DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-083/S-048
NDA 21-110/S-058

SUPPLEMENT APPROVAL

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

Dear Ms. Pfleger:

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-048	Rapamune (sirolimus) Oral Solution	September 30, 2010	September 30, 2010
NDA 21-110/S-058	Rapamune (sirolimus) Tablets	September 30, 2010	September 30, 2010

These "Changes Being Effected" supplemental new drug applications provide for the following revisions to the package insert (additions are reflected as underlined text, deletions are reflected by ~~strikethrough~~ text):

1. In the **FULL PRESCRIBING INFORMATION, 6 ADVERSE REACTIONS**, under the **6.4 Conversion from Calcineurin Inhibitors to Rapamune in Maintenance** subsection, the first paragraph, second sentence is revised to read:

   The safety and efficacy of conversion from calcineurin inhibitors to Rapamune in maintenance renal transplant population have not been established [see *Clinical Studies (14.4)*]. In ~~an ongoing~~ a study evaluation the safety and efficacy of conversion form calcineurin inhibitors to Rapamune (initial target sirolimus concentrations of 12-20 ng/mL and then 8-20 ng/mL, by chromatographic assay) in maintenance renal transplant patients, enrollment was stopped in the subset of patients (n=87) with a baseline glomerular filtration rate of less than 40 m/L/min.

2. In the **FULL PRESCRIBING INFORMATION, 6 ADVERSE REACTIONS,** under the **6.6 Postmarketing Experience, *Infections***, the words "*Clostridium difficile* enterocolitis" are added at the end of the subsection to read:

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

We also note several editorial corrections that do not require our approval.

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

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), 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 labeling text for the package insert and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. 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 this NDA, 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 MS Word format that includes the changes approved in this supplemental application.

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) 796-0763.

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

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
11/08/2010