DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-083/S-017
NDA 21-110/S-020

Wyeth Pharmaceuticals, Inc.
Attention: Randall B. Brenner
Associate Director, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Mr. Brenner:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act:

NDA Number	Supplement Number	Letter Date	Receipt Date	Drug Name
21-083	S-017	1/19/04	1/20/04	Rapamune® (sirolimus) Oral Solution
21-110	S-020	1/19/04	1/20/04	Rapamune® (sirolimus) Tablets

We acknowledge receipt of your submissions dated:

January 19, 2004
April 29, 2004
July 8, 2004
July 16, 2004

These "Changes Being Effected" supplemental new drug applications provide for the following revisions to the package insert (additions are double underlined and deletions are ~~strikethrough~~):

1. CLINICAL PHARMACOLOGY

- The following revisions were made in **Distribution**:

  The mean (± SD) blood-to-plasma ratio of sirolimus was 36 ± ~~17.9~~18 in stable renal allograft recipients after administration of oral solution, indicating that sirolimus is extensively partitioned into formed blood elements. The mean volume of distribution (V_{ss}/F) of sirolimus is 12 ± ~~7.52~~8 L/kg.

- The following information was added to **Metabolism**:

  Sirolimus is a substrate for both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein (P-gp). Sirolimus is extensively metabolized by the CYP3A4 isozyme in the intestinal wall and liver and undergoes counter-transport from enterocytes of the small intestine into the gut lumen by the P-gp drug efflux pump. Sirolimus is potentially recycled between enterocytes and the gut lumen to allow

continued metabolism by CYP3A4. Therefore, absorption and subsequent elimination of systemically absorbed sirolimus may be influenced by drugs that affect these proteins. Inhibitors of CYP3A4 and P-gp increase sirolimus concentrations. Inducers of CYP3A4 and P-gp decrease sirolimus concentrations. (See **WARNINGS** and **PRECAUTIONS, Drug Interactions** and **Other drug interactions**).

2. WARNINGS

- The following paragraph was added to the end of this section:

  Co-administration of sirolimus with strong inhibitors of CYP3A4 and/or P-gp (such as ketoconazole, voriconazole, itraconazole, erythromycin, telithromycin, or clarithromycin) or strong inducers of CYP3A4 and/or P-gp (such as rifampin or rifabutin) is not recommended (see **CLINICAL PHARMACOLOGY, Metabolism**, and **PRECAUTIONS, Drug Interactions** and **Other drug interactions**).

3. PRECAUTIONS

- The following information was added to the **Drug Interactions** section:

  Cyclosporine capsules MODIFIED:
  Cyclosporine is a substrate and inhibitor of CYP3A4 and P-gp.

  Because of the effect of cyclosporine capsules (MODIFIED), it is recommended that sirolimus should be taken 4 hours after administration of cyclosporine oral solution (MODIFIED) and/or cyclosporine capsules (MODIFIED) (see **DOSAGE AND ADMINISTRATION**).

  Studies assessing the effect of concomitant administration of cyclosporine capsules (MODIFIED) with sirolimus oral solution and with sirolimus tablets are summarized below.

- The following paragraph was added to the **Rapamune Oral Solution** subsection of the **Drug Interactions** section:

  In a single-dose cross-over drug-drug interaction study, 33 healthy volunteers received 5 mg sirolimus alone, 2 hours before, and 2 hours after a 300 mg dose of Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). When given 2 hours before Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]) administration, sirolimus C_{max} and AUC were comparable to those with administration of sirolimus alone. However, when given 2 hours after, the mean C_{max} and AUC of sirolimus were increased by 126% and 141%, respectively, relative to administration of sirolimus alone.

- The following paragraph was deleted from the **Rapamune Tablets** subsection of the **Drug Interactions** section:

  ~~Because of the effect of cyclosporine capsules (MODIFIED), it is recommended that sirolimus should be taken 4 hours after administration of cyclosporine oral solution (MODIFIED) and/or cyclosporine capsules (MODIFIED) (see **DOSAGE AND ADMINISTRATION**).~~

- The following paragraph of the **Drug Interactions** section was revised as indicated:

  Diltiazem: Diltiazem is a substrate and inhibitor of CYP3A4 and P-gp; sirolimus concentrations should be monitored and a dose adjustment may be necessary. The simultaneous oral administration of 10 mg of sirolimus oral solution and 120 mg of diltiazem to 18 healthy volunteers significantly affected the bioavailability of sirolimus. Sirolimus C_{max}, t_{max}, and AUC were increased 1.4-, 1.3-, and 1.6-fold, respectively. Sirolimus did not affect the pharmacokinetics of either diltiazem or its metabolites desacetyldiltiazem and desmethyldiltiazem. ~~If diltiazem is administered, sirolimus should be monitored and a dose adjustment may be necessary.~~

- The following information was added to the **Drug Interactions** section:

  Erythromycin: Erythromycin is a substrate and inhibitor of CYP3A4 and P-gp; co-administration of sirolimus oral solution or tablets and erythromycin is not recommended (see **WARNINGS**). The simultaneous oral administration of 2 mg of sirolimus oral solution and 800 mg q 8h of erythromycin as erythromycin ethylsuccinate tablets at steady state to 24 healthy volunteers significantly affected the bioavailability of sirolimus and erythromycin. Sirolimus C_{max} and AUC were increased 4.4- and 4.2-fold, respectively and t_{max} was increased by 0.4 hr. Erythromycin C_{max} and AUC were increased 1.6- and 1.7-fold, respectively, and t_{max} was increased by 0.3 hr.

- The following paragraph of the **Drug Interactions** section was revised as indicated:

  Ketoconazole: Ketoconazole is a strong inhibitor of CYP3A4 and P-gp; co-administration of sirolimus oral solution or tablets and ketoconazole is not recommended (see **WARNINGS**). Multiple-dose ketoconazole administration significantly affected the rate and extent of absorption and sirolimus exposure after administration of Rapamune® ~~(sirolimus)~~ Oral Solution, as reflected by increases in sirolimus C_{max}, t_{max}, and AUC of 4.3-fold, 38%, and 10.9-fold, respectively. However, the terminal $t_{1/2}$ of sirolimus was not changed. Single-dose sirolimus did not affect steady-state 12-hour plasma ketoconazole concentrations. ~~It is recommended that sirolimus oral solution and tablets should not be administered with ketoconazole.~~

- The following paragraph of the **Drug Interactions** section was revised as indicated:

  Rifampin: Rifampin is a strong inducer of CYP3A4 and P-gp; co-administration of sirolimus oral solution or tablets and rifampin is not recommended (see **WARNINGS**). Pretreatment of 14 healthy volunteers with multiple doses of rifampin, 600 mg daily for 14 days, followed by a single 20-mg dose of sirolimus oral solution, greatly increased sirolimus oral-dose clearance by 5.5-fold (range = 2.8 to 10), which represents mean decreases in AUC and C_{max} of about 82% and 71%, respectively. In patients where rifampin is indicated, alternative therapeutic agents with less enzyme induction potential should be considered.

- The following information was added to the **Drug Interactions** section:

  Verapamil: Verapamil is a substrate and inhibitor of CYP3A4 and P-gp; sirolimus concentrations should be monitored and a dose adjustment may be necessary. The simultaneous oral administration of 2 mg daily of sirolimus oral solution and 180 mg q 12h of verapamil at steady state to 26 healthy volunteers significantly affected the bioavailability of sirolimus and verapamil. Sirolimus C_{max} and AUC were increased 2.3- and 2.2-fold, respectively, without substantial change in t_{max}. The C_{max} and AUC of the pharmacologically active S(-) enantiomer of verapamil were both increased 1.5-fold and t_{max} was decreased by 1.2 hr.

- The following modifications were made to the **Other Drug Interactions** subsection:

  Co-administration of sirolimus with strong inhibitors of CYP3A4 and/or P-gp (such as ketoconazole, voriconazole, itraconazole, erythromycin, telithromycin, or clarithromycin) or strong inducers of CYP3A4 and/or P-gp (such as rifampin or rifabutin) is not recommended (see **WARNINGS**). Sirolimus is extensively metabolized by the CYP3A4 isoenzyme in the ~~gut~~intestinal wall and liver and undergoes counter-transport from enterocytes of the small intestine into the gut lumen by the P-gp drug efflux pump. Sirolimus is potentially recycled between enterocytes and the gut lumen to allow continued metabolism by CYP3A4. Therefore, absorption and the subsequent elimination of systemically absorbed sirolimus may be influenced by drugs that affect ~~this isoenzyme~~these proteins. Strong ~~I~~inhibitors of CYP3A4 and P-gp ~~may~~ significantly decrease the metabolism of sirolimus and increase sirolimus concentrations, while strong inducers of CYP3A4 and P-gp ~~may~~significantly increase the metabolism of sirolimus and decrease sirolimus concentrations.

  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.

  Sirolimus is a substrate for the multidrug efflux pump, P-gp in the small intestine. Therefore, absorption of sirolimus may be influenced by drugs that affect P-gp.

  Aside from those mentioned above, other ~~D~~drugs that ~~may~~increase sirolimus blood concentrations include (but are not limited to):

  Calcium channel blockers: nicardipine~~, verapamil~~.
  Antifungal agents: clotrimazole, fluconazole~~, itraconazole~~.
  ~~Macrolide a~~Antibiotics: ~~clarithromycin, erythromycin,~~ troleandomycin.
  Gastrointestinal prokinetic agents: cisapride, metoclopramide.
  Other drugs: bromocriptine, cimetidine, danazol, HIV-protease inhibitors (e.g., ritonavir, indinavir).

Aside from those mentioned above, other ~~D~~drugs that ~~may~~ decrease sirolimus concentrations include (but are not limited to):

Anticonvulsants: carbamazepine, phenobarbital, phenytoin.
Antibiotics: ~~rifabutin,~~ rifapentine.

~~This list is not all inclusive.~~

4. ADVERSE REACTIONS

- The following paragraph was added to the **Other Clinical Experience** subsection at the end of the **ADVERSE REACTIONS** section:

  The safety and efficacy of conversion from calcineurin inhibitors to sirolimus in maintenance renal transplant population has not been established. In an ongoing study evaluating the safety and efficacy of conversion from calcineurin inhibitors to sirolimus (target concentrations of 12 - 20 ng/mL) in maintenance renal transplant patients; enrollment was stopped in the subset of patients (n=90) with a baseline glomerular filtration rate of less than 40 mL/min. There was a higher rate of serious adverse events including pneumonia, acute rejection, graft loss and death in this sirolimus treatment arm.

5. DOSAGE AND ADMINISTRATION

- The seventh paragraph was modified with additional information as indicated:

  To minimize the variability of exposure to Rapamune, this drug should be taken consistently with or without food. Grapefruit juice reduces CYP3A4-mediated drug metabolism ~~of Rapamune~~ and potentially enhances P-gp mediated drug counter-transport from enterocytes of the small intestine. This juice must not be administered with Rapamune or used for dilution.

- The following paragraph of the **Blood Concentration Monitoring** subsection was modified as indicated:

  Whole blood trough concentrations of sirolimus should be monitored in patients receiving concentration-controlled Rapamune®. Monitoring is also necessary in pediatric patients, in patients with hepatic impairment, during concurrent administration of ~~strong~~ CYP3A4 and/or ~~p-glycoprotein~~P-gp inducers and inhibitors, and/or if cyclosporine dosage is markedly changed or discontinued (see **DOSAGE AND ADMINISTRATION**).

- The following subsection was removed from this section:

  ~~**Pouches**~~
  ~~When using the pouch, squeeze the entire contents of the pouch into only a glass or plastic container holding at least two (2) ounces (1/4 cup, 60 mL) of water or orange juice. No other liquids, including grapefruit juice, should be used for dilution. Stir vigorously and drink at once. Refill the container with an additional volume (minimum of four [4] ounces [1/2 cup, 120 mL] of water or orange juice, stir vigorously, and drink at once.~~

6. **HOW SUPPLIED**

- The following information was removed from this section:

  Rapamune® ~~(sirolimus)~~ Oral Solution is supplied at a concentration of 1 mg/mL in:

  ~~1.~~ Cartons:
  NDC # 0008-1030-06, containing a 2 oz (60 mL fill) amber glass bottle.
  ~~NDC # 0008-1030-15, containing a 5 oz (150 mL fill) amber glass bottle.~~

  In addition to the bottles, each carton is supplied with an oral syringe adapter for fitting into the neck of the bottle, sufficient disposable amber oral syringes and caps for daily dosing, and a carrying case.

  Rapamune® Tablets are available as follows:

  ~~2. Cartons:~~
  ~~NDC # 0008-1030-03, containing 30 unit of use laminated aluminum pouches of 1 mL.~~
  ~~NDC # 0008-1030-07, containing 30 unit of use laminated aluminum pouches of 2 mL.~~
  ~~NDC # 0008-1030-08, containing 30 unit of use laminated aluminum pouches of 5 mL.~~

- The following paragraph was modified in the **Storage** subsection:

  Rapamune® Oral Solution bottles ~~and pouches~~ should be stored protected from light and refrigerated at 2°C to 8°C (36°F to 46°F). Once the bottle is opened, the contents should be used within one month. If necessary, the patient may store ~~both the pouches and~~ the bottles at room temperatures up to 25°C (77°F) for a short period of time (e.g., ~~up to 24 hours for the pouches and~~ not more than 15 days for the bottles).

7. PATIENT INSTRUCTIONS

- The **PATIENT INSTRUCTIONS FOR RAPAMUNE® (SIROLIMUS) ORAL SOLUTION ADMINISTRATION/Pouches** section was removed.

8. Multiple **minor editorial changes** were made throughout the label**.**

We completed our review of these applications, as amended, 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 applications are approved, effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) submitted on July 16, 2004.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the

following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling to be submitted in *pdf* format. To assist in our review of the FPL and future submissions, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert) are submitted electronically, labeling does not need to be submitted in paper. For administrative purposes, these submissions should be designated **"FPL for approved supplement NDA 21-083/S-017 and NDA 21-110/S-020."** Approval of these submissions by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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 Rebecca D. Saville, Pharm.D., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

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

/s/

Renata Albrecht

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