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.

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