NDA 20-560

Merck Research Laboratories
Attention: Michele Flicker, MD, PhD
Director, Regulatory Affairs
P.O. Box 20000
Mail Drop RY 33-720
Rahway, NJ 07065

OCT 27 2000

WRITTEN REQUEST

Dear Dr. Flicker:

Reference is made to your Proposed Pediatric Study Request for Fosamax Tablets submitted on May 31, 2000, to NDA 20-560.

We acknowledge receipt of your submissions dated September 6 and 22, 2000.

To obtain needed pediatric information on alendronate sodium, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

Study 1, clinical study

Type of study:

A 2-year, randomized, double-blind, placebo-controlled, multicenter study.

Objective:

To characterize the efficacy and safety of alendronate in pediatric patients with osteogenesis imperfecta.

Indication to be studied:

The treatment of osteogenesis imperfecta.

Study design:

A multicenter, randomized, double-blind, placebo-controlled, parallel study of pediatric patients with osteogenesis imperfecta. During Year 1, patients should receive once-daily placebo or

alendronate 5 or 10 mg, depending on body weight. During Year 2, all patients will receive alendronate. Patients who received 5 mg once-daily alendronate during Year 1 may be switched to 35 mg once-weekly alendronate, patients who received 10 mg once-daily alendronate during Year 1 may be switched to 70 mg once-weekly alendronate, and patients who were on placebo and weigh < 40 kg may receive 35 mg once-weekly, and patients who were on placebo and weigh ≥ 40 kg may receive 70 mg once-weekly. All patients should receive supplemental calcium and vitamin D as appropriate standard care.

Age group of patients to be studied:

Four to sixteen years of age.

Number of patients to be studied:

A total of approximately 120 patients should be enrolled into the study: approximately 80 patients should be randomized to receive alendronate and approximately 40 patients should be randomized to receive placebo.

Entry Criteria:

- pediatric patients with phenotypic osteogenesis imperfecta type III or IV
- pediatric patients with phenotypic osteogenesis imperfecta type I with chronic pain and/or > 3 fractures (including vertebrae) per year due to minimal trauma during the previous 2 years, or with limb deformity requiring surgery.
- patients should be capable of standing or sitting upright for at least 30 minutes following dosing and complying with all dosing instructions.
- patients using drugs that alter gastric pH (i.e., H2 blockers, antacids) and patients who are pregnant should be excluded from participation in the study.

Clinical endpoints:

The primary efficacy endpoint should be the change in lumbar spine bone mineral density and content from baseline to month 12. Secondary endpoints should include change in femoral neck bone mineral content and density, fracture rate, bone pain, height, and biochemical markers of bone turnover.

Study evaluations:

Study evaluations should include measurement of serum levels of calcium, phosphate, PTH, and vitamin D, and urine levels of calcium and phosphate. Assessment of bone histomorphometry following bone biopsy should also be conducted.

Drug information:

- Dosage form: tablets
- Route of administration: oral
- Regimen- Year 1: patients < 40 kg 5 mg once daily or placebo
  patients ≥ 40 kg 10 mg once daily or placebo

  Regimen- Year 2: patients < 40 kg 35 mg once weekly
  patients ≥ 40 kg 70 mg once weekly
- Formulation: same as marketed

Drug-specific safety concerns:

Primary safety concerns include the effect of alendronate on the gastrointestinal tract (i.e., esophagitis, gastritis), linear growth, and bone quality. Although rare, uveitis and episcleritis may result from treatment with alendronate. Appropriate measures should be taken to monitor and assess these safety issues. An independent data safety monitoring board should be employed to periodically review interim safety data. The study protocol should include guidelines to the DSMB regarding stopping rules for safety concerns. In the event that the DSMB recommends premature termination of the trial due to safety concerns, submission of a final study report of the data up to that point will constitute fulfillment of the WR with regard to study 1. Any patient who has severe, uncontrolled pain of 3 months duration that interferes with activities of daily living and requires analgesic medication should be withdrawn from the study and if previously on placebo offered open-label alendronate treatment.

Statistical information:

Change from baseline in lumbar spine BMD Z-score at one year will be compared between alendronate and placebo using ANCOVA adjusted for baseline. The primary analysis population will be the intent-to-treat (ITT) population consisting of all randomized patients with an observation at baseline and at least one on-treatment observation.

An interim analysis will examine the primary endpoint using all data available as of March 31, 2001. The primary analysis population will be the intent-to-treat (ITT) population consisting of all randomized patients who have an observation at baseline and at least one on-treatment observation. Patients with data at 6 months only will have their 6-month values included in the analysis. The analysis will be conducted using a nominal 1% Type I error rate. Efficacy will have been demonstrated, and the double-blind portion of the study terminated, if the p-value of the interim analysis is smaller than 1%. All patients should then receive open-label, once-weekly alendronate for a total of up to two years of treatment. If the interim analysis fails to document efficacy, all patients should continue in their respective treatment groups at least until the final analysis of the blinded portion of the trial (i.e , end of Year 1).

The final analysis, if required, will be conducted at a nominal significance level determined in order to maintain an overall 5% Type I error rate for the entire study. If efficacy is demonstrated

in the final analysis, all patients should then receive open-label, once-weekly alendronate for a total of up to two years of treatment. If efficacy is not demonstrated by the final analysis, the trial should be terminated.

Submission of placebo-controlled data following the interim analysis (if efficacy is demonstrated), or the final analysis (i.e., end of Year 1) will constitute fulfillment of the Written Request with regard to study 1. While not required to fulfill the Written Request, a follow-up report including all data from the two-year trial should be submitted when available.

Study 2, clinical pharmacology study

Type of Study:

An open-label, two-period, randomized, single-dose, crossover, pharmacokinetic study.

Objective:

To measure the oral bioavailability of alendronate in pediatric patients with osteogenesis imperfecta.

Study design:

This will be an open-label, two-period, randomized, crossover study designed as a conventional pharmacokinetics study. Patients will receive single doses of alendronate as follows: patients < 40 kg will receive a 35-mg tablet and a 125 ug IV dose, each separated by two weeks; patients > 40 kg will receive a 70-mg tablet and a 125 ug IV dose, each separated by two weeks.

Age group of patients to be studied:

Four to sixteen years of age.

Number of patients to be studied:

Approximately twenty-four patients will be studied.

Entry criteria:

- pediatric patients with phenotypic osteogenesis imperfecta type III or IV
- pediatric patients with phenotypic osteogenesis imperfecta type I with chronic pain and/or > 3 fractures (including vertebrae) per year due to minimal trauma during the previous 2 years, or with limb deformity requiring surgery.
- patients should be capable of standing or sitting upright for at least 30 minutes following dosing and complying with all dosing instructions.
- patients using drugs that alter gastric pH (i.e., H2 blockers, antacids) and patients who are pregnant should be excluded from participation in the study.

Endpoints:

Total urinary excretion of alendronate following each dose and, thus, oral bioavailability of alendronate.

Drug information:

- Dosage form: tablets and solution
- Route of administration: oral and intravenous
- Regimen: all subjects will receive one oral and one intravenous dose
- Formulation: oral – same as marketed
  intravenous – [redacted] (b) (4)

Drug-specific safety concerns:

Concern for drug-specific safety is minimal because each patient will receive only two doses of the drug, separated by two weeks.

Statistical information:

A sample size of 12 patients in each body weight category (< 40 kg and ≥ 40 kg) to permit estimation of bioavailability of the dose-adjusted ratio of the 35-mg tablet and 70-mg tablet to the 125-ug IV to within 51%

Labeling that may result from the studies:

Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of reports to be submitted:

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before June 30, 2002. Please keep in mind that pediatric exclusivity only extends existing patent protection or exclusivity that has not expired or been previously extended at the time you submit your reports of the studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written

agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a **supplement to your approved NDA** with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

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

Sincerely yours,

John K. Jenkins, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

RH 10/26/00

cc:
Archival NDA 20-560
HFD-510/division file
HFD-510/RPM
HFD-510/Team Leaders and Reviewers
HFD-600/Office of Generic Drugs
HFD-2/M.Lumpkin
HFD-104/Peds/D.Murphy/Tcrescenzi
HFD-102/LRipper

Drafted by: Randy Hedin/9.14.99
Initialed by: Draft #1 BSchneider/EColman/TSahlroot/JWei/HAhn/EGalliers/
DOrloff/9.29/LRipper/10.2/JJenkins/10.5.00
Draft #2 EColman/JJenkins/10.6/LRipper/10.10.00
Draft #3 EColman/10.11/DOrloff/10.12/LRipper/10.16/JJenkins/10.23.00
Final: RHedin/10.26.00
filename: N20560irwr_lt1.doc

L'Ripper 10/26/00

(IR) INFORMATION REQUEST
PEDIATRIC WRITTEN REQUEST LETTER