DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-083/S-045
NDA 21-110/S-052

SUPPLEMENT APPROVAL

Wyeth Pharmaceuticals, Inc.
Attention: Donald G. Esherick
Director, Global Regulatory Affairs
P. O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Esherick:

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

NDA/Supplement Number	Drug Name	Document date	Receipt date
NDA 21-110/S-052	Rapamune (sirolimus) Tablets	August 7, 2009	August 7, 2009
NDA 21-083/S-045	Rapamune (sirolimus) Oral Solution	January 7, 2010	January 7, 2010

We acknowledge receipt of your submissions to NDA 21-110/S-052 dated November 6, 2009, December 4, 2009, and January 4, 2010.

These supplemental applications provide for revisions to the carton and immediate container labels for the Rapamune (sirolimus) Tablets (NDA 21-110) as well as the following revisions to the content of labeling for Rapamune (sirolimus) Tablets , NDA 21-110, and Rapamune (sirolimus) Oral Solution, NDA 21-083 (added text is indicated by underline, deleted text is indicated by ~~strikethrough~~).

HIGHLIGHTS OF PRESCRIBING INFORMATION

1. Under the **DOSAGE FORMS AND STRENGTHS**, **Rapamune Tablets** heading, the text is revised as follows:

   Rapamune Tablets: 0.5 mg, tan; 1 mg, white; 2 mg, yellow-to-beige (3.2)

FULL PRESCRIBING INFORMATION

2. Information on the addition of a new tablet strength is added under **3 DOSAGE FORMS AND STRENGTHS**, **3.2 Rapamune Tablets** as follows:

3.2 Rapamune Tablets

- 0.5 mg, tan, triangular-shaped tablets marked "RAPAMUNE 0.5 mg" on one side.
- 1 mg, white, triangular-shaped tablets marked "RAPAMUNE 1 mg" on one side.
- 2 mg, yellow-to-beige triangular-shaped tablets marked "RAPAMUNE 2 mg" on one side.

3. In section **6 ADVERSE REACTIONS**, **6.6 Postmarketing Experience, *Hematological/Lymphatic***, the reference number to the *Warnings and Precautions* section is revised as follows:

Hematological/Lymphatic – The concomitant use of Rapamune with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced HUS/TTP/TMA [see *Warnings and Precautions (~~5.1~~ 5.13)*]; pancytopenia, neutropenia.

4. In section **11 DESCRIPTION**, the second paragraph below the chemical structure is revised as follows:

Rapamune is available for administration as an oral solution containing 1 mg/mL sirolimus. Rapamune is also available as a tan, triangular-shaped tablet containing 0.5 mg sirolimus, as a white, triangular-shaped tablet containing 1 mg sirolimus, and as a yellow-to-beige triangular-shaped tablet containing 2 mg sirolimus.

5. Also in section **11 DESCRIPTION**, the fourth paragraph below the chemical structure is revised as follows:

The inactive ingredients in Rapamune Tablets include sucrose, lactose, polyethylene glycol 8000, calcium sulfate, microcrystalline cellulose, pharmaceutical glaze, talc, titanium dioxide, magnesium stearate, povidone, poloxamer 188, polyethylene glycol 20,000, glyceryl monooleate, carnauba wax, *dl*-alpha tocopherol, and other ingredients. The 0.5 mg and 2 mg dosage strengths also ~~contains iron oxide~~ contain yellow ~~10 and iron oxide~~ iron (ferric) oxide and brown ~~70.~~ iron (ferric) oxide.

6. In section **12 CLINICAL PHARMACOLOGY**, **12.3 Pharmacokinetics, Drug-Drug Interactions,** *Erythromycin*, the reference number to the *Warnings and Precautions* section has been modified as follows:

   Erythromycin: Erythromycin is a substrate and inhibitor of CYP3A4 and P-gp; co-administration of sirolimus oral solution or tablets and erythromycin is not recommended [see *Warnings and Precautions (~~5.1~~ 5.17), Drug Interactions (7.2)*]. The simultaneous oral administration of 2 mg daily of sirolimus oral solution and 800 mg q 8h of erythromycin as erythromycin ethylsuccinate tablets at steady state to 24 healthy volunteers significantly affected the bioavailability of sirolimus and erythromycin. Sirolimus C_{max} and AUC were increased 4.4- and 4.2-fold respectively and t_{max} was increased by 0.4 hr. Erythromycin C_{max} and AUC were increased 1.6- and 1.7-fold, respectively, and t_{max} was increased by 0.3 hr.

7. Section **16 HOW SUPPLIED/STORAGE AND HANDLING**, **16.2 Rapamune Tablets** has been revised as follows:

   16.2 Rapamune Tablets
   Rapamune Tablets are available as follows:

   - NDC 0008-1040-05, 0.5 mg, tan, triangular-shaped tablets marked "RAPAMUNE 0.5 mg" on one side; bottle containing 100 tablets.
   - NDC 0008-1040-10, 0.5 mg, tan, triangular-shaped tablets marked "RAPAMUNE 0.5 mg" on one side; in Redipak® cartons of 100 tablets (10 blister cards of 10 tablets each).
   - NDC 0008-1041-05, 1 mg, white, triangular-shaped tablets marked "RAPAMUNE 1 mg" on one side; bottle containing 100 tablets.
   - NDC 0008-1041-10, 1 mg, white, triangular-shaped tablets marked "RAPAMUNE 1 mg" on one side; in Redipak® cartons of 100 tablets (10 blister cards of 10 tablets each).
   - NDC 0008-1042-05, 2 mg, yellow-to-beige triangular-shaped tablets marked "RAPAMUNE 2 mg" on one side; bottle containing 100 tablets.

8. Section **17 PATIENT COUNSELING INFORMATION**, **17.2 Skin Cancer Events** is revised as follows:

   Patients should be told that exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor because of the increased risk for skin cancer [see *Warnings and Precautions (~~5.15~~ 5.16)]*.

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed upon labeling text of the content of labeling, which is identical to the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format submitted on January 4, 2010, and the agreed upon carton and immediate container labels submitted on August 7, 2009, to NDA 21-110/S-052.

CONTENT OF LABELING

Within 14 days from the date of this letter, please amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (CBE) supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format that includes the changes approved in these supplemental applications.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling for the package insert. For administrative purposes, please designate these submissions as "**SPL for approved NDA 21-083/S-045 and NDA 21-110/S-052**."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, which were submitted on August 7, 2009 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 21-110/S-052**." Approval of this submission by FDA is not required before the labeling is used.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

REPORTING REQUIREMENTS

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 Judit Milstein, Chief Project Management Staff, at (301) 796-0763.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, MD
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures: Content of Labeling
Carton and Container Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21110	SUPPL-52	WYETH PHARMACEUTICALS INC	RAPAMUNE (SIROLIMUS) 1MG TABLETS
NDA-21083	SUPPL-45	WYETH PHARMACEUTICALS INC	RAPAMUNE (SIROLIMUS)1MG/ML ORAL SOLUTION

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
01/25/2010