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: Lenore Fauhaber, Ph.D., M.B.A.
Associate Director, Regulatory Affairs
Health Care Research Center
P.O. Box 8006, SB4-2P3
Mason, OH 45040-8006

WRITTEN REQUEST
Amendment #2

Dear Dr. Fauhaber:

Please refer to your July 10 and October 15, 2003, correspondence to IND 31,029 requesting changes to FDA's April 19, 2002, Written Request as amended September 11, 2002, for pediatric studies for risedronate.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request.

- *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 to determine the safety and efficacy of risedronate in the treatment of children with mild, moderate, and 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 increasing the mean percent change from baseline to Month 12 in lumbar spine bone mineral density (BMD) in children with mild, moderate, and 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 124 patients will be recruited and randomized (approximately 2:1) to receive risedronate or placebo. The first year of this study will be placebo controlled and double blind. 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 four percent, no change in dose will be made. If the difference is less than four percent, the results will be discussed with the FDA and changes in dose may be considered. All patients will receive standard medical care. 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. However, open-label extension data (i.e., data beyond the 12-month time point) are not required to fulfill this Written Request.

- *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 mean percent change from baseline to Month 12 in lumbar spine BMD. Secondary endpoints should include the incidence and rate of morphometric vertebral fractures and the incidence and rate of clinical vertebral and nonvertebral fractures after one year of treatment.

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

Study 1: Descriptive summary of pharmacokinetic parameters.

Study 2: The primary endpoint, percentage change from baseline in lumbar spine BMD, will be compared between risedronate and placebo using Analysis of Variance with treatment group and stratification variables as main effects in the model. Additional factors or covariates may be considered if appropriate.

The primary analysis population will be the intent-to-treat population consisting of all randomized patients with a baseline and at least one on-treatment lumbar spine BMD measurement. Data for patients without a Month 12 evaluation will consist

of the last available observation (LOCF). Fracture data should be summarized descriptively by treatment group.

For convenience, the full text of the Written Request, as amended, follows. This Written Request supercedes the Written Request dated April 19, 2002, as amended September 11, 2002.

- *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 to determine the safety and efficacy of risedronate in the treatment of children with mild, moderate, and 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 increasing the mean percent change from baseline to Month 12 in lumbar spine bone mineral density (BMD) in children with mild, moderate, and 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 124 patients will be recruited and randomized (approximately 2:1) to receive risedronate or placebo. The first year of this study will be placebo controlled and double blind. 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 four percent, no change in dose will be made. If the difference is less than four percent, the results will be discussed with the FDA and changes in dose may be considered. All patients will receive standard medical care. 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. However, open-label extension data (i.e.,

data beyond the 12-month time point) are not required to fulfill this Written Request.

- *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 mean percent change from baseline to Month 12 in lumbar spine BMD. Secondary endpoints should include the incidence and rate of morphometric vertebral fractures and the incidence and rate of clinical vertebral and nonvertebral fractures after one year of treatment.

- *Drug information*:

Dosage form:	Cellulose film-coated tablets
Route of administration:	Oral
Formulation:	2.5 and 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, percentage change from baseline in lumbar spine BMD, will be compared between risedronate and placebo using Analysis of Variance with treatment group and stratification variables as main effects in the model. Additional factors or covariates may be considered if appropriate.

The primary analysis population will be the intent-to-treat population consisting of all randomized patients with a baseline and at least one on-treatment lumbar spine BMD measurement. Data for patients without a Month 12 evaluation will consist of the last available observation (LOCF). Fracture data should be summarized descriptively by treatment group.

- *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 studies that meet the terms of the Written Request dated April 19, 2002, amended September 11, 2002, and as amended by this letter must be submitted to the Agency on or before January 31, 2009, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

By this letter, we further confirm that we expect you to submit the final study report for study 2 following completion of the 3-year trial, including data from the open-label study extension.

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 NDA 20-835** 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.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to NDA 20-835. 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.

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}

Robert J. Meyer, M.D.
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/

Robert Meyer
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