DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-083/S-046
NDA 21-110/S-056

Wyeth Pharmaceuticals, Inc.
Attention: Sharon Pfleger
Manager, Worldwide Regulatory Affairs
P. O. Box 8299
Philadelphia, PA 19101-8299

Dear Ms. Pfleger:

Please refer to your Supplemental New Drug Applications dated and received May 18, 2010, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rapamune (sirolimus) Oral Solution (NDA 21-083) and Rapamune (sirolimus) Tablets (NDA 21-110).

We also refer to your amendments dated June 30, 2010.

These Prior Approval Supplemental New Drug Applications, submitted in response to the Division's Supplement Request letter dated February 10, 2010, provide for the following revisions to the package insert (additions are underlined):

1. The following two paragraphs were added at the end of the **5.10 Latent Viral Infections** section of the package insert:

   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 may be 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.

   <u>Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal have been reported in patients treated with immunosuppressants, including Rapamune. PML commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies and ataxia. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated. Consideration should be given to reducing the amount of immunosuppression in patients who develop PML. In transplant patients, physicians should also consider the risk that reduced immunosuppression represents to the graft.</u>

2. The following sentence was added in the **6.6 Postmarketing Experience**, ***Infections*** section:

- ***Infections*** – Tuberculosis. BK virus associated nephropathy has been observed in patients receiving immunosuppressants, including Rapamune. This infection may be associated with serious outcomes, including deteriorating renal function and renal graft loss. Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with immunosuppressants, including Rapamune [see Warnings and Precautions (5.10)].

We have completed the review of these supplemental new drug applications, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text (enclosed). Accordingly, these supplemental applications are approved effective on the date of this letter.

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), which was submitted on June 30, 2010. For administrative purposes, please designate this submission, "**SPL for NDA 21-083/S-046** and **NDA 21-110/S-056**."

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
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 call Diana Willard, Chief 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: LABELING

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21110	SUPPL-56	WYETH PHARMACEUTICALS INC	RAPAMUNE (SIROLIMUS) 1MG TABLETS
NDA-21083	SUPPL-46	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
07/02/2010