osteogenesis Imperfecta: There is no approved medical treatment for OI in the United States. Treatment has focused on fracture management and surgical correction of deformities. There

are published studies on the utility of various agents, including fluoride, calcitonin, anabolic steroids, growth hormone, and pamidronate, but there are no data from rigorous placebo-controlled trials. Allogeneic bone marrow transplantation has also been tried in a few children with Type III OI, which is the most severe non-lethal form.

D. Brief overview of clinical program

This study was performed in response to a Written Request for the study of the safety and efficacy of alendronate in the treatment of children with OI. There is reason to believe that a bisphosphonate might be beneficial in this population, based on the high bone turnover rates and low bone mineral density that accompany the disease. In addition, there have been a few uncontrolled studies that indicated that anti-resorptive therapy might be helpful.

The submission consists of 12-month safety and efficacy data from an ongoing study of the use of alendronate in children with osteogenesis imperfecta. The study was a randomized, placebo-controlled, multicenter trial that enrolled 139 patients with OI, aged 4-18 years. This is the first placebo-controlled study of the use of a bisphosphonate in patients with this disease. The patients were randomized 1:3 to receive placebo (PBO) or alendronate (ALN, 5 mg or 10 mg, depending on body weight) as double-blind therapy for up to two years, followed by an open-label extension. The primary efficacy outcome was change in BMD z-score from baseline to Month 12 of double-blind therapy. Key secondary outcomes were the proportions of patients with one or more radiologically-confirmed fractures and with one or more investigator-reported fractures (not necessarily confirmed radiologically). Based on an evaluation of the DSMB, the study had achieved its primary objective (lumbar spine BMD) and there were no other concerns that would preclude the continuation of the double-blind portion of the study for the second year. Accordingly, the results of data up to Month 12 were submitted in fulfillment of the Written Request. In addition, available safety and efficacy data up to Month 24 were submitted.

E. Efficacy

The study enrolled 139 patients with OI, aged 4-18 years. There were 78 boys and 61 girls. Seventy patients were < 12 years of age and 69 were > 12 years. The patients were roughly equally distributed among the three requested disease phenotypes (Type III, Type IV, and Type I OI associated with chronic pain and/or > three fractures/year for the two years prior to the study, or with limb deformity requiring surgery).

A total of 112 patients (86 ALN and 26 PBO) were included in the modified intention-to-treat analysis that carried forward the last observed data (MITT-

LOCF). Ninety-seven of these patients had data within the Month 12 range, and 15 had Month 6 data carried forward.

The primary efficacy endpoint was clearly met. At baseline, both groups had very low lumbar spine BMD z-scores (the z-scores were -4.6 in both treatment groups). There was a substantial increase in lumbar spine BMD associated with alendronate, 5 mg or 10 mg. The increase in ALN was 1 BMD z-score unit; this was equivalent to a placebo-subtracted increase of 26% in one year. Similar increases in lumbar spine bone mineral density were noted, whether the data were expressed as BMD (in gm/cm^2) or as bone mineral content (BMC). A responder analysis showed that a greater proportion of patients in ALN had increases of BMD that exceeded pre-specified thresholds, compared to PBO. Subgroup analyses showed that there was no group (weight, age, gender, race, pubertal status) in which the drug was not effective in increasing BMD. Increases in vertebral bone area and metacarpal cortical width were also seen in both treatment groups over the 12 months of double-blind therapy, but there were no significant between-group differences in these parameters. The sponsor obtained hip BMD data on only six patients; consequently, we have no indication of the efficacy of alendronate on peripheral skeletal sites in this population.

Alendronate treatment was associated with significant suppression of bone turnover markers, consistent with the known pharmacodynamic actions of the drug.

Despite these effects on bone turnover and BMD, an analysis of the key secondary efficacy endpoints, radiologically-confirmed and investigator-reported long-bone fractures, found no statistically significant or consistent treatment-related differences in fracture occurrence. About half the patients in each group suffered at least one fracture in the first 12 months, and the average number of fractures/patient was 1.1 in both groups.

Of interest, there was a trend in favor of alendronate in cumulative incidence of fractures and in proportions of patients with at least one investigator-reported fracture over the 12-month period (see Kaplan-Meier analysis in this review). Although the time to first fracture was numerically longer in ALN, compared to PBO, the difference between the groups was not significant. It will be important to analyze data following 24 months of double-blind treatment to see if this treatment difference holds up.

There were no other treatment-related benefits of the drug, relative to placebo. This includes an analysis of bone pain, bone pain frequency, and pediatric disability scores.

F. Safety

Safety data up to month 12 and data up to Month 24 were submitted. Safety data were recorded on all 139 randomized patients. Of the 139 patients, 89 (81.7%) of

ALN and 29 (96.7%) of PBO took at least 12 months of study medication (within pre-defined relative day range). The mean total duration of exposure in ALN was 317.7 days (range, 40 to 444 days) and, in PBO, 348.5 days (range, 270 to 378 days). The median exposure time was the same in both groups (356 days).

The study is ongoing, and, at the time of the submission 49 patients had received alendronate for up to two years. The sponsor included safety data past 12 months, and all safety data were analyzed in this review. For all safety data past 12 months (i.e., “Results up to 24 Months”), the median exposure times were 545 days in ALN (range 40-751) and 612 days in PBO (range 295-732).

Based on data submitted, the overall safety and tolerability of alendronate in the pediatric population with OI were favorable. The adverse event profile of alendronate was comparable to that of placebo, both in data up to 12 and up to 24 months. Six patients in the entire study population experienced at least one serious AE (excluding fractures) during the 12-month double-blind treatment period: Four in ALN (3.7%) and two in PBO (6.7%). Four more patients in ALN had a serious clinical adverse event after Month 12. In the opinion of the investigators, none of the serious AEs was related to study drug. However, I have reviewed the clinical reports and have concluded that it is possible that vomiting (leading to clinically serious dehydration) in two patients was related to alendronate. In addition, one case of leukopenia was reported in a patient taking alendronate. This is not known to occur with excessive frequency in adults treated with alendronate, but should be followed as a safety signal in children whether or not the drug is approved for this indication. No patient was withdrawn from therapy due to a serious AE.

Patients treated with alendronate had growth velocities (standing and sitting) that were at least as high as those of patients treated with placebo for the first twelve months; data available up to 24 months also showed no treatment-group differences in height velocities. The growth rates in pediatric patients with OI are less than in normal children, and there is substantial variability in growth measurements in affected individuals. Accordingly, a complete dataset up to Month 24 will help confirm the stability of this safety outcome.

A separate upper GI safety analysis was performed, and there was no indication that alendronate is associated with an increase in GI toxicity in this population, on the basis of the submitted data. However, I have raised the possibility that alendronate contributed to the vomiting that was associated with dehydration in two patients.

Histomorphometry data derived from iliac crest biopsies were scheduled for all patients at baseline and at Month 24. To date, results are available on only 10 patients (7ALN and 3 PBO). Although two ALN patients had a prolonged mineralization lag time, there was no associated increase in osteoid thickness, which would be indicative of osteomalacia. Review of the complete

histomorphometry dataset will be required before a full bone safety assessment is possible.

The sponsor addressed the potential problem of non-union or mal-union of fractures in OI patients treated with alendronate. This was not an overt clinical problem during the trial. However, it was not possible to conduct a formal comparison of the frequency of bone healing abnormalities between the two treatment groups, since not all patients had fractures at baseline and the total number of fractures present at baseline has not been evaluated. Thus we do not know whether alendronate may worsen the delay in fracture remodeling that is found in patients with OI. Further data are required to make this determination.

There were no deaths during the study (either in the first 12-month period or in the data reported for the 24-month period).

G. Dosing

The study employed two doses, 5 mg and 10 mg daily, based on body weight strata. If the drug is approved for this indication, the recommended dose regimens should be based on the data provided in the submission: patients weighing < 40 kg should be treated with Fosamax 5 mg daily, and patients weighing ≥ 40 kg should be given Fosamax 10 mg/day. No safety or efficacy data are available on once-weekly dosing regimens (e.g., 35 mg or 70 mg weekly) in the pediatric population.

H. Special populations

If approved for treatment of OI, the indications for use of Fosamax will extend to the population of pediatric patients aged 4-18 years.

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/s/

Bruce Schneider
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David Orloff
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