DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-083/S-005; S-007; S-008; S-009; S-010
NDA 21-110/S-001; S-005; S-007; S-009; S-010

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 listed below, which were submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act:

NDA #	Drug Product	Supplement number	Letter Date	Receipt Date
21-083	Rapamune® (sirolimus) Oral Solution, 1 mg/mL	S-005	January 26, 2001	January 29, 2001
		S-007	August 23, 2001	August 27, 2001
		S-008	November 28, 2001	November 30, 2001
		S-009	April 25, 2002	April 26, 2002
		S-010	May 6, 2002	May 7, 2002
21-110	Rapamune® (sirolimus) Tablets, 1 mg	S-001	January 26, 2001	January 29, 2001
		S-005	August 23, 2001	August 27, 2001
		S-007	November 28, 2001	November 30, 2001
		S-009	April 25, 2002	April 26, 2002
		S-010	May 6, 2002	May 7, 2002

We acknowledge receipt of your submissions dated February 2, 2001 (NDAs 21-083/S-005 and 21-110/S-001), and September 7, 2001 (NDAs 21-083/S-007 and 21-110/S-005).

These supplemental new drug applications provide for the following revisions to the package insert (additions are underlined and deletions are struck out):

- An editorial correction to the **DESCRIPTION** section:

  "The inactive ingredients in Rapamune® Oral Solution are Phosal 50 PG® (phosphatidylcholine, propylene glycol, ~~monodiglycerides~~ mono- and di-glycerides, ethanol, soy fatty acids, and ascorbyl palmitate) and polysorbate 80. Rapamune Oral Solution contains 1.5% - 2.5% ethanol."

- Correction of an error in the **CLINICAL PHARMACOLOGY/Absorption/*Food Effects*** subsection:

  "In 22 healthy volunteers receiving Rapamune Oral Solution, a high-fat meal ~~(1.88~~ (861.8 kcal, ~~54.7%~~ 54.9% kcal from fat) altered the bioavailability characteristics of sirolimus."

- Addition of a boxed warning to the **WARNINGS** section that provides information on excess mortality, graft loss, and hepatic artery thrombosis seen in two *de novo* liver transplantation studies:

  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 transplant patients, and therefore, such use is not recommended.

- Revisions to the **PRECAUTIONS/General** subsection:

  "In ~~the limited number of patients studied,~~ clinical trials, the concomitant administration of Rapamune and HMG-CoA reductase inhibitors and/or fibrates appeared to be well tolerated."

  "~~Nevertheless, all~~ During Rapamune therapy with cyclosporine, patients administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects as described in the respective labeling for these agents."

- An addition to the **PRECAUTIONS/Other Drug Interactions** subsection of the labeling to broaden the information about CY3A4 metabolism:

  "Care should be exercised when drugs or other substances that are metabolized by CYP3A4 are administered concomitantly with Rapamune."

- Addition of a new subsection, "*Herbal Preparations*," that contains information on the concomitant use of Rapamune® and St. John's Wort:

  "Herbal Preparations
  St John's Wort (*Hypericum perforatum*) induces CYP3A4 and P-glycoprotein. Since sirolimus is a substrate for both cytochrome CYP3A4 and P-glycoprotein, there is the

potential that the use of St. John's Wort in patients receiving Rapamune could result in reduced sirolimus levels."

- A revision of the **ADVERSE REACTIONS/Other clinical experience** section:

  "Cases of ~~pneumonitis~~ interstitial lung disease (including pneumonitis, and infrequently bronchiolitis obliterans organizing pneumonia [BOOP] and pulmonary fibrosis), some fatal, with no identified infectious etiology ~~,sometimes with an interstitial pattern,~~ have occurred in patients receiving immunosuppressive regimens including Rapamune. In some cases, the ~~pneumonitis~~ interstitial lung disease has resolved upon discontinuation ~~of Rapamune~~ or dose reduction of Rapamune. The risk may be increased as the trough Rapamune level increases."

  "Hepatotoxicity has been reported, including fatal hepatic necrosis with elevated sirolimus trough levels."

  "Abnormal healing following transplant surgery has been reported, including fascial dehiscence and anastomotic disruption (e.g., wound, vascular, airway, ureteral, biliary)."

- The addition of "pancytopenia" to the **ADVERSE REACTIONS/Other clinical experience** subsection:

  "There have been rare reports of pancytopenia."

- A revision of the **OVERDOSAGE** section:

  "In general, the adverse effects of overdose are consistent with those listed in the adverse reactions section (see **ADVERSE REACTIONS)."**

  "Based on the poor aqueous solubility and high erythrocyte and plasma protein binding of Rapamune, it is anticipated that Rapamune is not dialyzable to any significant extent."

- A revision to the third sentence of the **HOW SUPPLIED/Storage** subsection:

  "If necessary, the patient may store both the pouches and the bottles at room temperatures up to 25°C (77°F) for a short period of time (e.g., ~~several days, but not longer than 30 days~~ up to 24 hours for the pouches and not more than 15 days for the bottles)."

We have completed the review of these 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. Accordingly, these applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted May 6, 2002). In addition, all previous revisions as reflected in the most recently approved package insert must be included.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please mount individually ten of the copies on heavyweight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDAs (January 1999). For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 21-083/S-005, S-007, S-008, S-009, S-010 and

NDA 21-110/S-001, S-005, S-007, S-009, and S-010." Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about these drugs 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 this NDA 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 Matthew A. Bacho, Regulatory Project Manager, 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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NDA 21-083/S-005; 007; 008; 009; and 010. NDA 21-110/S-001; 005; 007; 009; and 010