NDA 21-110

Wyeth-Ayerst Research
Attention: Randall Brenner
Manager, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Brenner:

Please refer to your new drug application dated and received on October 29, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rapamune® (sirolimus) Tablets, 1 mg.

We acknowledge receipt of your submissions dated as follows:

November 4, 1999	April 4, 2000	July 24, 2000	August 16, 2000
December 3, 1999	June 5, 2000	July 26, 2000	August 17, 2000 (2)
December 21, 1999	June 15, 2000	August 9, 2000	August 18, 2000
February 25, 2000	July 5, 2000	August 10, 2000	August 21, 2000
February 29, 2000	July 6, 2000	August 15, 2000 (2)	August 25, 2000
March 30, 2000			

This new drug application provides for the use of Rapamune® (sirolimus) Tablets for the prophylaxis of organ rejection in patients receiving renal transplants.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, this application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted labeling (text for the package insert and patient package insert submitted August 21, 2000; immediate container labels submitted August 17, 2000 and August 18, 2000; and carton labels submitted August 17, 2000). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as they are available, in no case more than 30 days after they are printed. Please mount individually ten of the copies on heavyweight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDAs* (January

1999). For administrative purposes, this submission should be designated "FPL for approved NDA 21-110." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submission dated August 15, 2000. These commitments, along with any completion dates agreed upon, are listed below.

Clinical

1. In order to evaluate the optimal dose of sirolimus in renal transplant patients who are at high risk for acute rejection, you agree to conduct a well-controlled, comparative study or studies to further define the optimal dose or concentration in this population. Patients from any or all of the following groups might be included:
    - Black patients
    - Patients with retransplants.
    - Patients with high panel-reactive antibodies.
    - Patients with greater than or equal to 4 human leukocyte antigen mismatches.
    - Patients with multiorgan (e.g., kidney-pancreas) transplants.

2. You will conduct an appropriate study or studies to better define the type and duration of hyperlipidemia associated with the use of sirolimus. In particular, you will measure and analyze total fasting serum cholesterol and triglycerides, as well as high-density lipids/low-density lipids, and lipoprotein A. Transplant recipients with and without a lipid disorder prior to transplant will be included, and the use of lipid-lowering agents and other specific interventions will be evaluated.

3. As part of the continuing development of sirolimus, you will assess its effect on long-term renal function measuring and analyzing GFR in patients receiving kidney or other solid organ transplants.

4. In your ongoing and future studies of sirolimus, you will evaluate the impact of this drug on liver function tests in recipients of kidney or liver transplants who may have hepatitis B virus and/or hepatitis C virus infection.

5. You will collect and report 1-year follow-up safety data from the ongoing Phase 3 study 309. Data pertaining to GFR and serum creatinine will be included as follow-up information and will be submitted in March 2001.

6. You will collect long-term data from study 306 in which some patients have been on the tablet for several years. These data will be submitted in June 2001.

Clinical Pharmacology

7. You will evaluate the optimum therapeutic concentration range for sirolimus and the value of reduced cyclosporine concentrations in combination with sirolimus. You will employ therapeutic drug monitoring and logistic regression modeling in both high- and low-risk patients.

8. You will conduct a study or studies to evaluate the effect of ethnicity on the pharmacokinetics of sirolimus to facilitate the determination of the optimum dosing regimen among other ethnic origins. Such a determination will be made using a population pharmacokinetics analysis, preferably using mixed effects modeling.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55. We are deferring submission of your pediatric studies until December 31, 2004.

If you believe that this drug qualifies for a waiver of the pediatric study requirements, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

In addition, please submit three copies of the introductory promotional materials that you propose to use for Rapamune® Tablets. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Matthew A. Bacho, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

Renata Albrecht, M.D.
Acting Director
Division of Special Pathogen and
Immunologic Drug Products
Office of Evaluation IV
Center for Drug Evaluation and Research