DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21083/S-044 and S-047
NDA 21110/S-055 and S-057

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING COMMITMENT

Wyeth Pharmaceuticals, Inc.
Attention: Sharon Pfleger, M.S., RAC
Manager, Global Regulatory Affairs
PO Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Pfleger:

Please refer to your Supplemental New Drug Applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

NDA Number	Name of Drug Product	Supplement Number	Date of Supplement	Date of Receipt
021083	Rapamune® (sirolimus) Oral Solution, 1 mg/mL	S-044	September 8, 2010	September 8, 2010
021110	Rapamune® (sirolimus) Tablets, 1 mg, 2 mg, and 5 mg	S-055	September 8, 2010	September 8, 2010

We acknowledge receipt of your amendments dated November 22, 2010.

The September 8, 2010, submission constituted a complete response to our August 9, 2010, action letter. These supplemental applications consist of the proposed Risk Evaluation and Mitigation Strategy (REMS).

NDA Number	Name of Drug Product	Supplement Number	Date of Supplement	Date of Receipt
021083	Rapamune® (sirolimus) Oral Solution, 1 mg/mL	S-047	September 7, 2010	September 7, 2010
021110	Rapamune® (sirolimus) Tablets, 1 mg, 2 mg, and 5 mg	S-057	September 7, 2010	September 7, 2010

We acknowledge receipt of your amendments dated November 17, 2010.

These supplemental applications provide for revisions to the labeling for Rapamune® (sirolimus) and proposed medication guide.

A. SAFETY LABELING CHANGE

We also refer to our letter dated August 9, 2010 , notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Rapamune® (sirolimus). This information pertains to serious risk of hyperlipidemia that required treatment in up to 90% of patients and where lipid levels in a substantial number of patients exceeded the recommended normal target levels for cholesterol and trigylcerides despite antilipid management.

Your supplemental new drug applications NDA 21083/S-047 and NDA 21110/S-057 provide for revisions to the labeling for Rapamune® (sirolimus). The agreed upon changes to the language included in our August 9, 2010, letter are as follows (additions are noted by underline and deletion are noted by ~~strikethrough~~).

1. In the highlights section, the following has been revised as follows:

~~———~~ RECENT MAJOR CHANGES ———————

Dosage and Administration

• Therapeutic Drug Monitoring (*2.3*)	04/2010

Warnings and Precautions

• ~~Liver Transplantation (5.2)~~	~~09/2009~~
• Fluid Accumulation and Wound Healing (*5.6*)	04/2010
• Hyperlipidemia (*5.7*)	09/2010
• Latent Viral infections (*5.10*)	07/2010
• Assay for Sirolimus Therapeutic Drug Monitoring (*5.15*)	04/2010

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved ~~patient labeling~~Medication Guide.

2. 5 WARNINGS AND PRECAUTIONS

5.7 Hyperlipidemia

Increased serum cholesterol and triglycerides requiring treatment occurred more frequently in patients treated with Rapamune compared with azathioprine or placebo controls in Studies 1 and 2 [see Adverse Reactions (6.1)]. There were increased incidences of hypercholesterolemia (43-46%) and/or hypertriglyceridemia (45-57%) in patients receiving Rapamune compared with placebo controls (each 23%). The risk/benefit should be carefully considered in patients with established hyperlipidemia before initiating an immunosuppressive regimen including Rapamune.

Any patient who is administered Rapamune should be monitored for hyperlipidemia. If detected, interventions such as diet, exercise, and lipid-lowering agents should be initiated as outlined by the National Cholesterol Education Program guidelines.

In clinical trials~~,~~ of patients receiving Rapamune plus cyclosporine or Rapamune after cyclosporine withdrawal, up to 90% of patients required treatment for hyperlipidemia and hypercholesterolemia with anti-lipid therapy (e.g., statins, fibrates). Despite anti-lipid management, up to 50% of patients had fasting serum cholesterol levels > 240 mg/dL and triglycerides above recommended target levels. The~~the~~ concomitant administration of Rapamune and HMG-CoA reductase inhibitors~~and/or fibrates appeared to be well-tolerated.~~ resulted in adverse events such as CPK elevations (3%), myalgia (6.7%) and rhabdomyolysis (<1%). In these trials, the number of patients was too small and duration of follow-up too short to evaluate the long-term impact of Rapamune on cardiovascular mortality.

During Rapamune therapy with or without cyclosporine, patients who should be monitored for elevated lipids, and patients administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects, as described in the respective labeling for these agents.

3. **6 ADVERSE REACTIONS**

6.1 Clinical Studies Experience in Prophylaxis of Organ Rejection Following Renal Transplantation

Increased Serum Cholesterol and Triglycerides

The use of Rapamune in renal transplant patients was associated with increased serum cholesterol and triglycerides that may require treatment.

In Studies 1 and 2, in de novo renal transplant patients who began the study with fasting, total serum cholesterol < 200 mg/dL or fasting, total serum triglycerides < 200 mg/dL, there was an increased incidence of hypercholesterolemia (fasting serum cholesterol > 240 mg/dL) or hypertriglyceridemia (fasting serum triglycerides > 500 mg/dL), respectively, in patients receiving both Rapamune 2 mg and Rapamune 5 mg compared with azathioprine and placebo controls.

Treatment of new-onset hypercholesterolemia with lipid-lowering agents was required in 42-52% of patients enrolled in the Rapamune arms of Studies 1 and 2 compared with 16% of patients in the placebo arm and 22% of patients in the azathioprine arm. In other Rapamune renal transplant studies, up to 90% of patients required treatment for hyperlipidemia and hypercholesterolemia with anti-lipid therapy (e.g., statins, fibrates). Despite anti-lipid management, up to 50% of patients had fasting serum cholesterol levels > 240 mg/dL and triglycerides above recommended target levels [see Warnings and Precautions (5.7)].

4. **16 HOW SUPPLIED/STORAGE AND HANDLING**

Since Rapamune is not absorbed through the skin, there are no special precautions. However, if direct contact of the oral solution occurs with the skin or eyes~~mucous membranes occurs~~, wash skin thoroughly with soap and water; rinse eyes with plain water.

Do not use RAPAMUNE after the expiration date that is located on the blister and carton. The expiration date refers to the last day of that month.

5. **17 PATIENT COUNSELING INFORMATION**

Advise patients, their families, and their caregivers to read the Medication Guide and assist them in understanding its contents. The complete text of the Medication Guide is reprinted at the end of the document.
See FDA-Approved ~~Patient Labeling (17.4)~~ Medication Guide.

17.1 Dosage
Patients should be given complete dosage instructions [see *FDA-Approved Medication Guide~~Patient Counseling Information (17.4)~~*]

~~17.4 FDA-Approved Patient Labeling~~

6. The medication guide has been agreed upon as attached in the letter.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, Medication Guide, and Instructions for use) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your September 7, 2010, submission containing proposed carton and container labels. Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on November 17, 2010, as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 21083/S-047 and NDA 21110/ S-057**." Approval of this submission by FDA is not required before the labeling is used.

B. RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). The details of the REMS requirements were outlined in our REMS notification and complete response letter dated August 9, 2010.

Since Rapamune® (sirolimus) was approved on September 15, 1999 (NDA 21083, Oral Solution) and August 20, 2000 (NDA 21110, Tablets), we have become aware of the serious risk of hyperlipidemia which required treatment in up to 90% of patients and where lipid levels in a substantial number of patients exceeding the recommended normal target levels for cholesterol and triglycerides despite antilipid management. This information was submitted and received November 16, 2009 in response to a post marketing commitment trial. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

Your proposed REMS, submitted on November 11, 2010, and appended to this letter, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

a. An evaluation of patients' understanding of the serious risks of Rapamune® (sirolimus)
b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

Assessments of an approved REMS must include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 21083 and NDA 21110 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 21083 and NDA 21110
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 21083 and NDA 21110
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

C. FULFILLMENT OF POSTMARKETING COMMITMENT

We have received your submission on November 16, 2009 reporting on the following postmarketing commitment (PMC):

PMC 933-2
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.

We have reviewed your submissions and conclude that the above commitment was fulfilled. This completes all of your postmarketing commitments acknowledged in our September 15, 1999 letter.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Hyun Son, Pharm.D., Safety Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, M.D., MPH
Deputy Director for Safety
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

OZLEM A BELEN
11/23/2010