DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-083/S-040
NDA 21-110/S-050

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 dated and received March 25, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rapamune (sirolimus) Oral Solution (NDA 21-083) and Rapamune (sirolimus), Tablets (NDA 21-110).

We acknowledge receipt of your submissions dated May 14, August 24, and September 14, 2009.

These "Prior Approval" supplemental new drug applications provide for the following revisions to the package insert for Rapamune (additions are reflected with underlined text, repositioning of text is reflected by double underline, and deletions are reflected with ~~strikethrough~~ text).

HIGLIGHTS OF PRESCRIBING INFORMATION

1. In the **BLACK BOX WARNING**, the text of the header is revised as follows:

   WARNING: IMMUNOSUPPRESSION, ~~EXCESS MORTALITY~~USE IS NOT RECOMMENDED IN ~~*DE NOVO*~~ LIVER ~~TRANSPLANTATION, AND BRONCHIAL ANASTOMOTIC DEHISCENCE~~ OR LUNG TRANSPLANT PATIENTS

2. The **RECENT MAJOR CHANGES** section is revised as follows:

~~**Indications and Usage**~~	
~~Patients at high immunologic risk~~ (**Warnings and Precautions**	
~~1.~~● Liver Transplantation (~~*1.1*~~*5.2*~~)~~)	~~1/2007~~ 09/2009
~~**Dosing and Administration**~~	
● ~~Tablet administration (2)~~	~~10/2007~~ ~~3/2008~~

• ~~Therapeutic drug monitoring (*2.3*)~~	~~3/2008~~
• ~~Patients with hepatic impairment (*2.5*)~~	
~~Warnings and Precautions~~	
• ~~Increased Susceptibility to Infection and the Possible Development of Lymphoma (*5.1*)~~	~~10/2007~~ ~~1/2007~~
• ~~Angioedema (*5.5*)~~	~~6/2007~~ ~~10/2007~~
• ~~Proteinuria (*5.9*)~~	
• ~~Fluid Accumulation and Wound Healing (*5.6*)~~	
~~Adverse Reactions~~	
• ~~Conversion from Calcineurin Inhibitors to Rapamune in Maintenance Renal Transplant Population (*6.4*)~~	~~10/2007~~
• ~~Postmarketing Experience (*6.6*)~~	~~10/2007~~

FULL PRESCRIBING INFORMATION: CONTENTS*

3. The **BOX WARNING** text is revised as follows:

BOX WARNING: IMMUNOSUPPRESSION, ~~EXCESS MORTALITY~~ USE IS NOT RECOMMENDED IN *~~DE NOVO~~* LIVER ~~TRANSPLANTATION, AND BRONCHIAL ANASTOMOTIC DEHISCENCE~~ OR LUNG TRANSPLANT PATIENTS

4. The **14 CLINICAL STUDIES** section is revised as follows:

14.1 Prophylaxis of Organ Rejection
14.2 Cyclosporine Withdrawal Study
14.3 High-Immunologic Risk Patients
14.4 Conversion from Calcineurin Inhibitors to Rapamune in Maintenance Renal Transplant Patients
~~14.5 Pediatrics~~ 14.5 Conversion from a CNI-based Regimen to a Sirolimus-based Regimen in Liver Transplant Patients
14.6 Pediatrics

FULL PRESCRIBING INFORMATION

5. The **BOX WARNING** header text is revised as follows:

BOX WARNING: IMMUNOSUPPRESSION, ~~EXCESS MORTALITY~~USE IS NOT RECOMMENDED IN *~~DE NOVO~~* LIVER ~~TRANSPLANTATION, AND BRONCHIAL ANASTOMOTIC DEHISCENCE~~ OR LUNG TRANSPLANT PATIENTS

6. The last bullet is repositioned as the first bullet under the "Increased Susceptibility to infection… " as follows:

Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of renal transplant patients should use Rapamune®. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient [see *Warnings and Precautions (5.1)*].

- **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 [see *Warnings and Precautions (5.2, 5.3)*].**

1 INDICATIONS AND USAGE

7. In the **1.1 Prophylaxis of Organ Rejection in Renal Transplantation/In patients at low- to moderate-immunologic risk** subsection, the reference has been revised as follows:

In patients at low- to moderate-immunologic risk, it is recommended that Rapamune be used initially in a regimen with cyclosporine and corticosteroids; cyclosporine should be withdrawn 2 to 4 months after transplantation [see *Dosage and Administration (~~2.2~~2.1)*].

5 WARNINGS AND PRECAUTIONS

8. The **5.2 Liver Transplantation –- Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis (HAT)** subsection is revised as follows:

The safety and efficacy of Rapamune as immunosuppressive therapy have not been established in liver transplant patients; therefore, such use is not recommended. The use of Rapamune has been associated with adverse outcomes in patients following liver transplantation, including excess mortality, graft loss and Hepatic Artery Thrombosis (HAT).

In a study in *de novo* liver transplant patients, the use of Rapamune in combination with tacrolimus was associated with excess mortality and graft loss ~~in a study in *de novo* liver transplant patients~~ (22% in combination versus 9% on tacrolimus alone). 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 patients, the use of Rapamune in combination with cyclosporine or tacrolimus was associated with an increase in HAT (7% in combination versus 2% in the control arm); most cases of HAT occurred within 30 days post-transplantation, and most led to graft loss or death.

~~The safety and efficacy of Rapamune as immunosuppressive therapy have not been established in liver transplant patients; therefore, such use is not recommended.~~

In a clinical study in stable liver transplant patients 6-144 months post-liver transplantation and receiving a CNI-based regimen, an increased number of deaths was observed in the group converted to a Rapamune-based regimen compared to the group who was continued on a CNI-based regimen, although the difference was not statistically significant (3.8% versus 1.4%) [see *Clinical Studies (14.5)*].

14 CLINICAL STUDIES

9. A new section titled **Conversion from a CNI-based Regimen to a Sirolimus-based Regimen in Liver Transplant Patients** is created under the original 14.5 subsection as follows:

14.5 Conversion from a CNI-based Regimen to a Sirolimus-based Regimen in Liver Transplant Patients

Conversion from a CNI-based regimen to a Rapamune-based regimen was assessed in stable liver transplant patients 6-144 months post-transplant. The clinical study was a 2:1 randomized, multi-center, controlled trial conducted at 82 centers globally, including the US and Europe, and was intended to show that renal function was improved by conversion from a CNI to Rapamune without adversely impacting efficacy or safety. A total of 607 patients were enrolled.

The study failed to demonstrate superiority of conversion to a Rapamune-based regimen compared to continuation of a CNI-based regimen in baseline-adjusted GFR, as estimated by Cockcroft-Gault, at 12 months (62 mL/min in the Rapamune conversion group and 63 mL/min in the CNI continuation group). The study also failed to demonstrate non-inferiority, with respect to the composite endpoint consisting of graft loss and death (including patients with missing survival data) in the Rapamune conversion group compared to the CNI continuation group (6.6% versus 5.6%). The number of deaths in the Rapamune conversion group (15/393, 3.8%) was higher than in the CNI continuation group (3/214, 1.4%), although the difference was not statistically significant. The rates of premature study discontinuation (primarily due to adverse events or lack of

efficacy), adverse events overall (infections, specifically), and biopsy-proven acute liver graft rejection at 12 months were all significantly greater in the Rapamune conversion group compared to the CNI continuation group.

10. Numbering for the original ~~**14.5**~~ **Pediatrics** is revised to **14.6 Pediatrics**

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

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 package insert. These revisions are terms of the NDA approval. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-083/S-040 and NDA 21-110/S-050.

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) 796-1600.

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: Package Insert

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21083	SUPPL-40	WYETH PHARMACEUTICALS INC	RAPAMUNE (SIROLIMUS)1MG/ML ORAL SOLUTION
NDA-21110	SUPPL-50	WYETH PHARMACEUTICALS INC	RAPAMUNE (SIROLIMUS) 1MG TABLETS

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
09/24/2009