DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-083/S-034
NDA 21-110/S-045

Wyeth Pharmaceuticals, Inc.
Attention: David K. Ellis, Ph.D.
Assistant Vice President, Global Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Ellis:

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

NDA Number	Name of Drug Product	Supplement Number	Date of Supplement	Date of Receipt
21-083	Rapamune® (sirolimus) Oral Solution, 1 mg/mL	S-034	April 17, 2007	April 17, 2007
21-110	Rapamune® (sirolimus) Tablets, 1 mg, 2 mg, and 5 mg	S-045	April 17, 2007	April 17, 2007

These "Changes Being Effected" supplemental new drug applications provide for the following changes (underlined = added text, ~~strikethrough~~ = deleted text):

1. In the **INDICATIONS AND USAGE** section, the third paragraph has been revised as follows:

   In patients at high immunologic risk (defined as Black transplant recipients and/or repeat renal transplant recipients who lost a previous allograft for immunologic reason and/or patients with high-panel reactive antibodies [PRA; peak PRA level > 80%]), it is recommended that Rapamune be used in combination with cyclosporine and corticosteroids for the first year following transplantation (see **CLINICAL STUDIES, DOSAGE AND ADMINISTRATION**). The safety and efficacy of thi~~se~~s combination~~s~~ in high-risk patients have not been studied beyond one year; therefore, after the first year following transplantation, any adjustments to the immunosuppressive regimen should be considered on the basis of the clinical status of the patient.

2. The **WARNINGS** section has been revised as follows:

   Increased susceptibility to infection and the possible development of lymphoma and other malignancies, particularly of the skin, may result from immunosuppression (see **ADVERSE REACTIONS**). Oversuppression of the immune system can also increase susceptibility to infection including opportunistic infections such as tuberculosis, fatal infections, and sepsis. Only physicians experienced in immunosuppressive therapy and management of organ transplant

patients should use Rapamune. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

3. The **PRECAUTIONS/General** subsection has been revised as follows:

General
Rapamune is intended for oral administration only.

Fluid Accumulation and Wound Healing
mTOR inhibitors such as sirolimus have been shown in vitro to inhibit production of certain growth factors that may affect angiogenesis, fibroblast proliferation, and vascular permeability.

There have been reports of impaired or delayed wound healing in patients receiving Rapamune, including lymphocele and wound dehiscence (see **WARNINGS, ADVERSE REACTIONS, Other clinical experience)**. Lymphocele, a known surgical complication of renal transplantation, occurred significantly more often in a dose-related fashion in patients treated with Rapamune. Appropriate measures should be considered to minimize such complications. Patients with a body mass index (BMI) greater than 30 kg/m^2 may be at increased risk of abnormal wound healing based on data from the medical literature.

There have also been reports of fluid accumulation, including peripheral edema, lymphedema, pleural effusion and pericardial effusions (including hemodynamically significant effusions and tamponade requiring intervention in children and adults), in patients receiving Rapamune.

4. The **ADVERSE REACTIONS/Other clinical experience** subsection, has been revised as follows:

Other clinical experience: Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, exfoliative dermatitis, and hypersensitivity vasculitis, have been associated with the administration of sirolimus (see **WARNINGS**). Abnormal healing following transplant surgery has been reported, including fascial dehiscence, incisional hernia, and anastomotic disruption (e.g., wound, vascular, airway, ureteral, biliary) (see **WARNINGS**).

Cases of interstitial lung disease (including pneumonitis, and infrequently bronchiolitis obliterans organizing pneumonia [BOOP] and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving immunosuppressive regimens including Rapamune. In some cases, the interstitial lung disease has resolved upon discontinuation or dose reduction of Rapamune. The risk may be increased as the sirolimus trough concentration increases (see **PRECAUTIONS, General,** Interstitial Lung Disease). There have been reports of pulmonary hemorrhage. The concomitant use of sirolimus with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced HUS/TTP/TMA (see **PRECAUTIONS**).

Hepatotoxicity has been reported, including fatal hepatic necrosis, with elevated sirolimus trough concentrations. There have been reports of pericardial effusion (including hemodynamically significant effusions and tamponade requiring intervention in children and adults), pleural effusion, tuberculosis, neutropenia, proteinuria, nephrotic syndrome, pancytopenia, joint disorders, and

lymphedema. Azoospermia has been reported with the use of Rapamune and has been reversible upon discontinuation of Rapamune in most cases.

The safety and efficacy of conversion from calcineurin inhibitors to sirolimus in maintenance renal transplant population has not been established. In an ongoing study evaluating the safety and efficacy of conversion from calcineurin inhibitors to sirolimus (target concentrations of 12 - 20 ng/mL, by chromatographic assay) in maintenance renal transplant patients; enrollment was stopped in the subset of patients (n=90) with a baseline glomerular filtration rate of less than 40 mL/min. There was a higher rate of serious adverse events including pneumonia, acute rejection, graft loss and death in this sirolimus treatment arm. In addition, a 5-fold increase in the reports of tuberculosis among sirolimus (11/551) and comparator (1/273) treatment groups was observed with 2:1 randomization scheme.

We completed our review of these applications and they are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Submit revised content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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., Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Package Insert

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

/s/

Renata Albrecht

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