DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21083/S-051
NDA 21110/S-065

SUPPLEMENT APPROVAL

Wyeth Pharmaceuticals, Inc.,
a subsidiary of Pfizer, Inc.
Attention: Nhu Debi Tran, Pharm.D.
Director, Worldwide Regulatory Strategy
PO Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Tran:

Please refer to your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

NDA Number	Name of Drug Product	Supplement Number	Date of Submission	Date of Receipt
021083	Rapamune® (sirolimus) Oral Solution, 1 mg/mL	S-051	June 29, 2012	June 29, 2012
021110	Rapamune® (sirolimus) Tablets, 1 mg, 2 mg, and 5 mg	S-065	June 29, 2012	June 29, 2012

These "Prior Approval" supplemental new drug applications propose revisions to section 7.4 Inducers or Inhibitors of CYP3A4 and P-gp and section 12.3 Pharmacokinetics Other Drug-Drug Interactions to include hepatitis C protease inhibitors (e.g., boceprevir and telaprevir) as drugs that could potentially increase sirolimus blood concentrations as described below (added text is underlined, and deleted text is ~~strikethrough~~.)

A) The **RECENT MAJOR CHANGES** subsection of the **HIGHLIGHTS** section of the package insert has been deleted as follows:

~~**RECENT MAJOR CHANGES**~~
~~**Warnings and Precautions**~~

- ~~Hyperlipidemia (*5.7*) 09/2010~~
- ~~Latent Viral infections (*5.10*) 07/2010~~

B) 7.4 Inducers or Inhibitors of CYP3A4 and P-gp

Exercise caution when using sirolimus with drugs or agents that are modulators of CYP3A4 and P-gp. The dosage of Rapamune and/or the co-administered drug may need to be adjusted [see *Clinical Pharmacology (12.3)*].

- *Drugs that could increase sirolimus blood concentrations:*
  Bromocriptione, cimetidine, cisapride, clotrimazole, danazol, diltiazem, fluconazole, protease inhibitors (e.g., for HIV and ~~protesase inhibitors~~ hepatitis C that include drugs such as ~~(e.g.,~~ ritonavir, indinavir, boceprevir, and telaprevir), metoclopramide, nicardipine, troleandomycin, verapamil
- *Drugs and other agents that could decrease sirolimus concentrations:*
  Carbamazepine, phenobarbital, phenytoin, rifapentine, St. John's Wort (*Hypericum perforatum*)
- *Drugs with concentrations that could increase when given with Rapamune:*
  Verapamil

C) 12.3 Pharmacokinetics/Other Drug-Drug Interactions

Co-administration of Rapamune with other known strong inhibitors of CYP3A4 and/or P-gp (such as voriconazole, itraconazole, telithromycin, or clarithromycin) or other known strong inducers of CYP3A4 and/or P-gp (such as rifabutin) is not recommended [see *Warnings and Precautions (5.17), Drug Interactions (7.2)*]. In patients in whom strong inhibitors or inducers of CYP3A4 are indicated, alternative therapeutic agents with less potential for inhibition or induction of CYP3A4 should be considered.

Care should be exercised when drugs or other substances that are substrates and/or inhibitors or inducers of CYP3A4 are administered concomitantly with Rapamune. Other drugs that have the potential to increase sirolimus blood concentrations include (but are not limited to):
Calcium channel blockers: nicardipine.
Antifungal agents: clotrimazole, fluconazole.
Antibiotics: troleandomycin.
Gastrointestinal prokinetic agents: cisapride, metoclopramide.
Other drugs: bromocriptine, cimetidine, danazol, protease inhibitors (e.g., for HIV and hepatitis C that include drugs such as ritonavir, indinavir, boceprevir, and telaprevir). ~~HIV protease inhibitors (e.g. ritonavir, indinavir)~~

D) Medication Guide, under the section **Tell your doctor about all the medicines you take,**

Especially tell your doctor if you take:

- a medicine to lower your cholesterol or triglycerides
- cyclosporine (including Gengraf, Neoral, Sandimmune) or tacrolimus (Prograf) or other medicines that suppress the immune system
- an antibiotic
- an antifungal medicine

- a medicine for high blood pressure or heart problems
- an anti-seizure medicine
- medicines used to treat stomach acid, ulcers, or other gastrointestinal problems
- bromocriptine mesylate (Parlodel, Cycloset)
- danazol
- medicines to treat HIV or hepatitis C ~~an anti HIV medicine~~
- St. John's Wort

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 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 and Medication Guide), 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 this NDA, 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 this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, 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 number(s) and annual report date(s).

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

Sincerely,

{See appended electronic signature page}

Ozlem Belen, MD, MPH
Deputy Director for Safety
Division of Transplant and Ophthalmology 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
12/10/2012