DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-083/S-031
NDA 21-110/S-039

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 supplemental 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-031 | November 1, 2006 | November 2, 2006 |
| 21-110 | Rapamune® (sirolimus) Tablets, 1 mg, 2 mg, and 5 mg | S-039 | November 1, 2006 | November 2, 2006 |

We acknowledge receipt of your submission dated April 27, 2007 and May 2, 2007.

These "Changes Being Effected" supplemental applications provide for several labeling revisions to the package insert, including the addition of a new subsection under **PRECAUTIONS** section, describing proteinuria observed in maintenance of renal transplant patients converted from calcineurin inhibitors to Rapamune. These supplements also provide for the following additional revisions:

- Addition of information concerning delayed recovery of renal function from delayed graft function in the **PRECAUTIONS** and **ADVERSE REACTIONS** section.
- Addition of the term "nephrotic syndrome" in the **ADVERSE REACTIONS** section.
- Addition of the term "exfoliative dermatitis" in the **WARNINGS** and **ADVERSE REACTIONS** section.

The proposed revisions to the package insert are listed below (<u>underlined</u> = added text):

1. The second paragraph of the **WARNINGS** section reads as follows:

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

2. In the **PRECAUTIONS** section, additional text was added at the end of the "Renal Function" subsection and a new "Proteinuria" subsection was added after the Renal Function subsection as follows:

   In patients with delayed graft function, Rapamune may delay recovery of renal function.

   Proteinuria
   In a study evaluating conversion from calcineurin inhibitors to sirolimus in maintenance renal transplant patients 6-120 months post-transplant, increased urinary protein excretion was commonly observed from 6 through 24 months after conversion to Rapamune. In general, those patients with the greatest amount of urinary protein excretion prior to sirolimus conversion were those whose protein excretion increased the most after conversion. New onset of nephrotic proteinuria was also reported. In some patients, reduction in the degree of urinary protein excretion was observed following discontinuation of sirolimus. Periodic quantitative monitoring of urinary protein excretion is recommended. The safety and efficacy of conversion from calcineurin inhibitors to Rapamune in maintenance renal transplant population has not been established.

3. In the **ADVERSE REACTIONS**, **Other clinical experience** subsection, the first paragraph was revised to read 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 and anastomotic disruption (e.g., wound, vascular, airway, ureteral, biliary) (see **WARNINGS**).

4. In the **ADVERSE REACTIONS**, **Other clinical experience** subsection, the fourth paragraph was revised to read as follows:

   Hepatotoxicity has been reported, including fatal hepatic necrosis, with elevated sirolimus trough concentrations. There have been reports of neutropenia, proteinuria, nephrotic syndrome, pancytopenia, joint disorders, and lymphedema.

5. The following sentence was added as the last sentence of the **ADVERSE REACTIONS, Other clinical experience** subsection:

   In patients with delayed graft function, Rapamune may delay recovery of renal function (see **PRECAUTIONS**).

We have completed our review of these applications, as amended. These applications 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 these NDAs 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 J. 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

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

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/s/

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Renata Albrecht

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