DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-083/S-049
NDA 21-110/S-059

SUPPLEMENTS APPROVAL

Wyeth Pharmaceuticals, Inc.
Attention: Sharon Pfleger, M.S., RAC
Manager, Global Regulatory Affairs
PO Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Pfleger:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received on January 13, 2011, and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product	NDA Number	Supplement Number
RAPAMUNE® (sirolimus) Oral Solution, 1 mg/mL	21-083	S-049
RAPAMUNE® (sirolimus) Tablets, 1 mg, 2 mg, and 5 mg	21-110	S-059

We acknowledge receipt of your amendments dated June 3 and June 30, 2011.

These prior approval supplemental new drug applications provide for revisions to the **Instructions for Use** section of the package insert and the carton label to enhance safe use of Rapamune® (sirolimus) and ensure consistency with the **Medication Guide**.

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

The revisions to the package insert including the **Instructions for Use** section and carton label were as follows (additions are noted with underline and deletions noted with ~~strikethrough~~):

1. The **RECENT MAJOR CHANGES** subsection of the **HIGHLIGHTS** section of the package insert was revised as follows:

~~**Dosage and Administration**~~
~~Therapeutic Drug Monitoring (*2.3*)~~ ~~04/2010~~

Warnings and Precautions

~~• Fluid Accumulation and Wound Healing (*5.6*)~~	~~04/2010~~
• Hyperlipidemia (*5.7*)	09/2010
• Latent Viral infections (*5.10*)	07/2010
~~• Assay for Sirolimus Therapeutic Drug Monitoring (*5.15*)~~	~~04/2010~~

2. Please see the revisions in the enclosed marked-up version of the **Instructions for Use** section of the package insert.

3. The carton label was revised to include the same revisions as those made in the **Instructions for Use** section of the package insert and is also enclosed.

4. The carton label was also revised as follows:

   - DISPENSE WITH MEDICATION GUIDE ENCLOSED OR PROVIDED SEPARATELY was added.

   - ~~"Patient Instructions for RAPAMUNE Administration"~~ was revised to Instructions for Use for RAPAMUNE (sirolimus) Oral Solution.

   - PROTECT FROM LIGHT was added.

   - ~~U.S. Patents: See package insert~~ was removed.

   - The following was revised:

     ~~**Patient Kit contains:**~~
     ~~1 bottle of 60 mL oral solution~~
     ~~1 bottle adapter assembly~~
     ~~30 disposable syringes and caps~~
     ~~1 syringe carrying case~~
     ~~Package Insert~~
     ~~Medication Guide~~

     to:

     Each RAPAMUNE Oral Solution carton contains:
     a) a 2 oz. (60 mL fill) amber glass bottle of sirolimus
     (concentration of 1 mg/mL
     b) 1 oral syringe adapter for fitting into the neck of the bottle
     c) enough disposable amber oral syringes and caps for daily dosing
     d) 1 carrying case

Also contains: Package Insert and Medication Guide

You will also need:
• glass or plastic cup
• 6 oz. of water or orange juice only

5. Minor editorial and formatting changes were made throughout all sections of the package insert.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide, and Instructions for Use), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for these NDAs, including 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 MS Word format, that includes the changes approved in these supplemental applications, as well as annual reportable changes and annotate each change. To facilitate review of your submissions, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement numbers and annual report date(s).

CARTON LABEL

We acknowledge your June 30, 2011 submissions containing final printed carton label.

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 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 Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES:

Edited versions of the **Instructions for Use** section of package insert and carton label
Revised Content of Labeling
Revised Carton Label

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
07/11/2011