HFD-104
D MURPHY

NDA 21-083

Wyeth-Ayerst Research
Attention: Maureen Skowronek
Director, U.S. Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

SEP 15 1999

Dear Ms. Skowronek:

Reference is made to your Proposed Pediatric Study Request submitted on April 30, 1999, for Rapamune® (sirolimus) Oral Solution and Tablets to IND 39,160, (b) (4) and NDA 21-083.

To obtain needed pediatric information on Rapamune®, 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*: An open-label, comparative study of the effect of sirolimus versus the best local therapy on clinical outcomes and histologic progression of allograft nephropathy in high-risk pediatric renal transplant patients.
- *Indication to be studied (i.e., objective of each study)*: This study should evaluate the safety and efficacy of a sirolimus-containing regimen and characterize its pharmacokinetic profile in various age ranges of pediatric renal transplant patients.
- *Age groups in which the study will be performed*: The age groups are 0-5, 6-11, and 12-18 years.
- *Study endpoints and timing of assessments, including primary efficacy endpoints:* This study has two related primary endpoints. The first primary endpoint for efficacy of this study is the first occurrence of 1) recurrent rejection, 2) graft loss, or 3) death after 36 months of treatment. The time-to-occurrence of this endpoint should be the subject of the primary analysis, which consists of two parts: 1) time-to-event estimates should be calculated using the Kaplan-Meier method and 2) the statistical significance of differences between therapies (sirolimus regimen and "best local therapy" comparator) should be assessed by the log rank test. Since this is an open label study, there is the potential for differential assessment of the rejection endpoint for the two treatment arms. Graft failure and death endpoints are not as likely to be affected by the unblinded study design. Thus, the second primary endpoint for efficacy and safety is the first of 1) graft loss or 2) death at 36 months. Full pharmacokinetic profiles will be performed on patients from each age group.
- *Drug information*
  - *dosage form:* Oral Solution (1 mg/ml or 5 mg/ml) and Tablet (1 mg or 5 mg)
  - *route of administration:* Oral
  - *regimen:* Patients will generally get sirolimus on Study Day 1 and the drug will generally be administered p.o. four hours after the morning dose of cyclosporine. The daily dose of sirolimus will be 3 mg/m^2/day, with the total daily dose being rounded to the nearest whole milligram. At the discretion of the investigator, patients may receive sirolimus tablets and/or liquid.
- *Drug specific safety concerns*: Patients will be monitored for the development of hypercholesterolemia, hypertriglyceridemia, elevated lactate dehydrogenase (LDH), hypophosphatemia, hypokalemia, reduction in platelet and WBC counts, epistaxis, headache, stomatitis, dyspepsia, anemia, arthralgia, and infections. Adverse events reported with other macrolides should be considered as possible safety concerns.

- *Statistical information, including power of study and statistical assessments:* All analyses will be performed on an intent-to-treat basis unless otherwise indicated. Two additional subpopulations of patients will be analyzed: 1) a safety population of patients receiving at least one dose of study medication and 2) an efficacy population of patients who receive 21 or more doses of study medications.
- *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 studies must be submitted to the Agency on or before December 31, 2004. 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 STUDY**" 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 Matthew Bacho, Regulatory Project Manager, at (301) 827-2127.

Sincerely yours,

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

Distribution:
Archival IND 39,160/ (b) (4) NDA 21-083
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Drafted by: MAB/090999
Initialed by:
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PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)

Concurrence
HFD-104/ODEIV-Dir/Kweder
HFD-590/MO-TL/Cavaillé-Coll
HFD-590/MO/Tiernan
HFD-590/CPMS/Frank
HFD-104/ADRA/Hassall

DFS Keywords
Admin letter
Class immunosuppressant, other
Indic transplant, kidney
Pop pediatrics (0-18 years)