DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 31,029
NDA 20-835

Procter & Gamble Pharmaceuticals
Attention: Gary F. Galletta, Pharm.D.
U.S. Regulatory Affairs
Health Care Research Center
P.O. Box 8006, SB4-3K7
Mason, OH 45040-9462

WRITTEN REQUEST

Dear Dr. Galletta:

Reference is made to your Proposed Pediatric Study Request (PPSR) submitted to IND 31,029 on November 20, 2001, for Actonel (risedronate sodium) Tablets.

This PPSR was submitted in response to our September 17, 2001, denial letter in response to your initial PPSR submitted on May 16, 2001.

To obtain needed pediatric information on risedronate 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 the following information.

- *Type of studies*:

  Study 1: A single-dose pharmacokinetic study in pediatric patients with osteogenesis imperfecta (OI). This study is to be completed and submitted to the Agency prior to the initiation of Study 2.

  Study 2: A randomized, double-blind, placebo-controlled, parallel group study of one-year duration followed by a two-year open label extension to determine the safety and efficacy of risedronate in the treatment of children with moderate-to-severe osteogenesis imperfecta (OI).

- *Indication to be studied (i.e., objective of study)*: To determine whether one year of treatment with risedronate compared with placebo is effective in preventing vertebral and nonvertebral fractures diagnosed clinically and confirmed radiographically in children with moderate-to-severe OI.

- *Study Design*:

  Study 1: Single-dose, randomized, parallel-group study, in at least 12 male and 12 female pediatric patients with diagnosed OI following an overnight fast. Patients will be stratified by body weight and dose (4 groups total, n = 6 per group, n = 24 total): Patients weighing 10 – 30 kg will receive 2.5 mg (n = 6) or 5 mg (n = 6) of risedronate, and patients weighing > 30 kg will receive 5 mg (n = 6) or 10 mg (n = 6) of risedronate. An attempt should be made to include equal numbers of male and female patients.

  Study 2: Approximately 110 patients will be recruited and randomized (2:1) to receive risedronate or placebo. The first year of this study will be placebo controlled and double blind. At the end of one year of treatment, both risedronate- and placebo-treated patients will be given the option of switching to open-label risedronate for an additional two years. An interim assessment of bone mineral density will be performed by an Independent Data Safety Monitoring Board (DSMB) when six-months of bone mineral density data are available for a specified subgroup of patients. If the absolute difference between risedronate and placebo treatment in lumbar spine bone mineral density is at least five percent, no change in dose will be made. If the difference is less than five percent, the results will be discussed with the FDA and changes in dose may be considered. All patients will receive standard medical care.

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

  Study 1: Pediatric patients ≥ 4 to < 16 years of age.

  Study 2: Pediatric patients ≥ 4 to < 16 years of age. Approximately one-third of the patients should be ≥ 4 to < 10 years of age.

- *Study endpoints*:

  Study 1: Pharmacokinetic parameters, such as AUC, Cmax, Tmax, CL/F, Vss/F, and $t_{1/2}$ should be evaluated. If possible, the effect of demographic covariates (e.g., age, gender, and body weight) on pharmacokinetic parameters will be assessed.

  Study 2: The primary endpoint should be the incidence of vertebral plus nonvertebral fractures after one year of treatment. Secondary endpoints should include total body and lumbar spine bone mineral content after one year of treatment.

- *Drug information*:

Dosage form:	Cellulose film-coated tablet
Route of administration:	Oral
Formulation:	5 mg tablets
Regimen:	To be determined from pharmacokinetic study results.

- *Drug-specific safety concerns*: Primary safety concerns include the effects of risedronate on the gastrointestinal tract (e.g., esophagitis, gastritis), linear growth, and bone quality. Although rare, uveitis and episcleritis may result from treatment with risedronate. Appropriate measures should be taken to monitor and assess these safety issues. An independent 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 study 2. Any patient who has severe, uncontrolled pain 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 risedronate treatment.

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

  Study 1: Descriptive summary of pharmacokinetic parameters.

  Study 2: The primary endpoint, number of vertebral plus nonvertebral fractures at one year, will be compared between risedronate and placebo using statistical methods appropriate for count data. Fracture rates (number of fractures divided by actual time on study) will also be compared statistically between treatment groups.

  The primary analysis population will be the intent-to-treat population consisting of all randomized patients who receive at least one dose of study drug.

- *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.

Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before June 30, 2007. 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 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 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. 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,

{See appended electronic signature page}

Sandra L. Kweder, M.D.
Acting Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Sandra L. Kweder

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