DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-083/S-022, S-023
NDA 21-110/S-030, S-031

Wyeth Pharmaceuticals, Inc.
Attention: David K. Ellis, Ph.D.
Senior Director
Worldwide Regulatory Affairs
Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Ellis:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

NDA	Drug Product	Supplement Number	Letter Date	Receipt Date
21-083	Rapamune® (sirolimus) Oral Solution, 1 mg/mL	S-022	April 12, 2005	April 13, 2005
		S-023	July 13, 2005	July 14, 2005
21-110	Rapamune® (sirolimus) Tablets, 1 mg, 2 mg	S-030	April 12, 2005	April 13, 2005
		S-031	July 13, 2005	July 14, 2005

We acknowledge receipt of your submissions dated August 3, 2005 to NDA 21-083/S-022 and NDA 21-110/S-030. In addition we acknowledge your submissions dated September 23, 2005 to NDA 21-083/S-022, S-023, NDA 21-110/S-030, and NDA 21-110/S-031.

These "Changes Being Effected (CBE)" supplemental new drug applications provide for the following revisions to the package insert (additions are double underlined):

1. "Angioedema" and "hypersensitivity vasculitis" were added to the second paragraph of the **WARNINGS** section:

   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, 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.

Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, and hypersensitivity vasculitis, have been associated with the administration of sirolimus (see **ADVERSE REACTIONS**).

2. A new subsection was created in the **PRECAUTIONS** section directly following the ***Renal Function*** subsection and contains the following text:

Calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA)
The concomitant use of sirolimus with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced HUS/TTP/TMA.

3. Under the **ADVERSE REACTIONS: Other clinical experience section**, the following additions were made:

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 neutropenia and rare reports of pancytopenia. Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, and hypersensitivity vasculitis, have been associated with the administration of sirolimus (see **WARNINGS**). Hepatotoxicity has been reported, including fatal hepatic necrosis with elevated sirolimus trough concentrations. There have been rare reports of lymphedema. Abnormal healing following transplant surgery has been reported, including fascial dehiscence and anastomotic disruption (e.g., wound, vascular, airway, ureteral, biliary). The concomitant use of sirolimus with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced HUS/TTP/TMA.

We have completed the review of these supplemental new drug applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text (enclosed). Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (text for the package insert submitted September 23, 2005).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submission in Electronic Format – NDA*. Alternatively, you may submit

20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions as "**FPL for approved supplements NDA 21-083/S-021, S-022 and NDA 21-110/S-030, S-031".** Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about these drug products (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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 call Christine Lincoln, RN, MS, MBA, Project Manager at (301) 796-0752.

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

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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