DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-083/S-036 and S-037
NDA 21-110/S-047 and S-048

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 for Rapamune® (sirolimus) Oral Solution, 1 mg/mL and Rapamune® (sirolimus) Tablets, 1 mg, 2 mg, and 5 mg.

**A. "Prior Approval" Labeling Supplements**

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-036 | September 5, 2007 | September 5, 2007 |
| 21-110 | Rapamune® (sirolimus) Tablets, 1 mg, 2 mg, and 5 mg | S-047 | September 5, 2007 | September 5, 2007 |

These supplemental new drug applications provide for the following revision to the text of the package insert (<u>double-underlined</u> = added text, ~~strikethrough text~~ = deletion):

1. The **HIGHLIGHTS OF PRESCRIBING INFORMATION/RECENT MAJOR CHANGES/Dosage and Administration** subsection has been revised as follows:

**Dosage and Administration**

- Tablet administration *(2)* 10/2007
- <u>Therapeutic drug monitoring *(2.3)* 3/2008</u>
- Patients with hepatic impairment *(2.5)* <u>3/2008</u>~~6/2007~~

2. The **FULL PRESCIRBING INFORMATION/2 DOSAGE AND ADMINISTRATION/ 2.3 Therapeutic Drug Monitoring** subsection has been revised as follows:

> **2.3 Therapeutic Drug Monitoring**
>
> Monitoring of sirolimus trough concentrations is recommended for all patients, especially in those patients likely to have altered drug metabolism, in patients ³ 13 years who weigh less than 40 kg, in patients with hepatic impairment, when a change in the Rapamune dosage form is made, and during concurrent administration of strong CYP3A4 inducers and inhibitors. [see Drug Interactions (7)].

3. The **FULL PRESCIRBING INFORMATION/2 DOSAGE AND ADMINISTRATION/ 2.5 Patients with Hepatic Impairment** subsection has been revised as follows:

> **2.5 Patients with Hepatic Impairment**
>
> It is recommended that the maintenance dose of Rapamune be reduced by approximately one third in patients with mild or moderate hepatic impairment and by approximately one half in patients with severe hepatic impairment. It is not necessary to modify the Rapamune loading dose. [see *Clinical Pharmacology (12.3)*].

4. The **FULL PRESCIRBING INFORMATION/12 CLINICAL PHARMACOLOGY/12.3 Pharmacokinetics/Pharmacokinetics in Specific Populations**/*Hepatic Impairment* subsection, the 2nd paragraph has been revised as follows:

> The maintenance dose of Rapamune should be reduced by approximately one third in patients with mild to moderate hepatic impairment and by approximately one half in patients with severe hepatic impairment [see *Dosage and Administration (2.5)*]. It is not necessary to modify the Rapamune loading dose in patients with mild, moderate, and severe hepatic impairment. Therapeutic drug monitoring is necessary in all patients with hepatic impairment [see *Dosage and Administration (2.3)*].

5. The **FULL PRESCIRBING INFORMATION/12 CLINICAL PHARMACOLOGY/12.3 Pharmacokinetics/Pharmacokinetics in Specific Populations**/*Renal Impairment* subsection has been revised as follows:

> *Renal Impairment*
>
> The effect of renal impairment on the pharmacokinetics of sirolimus is not known. However, there is minimal (2.2%) renal excretion of the drug or its metabolites in healthy volunteers The loading and the maintenance doses of Rapamune need not be adjusted in patients with renal impairment [see *Dosage and Administration (2.6)*].

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

**B. "Changes Being Effected" Labeling Supplements**

Please also 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-037 | October 2, 2007 | October 2, 2007 |
| 21-110 | Rapamune® (sirolimus) Tablets, 1 mg, 2 mg, and 5 mg | S-048 | October 2, 2007 | October 2, 2007 |

These supplemental new drug applications provide for the following revision to the text of the package insert (double-underlined = added text):

The **FULL PRESCIRBING INFORMATION/2 DOSAGE AND ADMINISTRATION** section of the label has been revised as follows:

> **2 DOSAGE AND ADMINISTRATION**
> Rapamune is to be administered orally once daily, consistently with or without food [*see Dosage and Administration (2.4), Clinical Pharmacology (12.3)*].
>
> Tablets should not be crushed, chewed or split. Patients unable to take the tablets should be prescribed the solution and instructed in its use.

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

Please 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. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate these submissions, **"SPL for approved NDA 21-083/S-036, S-037, and NDA 21-110/S-047, S-048."**

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Special Pathogen and Transplant Products and two copies of both the promotional materials and the package insert directly 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

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 Son, Pharm.D., Senior Regulatory Management Officer, 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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