DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-083/S-042 and S-043
NDA 21-110/S-053 and S-054

SUPPLEMENT APPROVAL

Wyeth Pharmaceuticals, Inc.
Attention: David K. Ellis, PhD
Assistant Vice President, Regulatory Affairs
P. O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Ellis:

Please refer to your Supplemental New Drug Applications (sNDAs), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) as follows:

NDA/Supplement #	Drug name Dosage Form	Dated	Received on
NDA 21-083/S-042	Rapamune (sirolimus) Oral Solution	August 18, 2009	August 18, 2009
NDA 21-083/S-043	Rapamune (sirolimus) Oral Solution	October 26, 2009	October 27, 2009
NDA 21-110/S-053	Rapamune (sirolimus) Tablets	August 18, 2009	August 18, 2009
NDA 21-110/S-054	Rapamune (sirolimus) Tablets	October 26, 2009	October 27, 2009

We acknowledge receipt of your submission dated April 21, 2010, which constitutes a complete response to our Complete Response letter dated February 11, 2010 (for NDA 21-083/S-042 and NDA 21-110/S-053). This submission also contains revised labeling for NDA 21-083/S-043 and NDA 21-110/S-054.

These "Changes Being Effected" supplemental new drug applications provide for the following revisions to the content of labeling (added text is reflected with underline, deleted text is reflected with ~~strikethrough~~).

NDA 21-083/S-042 and NDA 21-110/S-053

HIGHLIGHTS OF PRESCRIBING INFORMATION

1. Under **RECENT MAJOR CHANGES**, the **Warnings and Precautions** subsection is revised as follows:

Warnings and Precautions	
Liver Transplantation (5.2)	9/2009
Fluid Accumulation and Wound Healing (5.6)	4/2010
Latent Viral Infections (5.10)	10/2009

FULL PRESCRIBING INFORMATION

2. In section **5 WARNINGS AND PRECAUTIONS, 5.6 Fluid Accumulation and Wound Healing** the second paragraph is revised as follows:

   There have also been reports of fluid accumulation, including peripheral edema, lymphedema, pleural effusion, ascites and pericardial effusions (including hemodynamically significant effusions and tamponade requiring intervention in children and adults), in patients receiving Rapamune.

3. In section **6 ADVERSE REACTIONS,** at the beginning of the **6.6 Postmarketing Experience** section, the ***Cardiovascular*** subsection is revised and a new ***Digestive System*** subsection is added as follows:

   - ***Body as a Whole*** – Lymphedema.

   - ***Cardiovascular*** – Pericardial effusion (including hemodynamically significant effusions and tamponade requiring intervention in children and adults) and fluid accumulation.

   - ***Digestive System***-Ascites

NDA 21-083/S-043 and NDA 21-110/S-054

HIGHLIGHTS OF PRESCRIBING INFORMATION

4. Under **RECENT MAJOR CHANGES**, the **Dosage and Administration** and **Warnings and Precautions** subsections are revised as follows:

Dosage and Administration	
Therapeutic Drug Monitoring (2.3)	4/2010

Warnings and Precautions	
Liver Transplantation (5.2)	9/2009
Latent Viral Infections (5.10)	10/2009
Assay for Sirolimus Therapeutic Drug Monitoring (5.15)	4/2010

FULL PRESCRIBING INFORMATION

5. In section **2 DOSAGE AND ADMINISTRATION**, the last paragraph of the **2.3 Therapeutic Drug Monitoring** subsection is revised as follows:

> The above recommended 24-hour trough concentration ranges for sirolimus are based on chromatographic methods. ~~On average, chromatographic methods (HPLC UV or LC/MS/MS) yield results that are approximately 20% lower that the immunoassay for whole blood concentration determination.~~ Currently in clinical practice, sirolimus whole blood concentrations are being measured by both chromatographic and immunoassay methodologies. Because the measured sirolimus whole blood concentrations depend on the type of assay used, the concentrations obtained by these different methodologies are not interchangeable [see *Warnings and Precautions (~~5.15~~* 5.15 , *Clinical Pharmacology (12.3)*]. Adjustments to the targeted range should be made according to the assay utilized to determine sirolimus trough concentrations. Since results are assay and laboratory dependent, and the results may change over time, adjustments to the targeted therapeutic range must be made with a detailed knowledge of the site-specific assay used. Therefore communication should be maintained with the laboratory performing the assay. A discussion of different assay methods is contained in Clinical Therapeutics, Volume 22, Supplement B, April 2000 [see *References (15)*].

6. In the **5 WARNINGS AND PRECAUTIONS** section, the **5.15 Assay for Sirolimus Therapeutic Drug Monitoring** subsection as been revised as follows:

> ~~The label-recommended 24-hour trough concentration ranges for sirolimus are based on chromatographic methods. Currently in clinical practice, sirolimus whole blood concentrations are being measured by both chromatographic and immunoassay methodologies. These concentration values are not interchangeable [see *Dosage and Administration (2.3), Clinical Pharmacology (12.3)*].~~Currently in clinical practice, sirolimus whole blood concentrations are being measured by various chromatographic and immunoassay methodologies. Patient sample concentration values from different assays may not be interchangeable [see *Dosage and Administration(2.3)*].

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, which is identical to the content of labeling submitted on April 21, 2010.

We also note that you have updated the following sections of the **FULL PRESCRIBING INFORMATION** of the content of labeling to provide consistency with cross-reference numbers.

7. In the **1 INDICATIONS AND USAGE**, the **1.1 Prophylaxis of Organ Rejection in Renal Transplantation** section, **In patients at high immunologic risk** subsection, the reference in the [see …*Clinical Studies*] is revised as follows:

   In patients at high-immunologic risk (defined as Black recipients and/or repeat renal transplant recipients who lost a previous allograft for immunologic reason and/or patients with high panel-reactive antibodies [PRA; peak PRA level > 80%]), it is recommended that Rapamune be used in combination with cyclosporine and corticosteroids for the first year following transplantation [see *Dosage and Administration (2.2), Clinical Studies (~~14.2~~14.3)*]

8. In the **1 INDICATIONS AND USAGE**, the **1.2 Limitations of Use** section, last paragraph, the reference in the [see *Clinical studies*] is revised as follows:

   The safety and efficacy of conversion from calcineurin inhibitors to Rapamune in maintenance renal transplant patients has not been established [see *Clinical Studies* (~~14.2~~) (14.4)]

9. In the **2 DOSAGE AND ADMINISTRATION**, the **2.2 Patients at High-Immunologic Risk** section, first paragraph, first sentence, the reference in the [see *Clinical Studies*] is revised as follows:

   In patients with high-immunologic risk, it is recommended that Rapamune be used in combination with cyclosporine and corticosteroids for the first 12 month following transplantation [see *Clinical Studies* ~~(14.2)~~ (14.3)].

10. In the **8 USE IN SPECIFIC POPULATIONS**, the last paragraph of the 8.4 Pediatric Use section, the reference in the [see *Clinical Studies*] is revised as follows:

    Safety and efficacy information from a controlled clinical trial in pediatric and adolescent (< 18 years of age) renal transplant patients judged to be at high-immunologic risk, defined as a history of one or more acute rejection episodes and/or the presence of chronic allograft nephropathy, do not support the chronic use of Rapamune Oral Solution or Tablets in combination with calcineurin inhibitors and corticosteroids, due to the higher incidence of lipid abnormalities and deterioration of renal function associated with these immunosuppressive regimens compared to calcineurin inhibitors, without increased benefit with respect to acute rejection, graft survival, or patient survival [see *Clinical Studies (~~14.5~~14.6)*]

CONTENT OF LABELING

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)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed content of labeling (text for the package insert and patient labeling), which was submitted on April 21, 2010. For administrative purposes, please designate this submission, "**SPL for NDA 21-083/S-042 and S-043** and **NDA 21-110/S-053 and S-054**."

Also, within 14 days from the date of this letter, please amend all pending supplemental applications for these NDAs, 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.

PROMOTIONAL MATERIALS

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the following address or by facsimile at 301-847-8444:

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

In addition, as required under 21 CFR 314.81(b)(3)(i), you must submit your updated final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA-2253, directly to the above address. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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 Christine Lincoln, RN, MPH, Regulatory Project Manager, at (301) 796-1600

Sincerely,

{See appended electronic signature page}

Ozlem Belen, MD, MPH
Deputy Director for Safety
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Content of Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21110	SUPPL-54	WYETH PHARMACEUTICALS INC	RAPAMUNE (SIROLIMUS) 1MG TABLETS
NDA-21110	SUPPL-53	WYETH PHARMACEUTICALS INC	RAPAMUNE (SIROLIMUS) 1MG TABLETS
NDA-21083	SUPPL-43	WYETH PHARMACEUTICALS INC	RAPAMUNE (SIROLIMUS)1MG/ML ORAL SOLUTION
NDA-21083	SUPPL-42	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/

OZLEM A BELEN
04/22/2010