



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 21-083/S-041  
NDA 21-110/S-051

**SUPPLEMENT APPROVAL**

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

Dear Dr. Ellis:

Please refer to your supplemental new drug application (NDA) dated August 5, 2009, and received on August 6, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NDA 21-083 Rapamune<sup>®</sup> (sirolimus) Oral Solution, 1 mg/mL and NDA 21-110 Rapamune<sup>®</sup> (sirolimus) Tablets 1 mg, 2 mg, and 5 mg.

We acknowledge receipt of your submission dated September 14, 2009 and October 2, 2009.

Reference is made to our letter dated July 7, 2009, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling of Rapamune<sup>®</sup> to address the risk of BK virus-associated nephropathy connected with the use of certain immunosuppressants.

We also refer to the letter we sent on September 1, 2009, informing you that we determined that a 30-day extension of the discussion period was warranted to allow us to complete our review and reach agreement on the content of the labeling. We also refer to modified labeling language that we sent to you on September 4, 2009.

These labeling supplements provide for the following changes to the package insert. (Underlined text = addition, strikethrough text = deletion)

1. The **HIGHLIGHTS OF PRESCRIBING INFORMATION** has been revised as follows:

<b>RECENT MAJOR CHANGES</b>	
Warnings and Precautions	
• Liver Transplantation (5.2)	9/2009
• Latent Viral Infections (5.10)	10/2009

**WARNINGS AND PRECAUTIONS**

- Hypersensitivity Reactions (5.4)
- Angioedema (5.5)
- Fluid Accumulation and Wound Healing (5.6)
- Hyperlipidemia (5.7)
- Renal Function (5.8)
- Proteinuria (5.9)
- Latent Viral Infections (5.10)
- Interstitial Lung Disease (5.10~~1~~)
- *De Novo* Use Without Cyclosporine (5.1~~2~~)
- Increased Risk of Calcineurin Inhibitor-induced HUS/TTP/TMA (5.1~~2~~~~3~~)

2. The **FULL PRESCRIBING INFORMATION: CONTENTS\*** has been revised as follows

**5 WARNINGS AND PRECAUTIONS**

- 5.1 Increased Susceptibility to Infection and the Possible Development of Lymphoma
- 5.2 Liver Transplantation – Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis (HAT)
- 5.3 Lung Transplantation – Bronchial Anastomotic Dehiscence
- 5.4 Hypersensitivity Reactions
- 5.5 Angioedema
- 5.6 Fluid Accumulation and Wound Healing
- 5.7 Hyperlipidemia
- 5.8 Renal Function
- 5.9 Proteinuria
- 5.10 Latent Viral Infections
- 5.10~~1~~ Interstitial Lung Disease
- 5.1~~2~~ *De Novo* Use Without Cyclosporine
- 5.1~~2~~~~3~~ Increased Risk of Calcineurin Inhibitor-Induced Hemolytic Uremic Syndrome/Thrombotic Thrombocytopenic Purpura/Thrombotic Microangiopathy (HUS/TTP/TMA)
- 5.1~~3~~~~4~~ Antimicrobial Prophylaxis
- 5.1~~4~~~~5~~ Assay for Sirolimus Therapeutic Drug Monitoring
- 5.1~~5~~~~6~~ Skin Cancer Events
- 5.1~~6~~~~7~~ Interaction with Strong Inhibitors and Inducers of CYP3A4 and/or P-gp

3. Section 5.10 has been added to the **WARNINGS AND PRECAUTIONS** section as follows:

**5.10 Latent Viral Infections**

Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include BK virus-associated nephropathy, which has been observed in patients receiving immunosuppressants, including Rapamune. This infection is associated with serious outcomes, including deteriorating renal function and renal graft loss [see *Adverse Reactions* (6.6)]. Patient monitoring may help detect patients at risk for BK virus-associated nephropathy. Reduction in immunosuppression should be considered for patients who develop evidence of BK virus-associated nephropathy.

4. The section numbers have been changed to be sequential after section **5.10 Latent Viral Infections**.
5. Section 6.6 Postmarketing Experience/Infections subsection has been revised as follows:

### **6.6 Postmarketing Experience**

- ***Infections*** – Tuberculosis. BK virus associated nephropathy has been observed in patients receiving immunosuppressants, including Rapamune. This infection is associated with serious outcomes, including deteriorating renal function and renal graft loss [see *Warnings and Precautions (5.10)*].

We have completed our review of these supplemental applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text (text for the package insert).

### **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/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert). 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 supplements NDA 21-083/S-041 and NDA 21-110/S-051**”.

In addition, within 21 days of the date of this letter, amend any pending applications for the NDA with content of labeling in structured product labeling (SPL) format to include the changes approved in this application. Failure to make these changes within the specified period of time could make your product misbranded under 21 USC 321(n) and 352(a).

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

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, please contact Hyun J. Son Pharm.D., Safety Regulatory Project Manager, at (301)796-1600.

Sincerely,

*{See appended electronic signature page}*

Ozlem Belen, M.D., 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-41	WYETH PHARMACEUTICALS INC	RAPAMUNE (SIROLIMUS) 1MG/ML ORAL SOLUTION
NDA-21110	SUPPL-51	WYETH PHARMACEUTICALS INC	RAPAMUNE (SIROLIMUS) 1MG TABLETS

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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OZLEM A BELEN  
10/08/2009