DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-083/S-029
NDA 21-110/S-037

Wyeth Pharmaceuticals, Inc.
Attention: David K. Ellis, Ph.D.
Assistant Vice President, Global Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Ellis:

Please refer to your New Drug Applications for Rapamune® (sirolimus) Oral Solution and Rapamune® (sirolimus) Tablets as follows:

NDA Number	Name of Drug Product	Supplement Number	Date of Supplement	Date of Receipt
21-083	Rapamune® (sirolimus) Oral Solution, 1 mg/mL	S-029	March 29, 2006	March 30, 2006
21-110	Rapamune® (sirolimus) Tablets, 1 mg, 2 mg, and 5 mg	S-037	March 29, 2006	March 30, 2006

We acknowledge receipt of your submission dated:

June 12, 2006
August 3, 2006
January 4, 2007
January 29, 2007

These supplemental new drug applications provide for the addition of new dosing recommendations for use of Rapamune® (in combination with cyclosporine) for the prophylaxis of rejection in high-risk renal transplant recipients.

We have completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, with the labeling changes included in this letter.

We note that the Changes Being Effected (CBE) supplemental applications for NDA ~~--- ----------~~ and NDA ~~----------~~ submitted November 1, 2006 are still under review. We request that you submit revised labeling to these pending CBE applications incorporating the changes approved in this letter.

Approved revisions to the package insert (~~strikethrough~~ = deleted text, underlined = added text and dotted underlined = text previously approved in other submissions that has been relocated) include:

1. In the **CLINICAL PHARMACOLOGY, Pharmacokinetics in renal transplant patients** section, the title of the third table reads as follows:

AVERAGE RAPAMUNE DOSES AND SIROLIMUS TROUGH CONCENTRATIONS (MEAN ± SD) IN LOW- TO MODERATE- RISK RENAL TRANSPLANT PATIENTS AFTER MULTIPLE DOSE TABLET ADMINISTRATION

2. The last section within **Pharmacokinetics in renal transplant patients** has been revised as follows:

Average Rapamune doses and sirolimus whole blood trough concentrations for tablets administered daily in combination with cyclosporine and corticosteroids in high-risk renal transplant patients (Study 5; see **CLINICAL STUDIES**) are summarized in the table below.

AVERAGE RAPAMUNE DOSES AND SIROLIMUS TROUGH CONCENTRATIONS(MEAN ± SD) IN HIGH-RISK RENAL TRANSPLANT PATIENTS AFTER MULTIPLE-DOSE TABLET ADMINISTRATION

	Rapamune with Cyclosporine Therapy
Rapamune Dose (mg/day)	
Months 3 to 6	5.1 ± 2.4
Months 6 to 9	5.1 ± 2.3
Months 9 to 12	5.0 ± 2.3
Sirolimus C_{min} (ng/mL)[a]	
Months 3 to 6[b]	11.8 ± 4.2
Months 6 to 9[c]	11.3 ± 5.2
Months 9 to 12[d]	11.2 ± 3.8

a: Expressed by chromatography
b: n=109
c: n=113
d: n=127

3. In the **CLINICAL STUDIES** section, second to the last paragraph reads as follows:

High-Risk Patients: Rapamune was studied in a one-year, clinical trial in high-risk patients (Study 5) who were defined as Black transplant recipients and/or repeat renal transplant recipients who lost a previous allograft for immunologic reason and/or patients with high-panel reactive antibodies (PRA; peak PRA level > 80%). Patients received concentration-controlled sirolimus and cyclosporine (MODIFIED), and corticosteroids per local practice. Antibody induction was allowed per protocol as prospectively defined at each transplant center, and was used in 88.4% of patients. The study was conducted at 35 centers in the United States. At total of 224 patients received a transplant and at least one dose of sirolimus and cyclosporine and was comprised of 77.2% Black patients, 24.1% repeat renal transplant recipients, and 13.5% patients with high PRA. Efficacy was assessed with the following endpoints, measured at 12 months: efficacy failure (defined as the first occurrence of biopsy-confirmed acute rejection, graft loss, or death), first occurrence of graft loss or death, and renal function as measured by the calculated GFR using the Nankivell formula. The table below summarizes the results of these endpoints.

EFFICACY FAILURE, GRAFT LOSS OR DEATH AND CALCULATED GLOMERULAR FUNCTION RATES (mL/min) BY NANKIVELL EQUATION AT 12 MONTHS POST-TRANSPLANT: STUDY 5

Parameter	Rapamune with Cyclosporine, Corticosteroids (n = 224)
Efficacy Failure (%)	23.2
Graft Loss or Death (%)	9.8
Renal Function (mean ± SEM)[a, b]	52.6 ± 1.6 (n = 222)

a: Calculated glomerular filtration rate by Nankivell equation
b: Patients who had graft loss were included in this analysis with GFR set to 0.

Patient survival at 12 months was 94.6%. The incidence of biopsy-confirmed acute rejection was 17.4% and the majority of the episodes of acute rejection were mild in severity.

4. In the **INDICATIONS AND USAGE** section, the second, third and last paragraphs were modified as follows:

In patients at low to moderate immunologic risk, it~~It~~ is recommended that Rapamune be used initially in a regimen with cyclosporine and corticosteroids~~. In patients at low to moderate immunologic risk~~ cyclosporine should be withdrawn 2 to 4 months after transplantation and the Rapamune® dose should be increased to reach recommended blood concentrations (see **DOSAGE AND ADMINISTRATION**). Cyclosporine withdrawal has not been studied in patients with Banff grade III acute rejection or vascular rejection prior to cyclosporine withdrawal, those who are dialysis-dependent, or with serum creatinine > 4.5 mg/dL, black patients, re-transplants, multi-organ transplants, or patients with high-panel reactive antibodies (see **CLINICAL STUDIES**).

In patients at high immunologic risk (defined as Black transplant recipients and/or repeat renal transplant recipients who lost a previous allograft for immunologic reason and/or patients with high-panel reactive antibodies [PRA; peak PRA level > 80%]), it is recommended that Rapamune be used in combination with cyclosporine and corticosteroids for the first year following transplantation (see **CLINICAL STUDIES, DOSAGE AND ADMINISTRATION**). The safety and efficacy of ~~cyclosporine withdrawal~~these combinations in high-risk patients have not been ~~adequately~~ studied beyond one year~~; and it is therefore not recommended. This includes patients with Banff grade III acute rejection or vascular rejection prior to cyclosporine withdrawal, those who are dialysis-dependent, or with serum creatinine > 4.5 mg/dL, black patients, re-transplants, multi-organ transplants, patients with high panel of reactive antibodies (See **CLINICAL STUDIES**).~~ therefore, after the first year following transplantation, any adjustments to the immunosuppressive regimen should be considered on the basis of the clinical status of the patient.

In pediatric patients, the~~The~~ safety and efficacy of Rapamune® have not been established in ~~pediatric~~ patients less than 13 years old, or in pediatric (< 18 years) renal transplant recipients considered at high immunologic risk (see **PRECAUTIONS, Pediatric use**, and **CLINICAL STUDIES, Pediatrics**).

5. The 6th and 7th paragraphs of the **WARNINGS** section were revised as follows:

Renal function should be closely monitored during the co-administration of Rapamune® ~~in combination~~ with cyclosporine ~~since~~because long-term administration of the combination ~~can~~has been associated with deterioration of renal function. Appropriate adjustment of the immunosuppression regimen, including discontinuation of Rapamune and/or cyclosporine, should be considered in patients with elevated or increasing serum creatinine levels. Caution should be exercised when using other drugs which are known to impair renal function. In patients at low to moderate immunologic risk continuation of combination therapy with cyclosporine beyond 4 months following transplantation should only be considered when the benefits outweigh the risks of this combination for the individual patients (see **PRECAUTIONS**).

In clinical trials, Rapamune has been administered concurrently with corticosteroids and with ~~the following formulations of~~ cyclosporine. The formulations of cyclosporine include:

6. Under **ADVERSE REACTIONS**, after **Rapamune following cyclosporine withdrawal** section, a new section was inserted as follows:

High-Risk Patients: Safety was assessed in (see **CLINICAL STUDIES**) 224 patients who received at least one dose of sirolimus with cyclosporine. Overall, the incidence and nature of adverse events was similar to those seen in previous combination studies with Rapamune. The incidence of malignancy was 1.3% at 12 months.

7. The **DOSAGE AND ADMINISTRATION** section was revised as follows:

In patients at low to moderate immunologic risk, it~~It~~ is recommended that Rapamune Oral Solution and Tablets be used initially in a regimen with cyclosporine and corticosteroids~~.~~; ~~C~~cyclosporine should be withdrawn~~al is recommended~~ 2 to 4 months after transplantation ~~in patients at low to moderate immunologic risk~~, and the Rapamune dose should be increased to reach recommended blood concentrations. Cyclosporine withdrawal has not been studied in patients with Banff grade III acute rejection or vascular rejection prior to cyclosporine withdrawal, those who are dialysis-dependent, or with serum creatinine > 4.5 mg/dL, black patients, re-transplants, multi-organ transplants, or patients with high-panel reactive antibodies (See **INDICATIONS AND USAGE** and **CLINICAL STUDIES**).

Rapamune and cyclosporine combination-therapy

For *de novo* transplant recipients, a loading dose of Rapamune corresponding to 3 times the maintenance dose should be given. A daily maintenance dose of 2-mg is recommended for use in renal transplant patients, with a loading dose of 6 mg. Although a daily maintenance dose of 5 mg, with a loading dose of 15 mg was used in clinical trials of the oral solution and was shown to be safe and effective, no efficacy advantage over the 2-mg dose could be established for renal transplant patients. Patients receiving 2 mg of Rapamune Oral Solution per day

demonstrated an overall better safety profile than did patients receiving 5 mg of Rapamune Oral Solution per day.

Rapamune following cyclosporine withdrawal

Initially, patients considered for cyclosporine withdrawal should be receiving Rapamune and cyclosporine combination therapy. At 2 to 4 months following transplantation, cyclosporine should be progressively discontinued over 4 to 8 weeks and the Rapamune® dose should be adjusted to obtain whole blood trough concentrations within the range of 12 to 24 ng/mL (chromatographic method). Therapeutic drug monitoring should not be the sole basis for adjusting Rapamune therapy. Careful attention should be made to clinical signs/symptoms, tissue biopsy, and laboratory parameters. Cyclosporine inhibits the metabolism and transport of sirolimus, and consequently, sirolimus concentrations will decrease when cyclosporine is discontinued unless the Rapamune dose is increased. The Rapamune® dose will need to be approximately 4-fold higher to account for both the absence of the pharmacokinetic interaction (approximately 2-fold increase) and the augmented immunosuppressive requirement in the absence of cyclosporine (approximately 2-fold increase).

In patients at high immunologic risk (defined as Black transplant recipients and/or repeat renal transplant recipients who lost a previous allograft for immunologic reason and/or patients with high-panel reactive antibodies [PRA; peak PRA level > 80%]), it is recommended that Rapamune be used in combination with cyclosporine and corticosteroids for the first year following transplantation (see **CLINICAL STUDIES**). The safety and efficacy of ~~cyclosporine withdrawal~~this combination in high-risk patients has not been ~~adequately~~ studied beyond one year.~~and it is therefore not recommended. This includes patients with Banff grade III acute rejection or vascular rejection prior to cyclosporine withdrawal, those who are dialysis-dependent, or with serum creatinine > 4.5 mg/dL, black patients, re-transplants, multi-organ transplants, patients with high panel of reactive antibodies (See **INDICATIONS AND USAGE** and **CLINICAL STUDIE**S)~~. Therefore, after the first year following transplantation, any adjustments to the immunosuppressive regimen should be considered on the basis of the clinical status of the patient.

~~Two-mg of Rapamune oral solution has been demonstrated to be clinically equivalent to 2-mg Rapamune oral tablets and hence, are interchangeable on a mg to mg basis. However, it is not known if higher doses of Rapamune oral solution are clinically equivalent to higher doses of tablets on a mg to mg basis. (See **CLINICAL PHARMACOLOGY: Absorption**). Rapamune is to be administered orally once daily.~~

~~**Rapamune and cyclosporine combination therapy:** The initial dose of Rapamune should be administered as soon as possible after transplantation. For *de novo* transplant recipients, a loading dose of Rapamune of 3 times the maintenance dose should be given. A daily maintenance dose of 2 mg is recommended for use in renal transplant patients, with a loading dose of 6 mg. Although a daily maintenance dose of 5 mg, with a loading dose of 15 mg was used in clinical trials of the oral solution and was shown to be safe and effective, no efficacy advantage over the 2-mg dose could be established for renal transplant patients. Patients receiving 2 mg of Rapamune Oral Solution per day demonstrated an overall better safety profile than did patients receiving 5 mg of Rapamune Oral Solution per day.~~

~~**Rapamune following cyclosporine withdrawal:** Initially, patients considered for cyclosporine withdrawal should be receiving Rapamune and cyclosporine combination therapy. At 2 to 4 months following transplantation, cyclosporine should be progressively discontinued over 4 to 8 weeks and the Rapamune® dose should be adjusted to obtain whole blood trough concentrations within the range of 12 to 24 ng/mL (chromatographic method). Therapeutic drug monitoring should not be the sole basis for adjusting Rapamune therapy. Careful attention should be made to clinical signs/symptoms, tissue biopsy, and laboratory parameters. Cyclosporine inhibits the metabolism and transport of sirolimus, and consequently, sirolimus concentrations will decrease when cyclosporine is discontinued unless the Rapamune dose is increased. The Rapamune® dose will need to be approximately 4-fold higher to account for both the absence of the pharmacokinetic interaction (approximately 2-fold increase) and the augmented immunosuppressive requirement in the absence of cyclosporine (approximately 2-fold increase).~~

For patients receiving Rapamune with cyclosporine, Rapamune therapy should be initiated with a loading dose of up to 15 mg on day 1 post-transplantation. Beginning on day 2, an initial maintenance dose of 5 mg/day should be given. A trough level should be obtained between days 5 and 7, and the daily dose of Rapamune should thereafter be adjusted (See **Blood Concentration Monitoring**).

The starting dose of cyclosporine should be up to 7 mg/kg/day in divided doses and the dose should subsequently be adjusted to achieve target whole blood trough concentrations (See **Blood Concentration Monitoring**). Prednisone should be administered at a minimum of 5 mg/day.

Antibody induction therapy may be used**.**

Rapamune use in all renal allograft recipients. The initial dose of Rapamune should be administered as soon as possible after transplantation. Frequent Rapamune® dose adjustments based on non-steady-state sirolimus concentrations can lead to overdosing or underdosing because sirolimus has a long half-life. Once Rapamune® maintenance dose is adjusted, patients should be retained on the new maintenance dose at least for 7 to 14 days before further dosage adjustment with concentration monitoring. In most patients dose adjustments can be based on simple proportion: new Rapamune® dose = current dose x (target concentration / current concentration). A loading dose should be considered in addition to a new maintenance dose when it is necessary to considerably increase sirolimus trough concentrations: Rapamune® loading dose = 3 x (new maintenance dose - current maintenance dose). The maximum Rapamune® dose administered on any day should not exceed 40 mg. If an estimated daily dose exceeds 40 mg due to the addition of a loading dose, the loading dose should be administered over 2 days. Sirolimus trough concentrations should be monitored at least 3 to 4 days after a loading dose(s).

Two-mg of Rapamune oral solution has been demonstrated to be clinically equivalent to 2-mg Rapamune oral tablets and hence, are interchangeable on a mg to mg basis. However, it is not known if higher doses of Rapamune oral solution are clinically equivalent to higher doses of tablets on a mg to mg basis. (See **CLINICAL PHARMACOLOGY: Absorption**.) Rapamune is to be administered orally once daily.

8. The fourth paragraph of the **DOSAGE AND ADMINISTRATION, Blood Concentration Monitoring** section reads as follows:

In a concentration-controlled clinical trial in high-risk adult patients (Study 5), the mean whole blood trough concentrations of sirolimus and cyclosporine, during 12 months following transplantation, were as follows:

Drug	Period post-transplant	Protocol-specified target Cmin range (ng/mL)	Mean ± SD Cmin	Observed Cmin range (10^{th} to 90^{th} percentile)
Sirolimus (given with cyclosporine)	Up to Week 2	10-15	15.7 ± 10.0	5.4 – 27.3
	Week 2 to Week 26	10-15	11.8 ± 5.3	6.2 – 16.9
	Week 26 to Week 52	10-15	11.5 ± 4.8	6.3 – 17.4
Cyclosporine	Up to Week 2	200-300	216.9 ± 135.4	56.0 – 432.0
	Week 2 to Week 26	150-200	173.8 ± 104.7	71.0 – 288.0
	Week 26 to Week 52	100-150	135.8 ± 109.5	54.5 – 217.5

Sirolimus was measured by HPLC; cyclosporine was measured by monoclonal TDx or equivalent assay.

Submit revised content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to Division of Special Pathogen and Transplant Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

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
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

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}

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

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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