**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-223

Novartis Pharmaceuticals Corporation
Attention: Lynn Mellor
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

WRITTEN REQUEST #2

Dear Ms. Mellor:

Please refer to your correspondence dated April 18, 2006, requesting changes to FDA's August 19, 2002, Written Request for pediatric studies for zoledronic acid, as amended November 19, 2002.

We have reviewed your proposed changes and are amending the Written Request. For convenience, the full text of the Written Request, as amended, follows. This Written Request supersedes the Written Request dated August 19, 2002, as amended November 19, 2002.

- *Type of studies*:

  Study 1: A single-dose study to determine the pharmacokinetics (PK) of zoledronic acid upon intravenous administration to pediatric patients with osteogenesis imperfecta (OI).

  Study 2: A randomized, parallel-group study to compare the safety and efficacy of intravenous zoledronic acid to intravenous pamidronate in the treatment of children with moderate-to-severe OI.

- *Indication to be studied (i.e., objective of study)*: To assess the effect of zoledronic acid on bone mineral density (BMD) in the lumbar spine of patients with moderate-to-severe OI.

- *Study design*:

  Study 1: A single-dose population pharmacokinetic (PK) study in pediatric patients with OI. A pre-dose blood sample should be collected from each patient. Patients who are 1-2 years of age should have three post-dose random blood samples. Patients who are 3-8 years of age should have four post-dose random blood samples. Patients who are 9-17 years of age should have six random post-dose blood

samples. Post-dose fixed sampling should be avoided. The timing of blood samples should cover the absorption and elimination phases for the pharmacokinetic profiles in the different patient groups. Urine samples should only be collected from patients 3 through 17 years of age. Zoledronic acid plasma concentration-time profiles, and zoledronic acid urinary excretion data, should be characterized. Further, an attempt should be made to include approximately equal numbers of male and female patients. This population PK study may be part of the clinical safety and efficacy study.

Study 2: Approximately 132 patients ≥1 through 17 years of age should be randomized (1:1) to receive zoledronic acid or pamidronate. All patients should receive standard medical care (i.e., supplemental calcium and vitamin D).

Zoledronic acid patients ≥1 to < 3 years of age should be administered 0.025 mg/kg as a 30 to 45-minute intravenous infusion every 3 months for one year. Patients ≥ 3 years to ≤ 17 years of age should be administered 0.05 mg/kg as a 30-minute intravenous infusion every 3 months for one year.

Pamidronate should be administered as a 4-hour intravenous infusion. Patients ≥ 1 year to < 2 years of age should be administered 0.5 mg/kg/day on each of three consecutive days every 2 months for one year. Patients ≥ 2 years to < 3 years of age should be administered 0.75 mg/kg/day on each of three consecutive days every 3 months for one year. Patients ≥ 3 years to ≤ 17 years of age should be administered 1 mg/kg/day on each of three consecutive days every 3 months for one year.

- *Age group in which studies will be performed*:

Study 1: Pediatric patients ≥1 to ≤ 17 years of age. At least 4 patients 12 months through 8 years of age, and at least 4 patients 9 through 17 years of age should complete the study.

Study 2: Pediatric patients ≥1 to ≤ 17 years of age. At least one-third of the patients should be 12 months through 8 years of age.

- *Study endpoints:*

Study 1: Plasma clearance and volume of distribution should be endpoints for all patients, and renal clearance should also be an endpoint for patients 3-17 years of age. In addition, the effect of age, gender, and body weight on PK parameters should be analyzed.

Study 2: The primary endpoint should be a comparison of the percent change in lumbar spine bone mineral density (BMD) from baseline to month 12 in zoledronic acid-

treated patients versus pamidronate-treated patients. The assessment of BMD should be by a central reader who is masked to the patients treatment assignment. Secondary endpoints should include a comparison of the number of clinical fractures that occur over a one-year period in zoledronic acid treated patients compared with pamidronate-treated patients. In addition, bone pain, height or supine length, and biochemical markers of bone turnover should be secondary endpoints. Biochemical marker data will not be collected in patients < 3 years old.

- *Drug information:*

  Zoledronic acid

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|---|---|
| Dosage form: | sterile solution |
| Route of administration: | intravenous |
| Formulation: | 5 mg per vial |
| Regimen: | Zoledronic acid patients ≥1 to < 3 years of age should be administered 0.025 mg/kg as a 30-minute intravenous infusion every 3 months for one year. Patients ≥ 3 years to ≤ 17 years of age should be administered 0.05 mg/kg as a 30-minute intravenous infusion every 3 months for one year. |

  Pamidronate

| | |
|---|---|
| Dosage form: | sterile lyophilized powder |
| Route of administration: | intravenous |
| Formulation: | 30 mg or 90 mg per vial |
| Regimen: | Pamidronate should be administered as a 4-hour intravenous infusion. Patients ≥ 1 year to < 2 years of age should be administered 0.5 mg/kg/day on each of three consecutive days every 2 months for one year. Patients ≥ 2 years to < 3 years of age should be administered 0.75 mg/kg/day on each of three consecutive days every 3 months for one year. Patients ≥ 3 years to ≤ 17 years of age should be administered 1 mg/kg/day on each of three consecutive days every 3 months for one year. |

- *Drug-specific safety concerns*: The primary safety concerns include the effects of zoledronic acid and pamidronate on linear growth, bone quality, and renal function. Although rare, uveitis and episcleritis may possibly result from treatment with zoledronic acid and pamidronate. Appropriate measures should be taken to monitor and assess these safety issues. An independent data safety monitoring board (DSMB) 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 the clinical study. Any patient who has severe, uncontrolled pain that interferes with activities of daily living, and requires analgesic medication should be referred for evaluation by a physician independent of the clinical trial.

- *Statistical information, including power of study and statistical assessments**:***

  Study 1: Descriptive summary of pharmacokinetic parameters.

  Study 2: Treatment group comparisons for percent change from baseline to month 12 in lumbar spine BMD should be assessed by a one-sided 97.5% confidence interval for the difference in means. To test the null hypothesis that zoledronic acid is inferior to pamidronate in percent change lumbar spine BMD, a non-inferiority (NI) margin of -13% should be applied. Noninferiority of zoledronic acid to pamidronate will be concluded if the lower bound of the one-sided 97.5% confidence interval exceeds the NI margin. The ultimate selection of the NI margin is a review issue based on available data at the time of the review.

  With 66 patients per group, the trial has 80% power to rule out a -13% NI margin assuming zoledronic acid is 2% superior to pamidronate in lumbar spine BMD. The calculation reflects a one-sided 2.5% level of significance, standard deviation of 29%, and 10% upward adjustment for dropouts and missing data.

  Analysis of data from both the intent-to-treat (ITT) population using last-observation-carried-forward, and the completers population should be performed. The ITT population should include all randomized patients who have lumbar spine BMD data at baseline and after randomization.

  Also, summary data should be provided by treatment group for the number of clinical fractures that occur over a one-year period, change in femoral neck bone mineral content, if possible, and density, bone pain, height, and biochemical markers of bone turnover.

- *Labeling that may result from the study*: 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. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities.

- *Timeframe for submitting reports of the studies*: Reports of the above studies must be submitted to the Agency on or before April 30, 2008. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

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.

Submit reports of the studies as a supplement to an 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. In addition, 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.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

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 301-796-1224.

Sincerely yours,

*{See appended electronic signature page}*

Curtis Rosebraugh, M.D.
Deputy Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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Curtis Rosebraugh
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