DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-083/S-014
NDA 21-110/S-013

Wyeth Pharmaceuticals, Inc.
Attention: Diane Mitrione
Assistant Vice President
Worldwide Regulatory Affairs
Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Mitrione:

Please refer to your supplemental new drug applications, dated February 13, 2003, received February 14, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act:

NDA #	Drug Product	Supplement number
21-083	Rapamune® (sirolimus) Oral Solution, 1 mg/mL	S-014
21-110	Rapamune® (sirolimus) Tablets, 1 mg, 2 mg	S-013

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

1. DESCRIPTION

・Information concerning the 2 mg tablet was added to this section:

> Rapamune® is available for administration as an oral solution containing 1 mg/mL sirolimus ~~and.~~ Rapamune is also available as a white, triangular-shaped tablet containing 1 mg sirolimus, and as a yellow to beige triangular-shaped tablet containing 2 mg sirolimus.
>
> The 2 mg dosage strength also contains iron oxide yellow 10 and iron oxide brown 70.

2. WARNINGS

· The boxed warning located at the end of this section was revised to read:

Liver Transplantation – Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis (HAT):
The use of sirolimus in combination with tacrolimus was associated with excess mortality and graft loss in a study in de novo liver transplant recipients. Many of these patients had evidence of infection at or near the time of death.

In this and another study in de novo liver transplant recipients, the use of sirolimus in combination with cyclosporine or tacrolimus was associated with an increase in HAT; most cases of HAT occurred within 30 days post-transplantation and most led to graft loss or death. ~~The safety and efficacy of Rapamune® (sirolimus) as immunosuppressive therapy have not been established in liver or lung transplant patients, and therefore, such use is not recommended.~~

Lung Transplantation – Bronchial Anastomotic Dehiscence:
Cases of bronchial anastomotic dehiscence, most fatal, have been reported in de novo lung transplant patients when sirolimus has been used as part of an immunosuppressive regimen.

The safety and efficacy of Rapamune® (sirolimus) as immunosuppressive therapy have not been established in liver or lung transplant patients, and therefore, such use is not recommended.

3. HOW SUPPLIED

· Information concerning the 2 mg tablet was added to the end of this section:

2 mg, yellow to beige triangular-shaped tablets marked "RAPAMUNE 2 mg" on one side.
NDC # 0008-1032-05, bottle of 100 tablets.
NDC # 0008-1032-10, Redipak® cartons of 100 tablets (10 blister cards of 10 tablets each [2 x 5]).

4. The phrase "Rapamune treated patients" was changed to "patients treated with Rapamune" throughout the package insert.

We have completed the review of these supplemental new drug applications 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 final printed labeling submitted on February 13, 2003. Accordingly, these supplemental new drug applications are approved effective on the date of this letter.

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 Robin Anderson, Labeling Reviewer at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
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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