CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 021083

Trade Name: RAPAMUNE ORAL SOLUTION 1mg/mL

Generic Name: SIROLIMUS

Sponsor: WYETH-AYERST RESEARCH

Approval Date: 09/15/99

INDICATION(s): PROPHYLAXIS OF ORGAN REJECTION IN PATIENTS RECEIVING RENAL TRANSPLANTS

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APPROVAL LETTER

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:

Please refer to your new drug application (NDA), dated and received on December 15, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rapamune® (sirolimus) Oral Solution, 1mg/mL.

We acknowledge receipt of your submissions dated:

January 6, 1999	April 12, 1999	May 24, 1999	July 13, 1999
January 14, 1999	April 13, 1999	May 26, 1999	July 14, 1999
February 17, 1999	April 15, 1999	May 28, 1999 (2)	July 28, 1999
February 19, 1999	April 21, 1999	June 1, 1999	August 5, 1999
March 11, 1999	April 26, 1999	June 4, 1999	August 6, 1999 (3)
March 15, 1999	April 28, 1999	June 10, 1999	August 9, 1999
March 17, 1999	April 29, 1999	June 11, 1999	August 17, 1999
March 22, 1999	April 30, 1999	June 14, 1999 (2)	August 19, 1999
March 23, 1999	May 4, 1999	June 18, 1999	August 24, 1999 (4)
March 29, 1999	May 7, 1999	June 21, 1999	August 25, 1999 (2)
March 31, 1999	May 13, 1999	June 25, 1999	August 30, 1999
April 1, 1999	May 17, 1999	June 29, 1999	September 9, 1999
April 8, 1999 (2)	May 21, 1999	July 9, 1999	September 14, 1999

This new drug application provides for the use of Rapamune® (sirolimus) Oral Solution 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, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the package insert submitted September 14, 1999, the patient package insert submitted September 14, 1999, and the immediate container and carton labels submitted August 5, 1999. 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 it is available, in no case more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-083." 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 30, 1999. 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 (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. You will create a registry for collecting safety data on pregnancies that occur during the use of Rapamune®.

4. You will collect and report long-term follow-up safety and efficacy data from the ongoing Phase 3 studies, studies 301 and 302. Data pertaining to glomerular filtration rate (GFR) and serum creatinine will be included as follow-up information. These data should be collected throughout the entire duration of the study whether or not patients remain on study drug. Please note that study 301 is a 2-year study and study 302 is a 3-year study.

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

6. 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.

Clinical Pharmacology

7. In a crossover study with healthy volunteers, you will evaluate the drug-drug interaction potential of sirolimus when co-administered with SangCya® and Sandimmune®. Furthermore, you will evaluate the various administration times of sirolimus and cyclosporine (Neoral®), in order to determine the magnitude of the sirolimus concentration increase when patients do not take sirolimus 4 hours after the cyclosporine dose.

8. 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.

9. You will evaluate the sirolimus-erythromycin pharmacokinetic interaction in a crossover study with healthy volunteers.

10. You will conduct a study or studies to evaluate the effect of ethnicity on the pharmacokinetics of sirolimus so as 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.

11. You will evaluate the interactions between sirolimus and verapamil.

Preclinical

12. You will submit the report for the second carcinogenicity study in mice to the Agency upon issuance. This is projected for the first quarter of 2000.

13. In order to qualify the degradation product WAY-126792 (seco-rapamycin), you will conduct the following studies: a 3-month study in monkeys, a segment II reproductive study, the standard ICH battery of genotoxicity assays, and studies to further evaluate the immunosuppressive activity of seco-rapamycin.

14. You will conduct a combination study with sirolimus and cyclosporine that will incorporate physiologic and morphologic parameters of nephrotoxicity and a recovery period.

15. a) You will provide us with the data published in the literature and/or data generated from additional studies to better define the effect of the p-glycoprotein efflux system on sirolimus pharmacokinetics.

    b) Studies are ongoing using a subclone of the human intestinal Caco-2 cell line with induced CYP3A4 activity to examine the combined effects of metabolism and efflux on sirolimus disposition. To gain a better understanding of the roles of intestinal metabolism and efflux, you agree to complete this in vitro study and submit the data for our review.

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, as per 21 CFR 314.82(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. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

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.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule

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

In addition, once the package insert has been finalized, please submit three copies of the introductory promotional materials that you propose to use for this/these product(s). All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Special Pathogen and Immunologic Drug Products and two copies of both the promotional materials and the package insert(s) 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.

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

Sincerely yours,

/S/

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