WR HFD-510

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-819

2/22/01

Abbott Laboratories
Attention: Jennifer Blosl, Pharm. D.
Regulatory Affairs Specialist
200 Abbott Park Road, D389, Building AP30
Abbott Park, IL 60064-6157

Dear Dr. Blosl:

Reference is made to your Proposed Pediatric Study Request submitted to NDA 20-819 on October 12, 2000, for Zemplar (paricalcitol injection).

To obtain needed pediatric information on paricalcitol injection, 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 study:

- *Type of study*: A 16-week, randomized, double-blind, placebo-controlled, multicenter study.
- *Objective*: To characterize the efficacy and safety of Zemplar in pediatric patients with end-stage renal disease (ESRD).
- *Indication to be studied (i.e., objective of study)*: The treatment of secondary hyperparathyroidism due to end-stage renal failure in patients on hemodialysis.
- *Age group in which study will be performed*: ESRD patients aged 2 years to 20 years; approximately one-quarter of the patients should be under the age of 10 years.
- *Number of patients*: Approximately 28 patients should be randomized.

- *Study design*: A multicenter, randomized, double-blind, placebo-controlled, parallel group study. There should be an approximately 2- to 6-week pre-treatment washout phase during which patients should not receive calcitonin or vitamin D (or analogues). Patients should be eligible for randomization to Zemplar or placebo if after a minimum of 2 weeks of washout their level of serum iPTH is $\geq$ 300 pg/mL, serum Ca is $\leq$ 10.5 mg/dL, and their Ca X P product is $\leq$ 70. Patients not meeting these criteria by the end of week 6 of the washout phase should be discontinued from the study.

  The initial dose of study drug should be based on body weight and the degree of secondary hyperparathyroidism as determined by the last iPTH value obtained at the final week of the washout phase as follows: level of iPTH < 500 pg/mL, initial dose 0.04 mcg/kg; level of iPTH > 500 pg/mL, initial dose 0.08 mcg/kg.

  Drug treatment should consist of intravenous injection of either Zemplar or placebo at the end of each regularly scheduled dialysis, approximately 3 times per week. Decisions to maintain, increase, or decrease a dose should be based on a pre-specified algorithm for levels of iPTH, Ca, and Ca X P.

- *Study endpoints*: The primary efficacy endpoint is the proportion of patients achieving at least a 30% decrease from baseline iPTH sustained for at least two consecutive approximately weekly iPTH measurements. A secondary endpoint will be the proportion of patients in each group who achieve two consecutive iPTH values below 300 pg/mL. The incidence of hypercalcemia (corrected serum calcium > 11.2 mg/dL), a secondary safety endpoint, is to be assessed descriptively.

- *Drug information*:

Dosage form:	Injection
Route of administration:	Intravenous
Regimen:	Initial dose 0.04 to 0.08 mcg/kg, titrated per algorithm
Formulation:	Marketed

- *Drug specific safety concerns*: The principal safety concerns are elevated levels of serum calcium and phosphorus and inappropriately low levels of serum iPTH. Drug treatment should be withheld and/or the dose should be reduced if a patient develops hypercalcemia (> 11.0 mg/dL), a Ca X P product > 75, or a iPTH level < 200 pg/mL. To limit exposure to inappropriately high levels of iPTH, patients should be withdrawn from the study if their iPTH values increase by $\geq$ 250 pg/mL from the baseline level for two consecutive weeks, provided that serum phosphorus remains $\leq$ 6.9 mg/dL. An independent external Data Safety Monitoring Board should oversee the conduct of the trial.

- *Statistical information, including power of study and statistical assessments*: Efficacy should be determined from iPTH values obtained approximately weekly during the treatment phase and at the follow-up visit. The primary efficacy analysis population will be all randomized patients with a baseline and at least two on-treatment iPTH measurements. A between-treatment group comparison of the incidence rates of two consecutive $\geq 30\%$ decreases from baseline iPTH will be made using appropriate categorical methods. All hypothesis tests will be two-tailed and p-values < 0.05 will be considered statistically significant. The primary safety analysis population will be all randomized patients who receive at least one dose of study medication.

- *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 study*: Reports of the above study must be submitted to the Agency on or before November 30, 2003. Please remember that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired or been previously extended 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}

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