DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-083/S-024 and S-025
NDA 21-110/S-032 and S-034

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, 1 mg/mL and Rapamune® (sirolimus) Tablets, 1 mg, 2 mg, and 5 mg.

A. Approval of "Prior Approval" Labeling Supplements

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

NDA Number	Name of Drug Product	Supplement Number	Date of Supplement	Date of Receipt
21-083	Rapamune® (sirolimus) Oral Solution, 1 mg/mL	S-024	August 1, 2005	August 2, 2005
21-110	Rapamune® (sirolimus) Tablets, 1 mg, 2 mg, and 5 mg	S-032	August 1, 2005	August 2, 2005

We acknowledge receipt of your submissions dated:

March 23, 2006
April 5, 2006
April 26, 2006
May 2, 2006
May 24, 2006
June 1, 2006

These supplemental new drug applications provide additional safety, efficacy, and pharmacokinetic information for Study 4 (or 0468H1-310-GL) at 36, 48 and up to 60 months. The information is submitted in support of proposed labeling changes to the **CLINICAL PHARMACOLOGY, CLINICAL STUDIES, PRECAUTIONS, ADVERSE REACTIONS,** and **DOSAGE AND ADMINISTRATION** sections of the package insert for Rapamune®.

These supplemental new drug applications, as amended, provide for the following revisions to the text of the package insert (~~strikethrough~~ = deleted text and double-underlined = added text):

1. A table in the **CLINICAL PHARMACOLOGY/Pharmacokinetics in renal transplant patients** was revised as follows:

Average Rapamune doses and sirolimus whole blood trough concentrations for tablets administered daily in combination with cyclosporine and following cyclosporine withdrawal, in combination with corticosteroids in renal transplant patients (Study 4; see **CLINICAL STUDIES**) are summarized in the table below.

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

	Rapamune with Cyclosporine Therapy[a]	Rapamune Following Cyclosporine Withdrawal[a]
Rapamune Dose (mg/day)		
Months 4 to 12	2.1 ± 0.7	8.2 ± 4.2
Months 12 to 24	2.0 ± 0.8	6.4 ± 3.0
Months 24 to 36	2.0 ± 0.8	5.3 ± 2.5
Sirolimus C_{min}, (ng/mL)[b]		
Months 4 to 12	10.7 ± 3.8	23.3 ± 5.0
Months 12 to 24	11.2 ± 4.1	22.5 ± 4.8
Months 24 to 36	11.4 ± 4.2	20.4 ± 5.4

a: 215 patients were randomized to each group.
b: Expressed by immunoassay and equivalence.

2. The text and tables of the **CLINICAL STUDIES/Rapamune® Tablets** section pertaining to Study 4 was modified as follows:

In Study 4 (cyclosporine withdrawal study), the safety and efficacy of Rapamune as a maintenance regimen were assessed following cyclosporine withdrawal at 3 to 4 months post renal transplantation. Study 4 was a randomized, multicenter, controlled trial conducted at 57 centers in Australia, Canada, and Europe. Five hundred twenty-five (525) patients were enrolled. All patients in this study received the tablet formulation. This study compared patients who were administered Rapamune, cyclosporine, and corticosteroids continuously with patients who received the same standardized therapy for the first 3 months after transplantation (prerandomization period) followed by the withdrawal of cyclosporine. During cyclosporine withdrawal the Rapamune dosages were adjusted to achieve targeted sirolimus whole blood trough concentration ranges (20 to 30 ng/mL until month 12, then 15 to 25 ng/mL thereafter, experimental immunoassay). At 3 months, 430 patients were equally randomized to either Rapamune with cyclosporine therapy or Rapamune as a maintenance regimen following cyclosporine withdrawal.

Eligibility for randomization included no Banff Grade 3 acute rejection episode or vascular rejection in the 4 weeks before random assignment; serum creatinine ≤ 4.5 mg/dL; and adequate renal function to support cyclosporine withdrawal (in the opinion of the investigator). The primary efficacy endpoint was graft survival at 12 months after transplantation. Secondary efficacy endpoints were the rate of biopsy-confirmed acute rejection, patient survival, incidence of efficacy failure (defined as the first occurrence of either biopsy-proven acute rejection, graft loss, or death), and treatment failure (defined as the first occurrence of either discontinuation, acute rejection, graft loss, or death).

The safety and efficacy of cyclosporine withdrawal in high-risk patients have not been adequately studied 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, serum creatinine > 4.5 mg/dL, black patients, re-transplants, multi-organ transplants, or patients with high panel of reactive antibodies (See **INDICATIONS AND USAGE**).

The following table ~~below~~ summarizes the resulting graft and patient survival at 12, 24, and 36 months for this trial. At 12, 24, and 36 months, graft and patient survival were similar for both groups.

GRAFT AND PATIENT SURVIVAL (%): STUDY 4
(CYCLOSPORINE WITHDRAWAL STUDY)[a]

Parameter	Rapamune with Cyclosporine Therapy (n = 215)	Rapamune Following Cyclosporine Withdrawal (n = 215)
Graft Survival		
Month 12[b]	~~95.8~~95.3[c]	97.2
Month 24	~~91.2~~91.6	~~93.5~~94.0
Month 36[d]	~~85.1~~87.0	~~91.2~~91.6
Patient Survival		
Month 12	97.2	98.1
Month 24	~~94.0~~94.4	~~95.3~~95.8
Month 36[d]	~~88.4~~91.6	~~93.5~~94.0

a: Includes patients who prematurely discontinued treatment.
b: Primary efficacy endpoint.
c. Survival including loss to follow-up as an event.
d. Initial planned duration of the study.

The following table ~~below~~ summarizes the results of first biopsy-proven acute rejection at 12 and 36 months. There was a significant difference in first biopsy-proven rejection between the two groups during post-randomization through 12 months. Most of the post-randomization acute rejections occurred in the first 3 months following randomization.

INCIDENCE OF FIRST BIOPSY-PROVEN ACUTE REJECTION (%) BY TREATMENT GROUP AT 36 MONTHS: STUDY 4 (CYCLOSPORINE WITHDRAWAL STUDY) [a,b]

Period	Rapamune with Cyclosporine Therapy (n = 215)	Rapamune Following Cyclosporine withdrawal (n = 215)
Prerandomization[~~b~~c]	9.3	10.2
Postrandomization through 12 months[~~b~~c]	4.2	9.8
Postrandomization from 12 to 36 months	1.4	0.5
Postrandomization through 36 months	5.6	10.2
Total at 36 months	14.9	20.5

a: Includes patients who prematurely discontinued treatment.
b: All patients received corticosteroids.
~~b~~c: Randomization occurred at 3 months ± 2 weeks.

Patients receiving renal allografts with ≥ 4 HLA mismatches experienced significantly higher rates of acute rejection following randomization to the cyclosporine withdrawal group compared with patients who continued cyclosporine (15.3% vs 3.0%). Patients receiving renal allografts with ≤ 3 HLA mismatches, demonstrated similar rates of acute rejection between treatment groups (6.8% vs 7.7%) following randomization.

The following table ~~below~~ summarizes the mean calculated GFR in Study 4 (cyclosporine withdrawal study).

CALCULATED GLOMERULAR FILTRATION RATES (mL/min) BY NANKIVELL EQUATION AT 12, 24, and 36 MONTHS
POST TRANSPLANT: STUDY 4 (CYCLOSPORINE WITHDRAWAL STUDY)[a, b, c]

Parameter	Rapamune with Cyclosporine Therapy	Rapamune Following Cyclosporine Withdrawal
Month 12		
Mean ± SEM	53.2 ± 1.5	59.3 ± 1.5
	n = 208	n = 203
Month 24		
Mean ± SEM	48.4 ± 1.7	58.4 ± 1.6
	n = 203	n = 201
Month 36		
Mean ± SEM	~~47.3 ± 1.8~~47.0 ± 1.8	~~59.4 ± 1.8~~58.5 ± 1.9
	(n = ~~194~~196)	(n = ~~194~~199)

a: Includes patients who prematurely discontinued treatment.
b: Patients who had a graft loss were included in the analysis and had their GFR set to 0.0.
c: All patients received corticosteroids.

The mean GFR at 12, 24, and 36 months, calculated by the Nankivell equation, was significantly higher for patients receiving Rapamune as a maintenance regimen following cyclosporine withdrawal than for those in the Rapamune with cyclosporine therapy group. Patients who had an acute rejection prior to randomization had a significantly higher GFR following cyclosporine withdrawal compared to those in the Rapamune with cyclosporine group. There was no significant difference in GFR between groups for patients who experienced acute rejection postrandomization.

Although the initial protocol was designed for 36 months, there was a subsequent amendment to extend this study. The results for the cyclosporine group at months 48 and 60 were consistent with the results at month 36. Fifty-two percent (112/215) of the patients in the Rapamune® with cyclosporine withdrawal group remained on therapy to month 60 and showed sustained GFR.

3. The fourth paragraph of the **PRECAUTIONS/Lipids** section was modified as follows:

In Study 4 (cyclosporine withdrawal study) during the prerandomization period, mean fasting serum cholesterol and triglyceride values rapidly increased, and peaked at 2 months with mean cholesterol values > 240 mg/dL and triglycerides > 250 mg/dL. After randomization mean cholesterol and triglyceride values remained higher in the cyclosporine withdrawal arm compared to the Rapamune® and cyclosporine combination.

4. The **ADVERSE REACTIONS/Rapamune following cyclosporine withdrawal** section and table was modified as follows:

Rapamune following cyclosporine withdrawal: The incidence of adverse reactions was determined through 36 months in a randomized, multicenter controlled trial (Study 4) in which 215 renal transplant patients received Rapamune as a maintenance regimen following cyclosporine withdrawal and 215 patients received Rapamune with cyclosporine therapy. All patients were treated with corticosteroids. The safety profile prior to randomization (start of cyclosporine withdrawal) was similar to that of the 2-mg Rapamune groups in Studies 1, 2, and 3. Following randomization (at 3 months) patients who had cyclosporine eliminated from their therapy experienced significantly higher incidences of abnormal liver function tests (including increased AST/SGOT and increased ALT/SGPT), hypokalemia, thrombocytopenia, abnormal healing, ileus, and rectal disorder. Conversely, the incidence of hypertension, cyclosporine toxicity, increased creatinine, abnormal kidney function, toxic nephropathy, edema, hyperkalemia, hyperuricemia, and gum hyperplasia was significantly higher in patients who remained on cyclosporine than those who had cyclosporine withdrawn from therapy. Mean systolic and diastolic blood pressure improved significantly following cyclosporine withdrawal.

In Study 4 (cyclosporine withdrawal study), at 36 months, the incidence of Herpes zoster infection was significantly lower in patients receiving Rapamune following cyclosporine withdrawal compared with patients who continued to receive Rapamune and cyclosporine.

The incidence of malignancies in Study 4 is presented in the table below. In Study 4, the incidence of lymphoma/lymphoproliferative disease was similar in all treatment groups. The overall incidence of malignancy was higher in patients receiving Rapamune plus cyclosporine compared with patients who had cyclosporine withdrawn. Conclusions regarding these differences in the incidence of malignancy could not be made because Study 4 was not designed to consider malignancy risk factors or systematically screen subjects for malignancy. In addition, more patients in the Rapamune with cyclosporine group had a pretransplantation history of skin carcinoma.

INCIDENCE (%) OF MALIGNANCIES IN STUDY 4 (CYCLOSPORINE WITHDRAWAL STUDY) AT 36 MONTHS POST-TRANSPLANT[a,b]

Malignancy	Nonrandomized (n = 95)	Rapamune with Cyclosporine Therapy (n = 215)	Rapamune Following Cyclosporine Withdrawal (n = 215)
Lymphoma/lymphoproliferative disease	**1.1**	**1.4**	**0.5**
Skin Carcinoma			
Any Squamous Cell[c]	~~1.1~~3.2	~~1.9~~3.3	2.3
Any Basal Cell[c]	3.2	~~4.7~~6.5	2.3
Melanoma	0.0	0.5	0.0
Miscellaneous/Not Specified	1.1	0.9	0.0
Total	**4.2**	**~~6.5~~7.9**	**3.7**
Other Malignancy	**~~1.1~~3.2**	**3.3**	**~~1.4~~1.9**

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.
c: Patients may be counted in more than one category.

5. The **DOSAGE AND ADMINISTRATION/Rapamune following cyclosporine withdrawal** section was modified as follows:

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~~16 to 24 ng/mL (chromatographic method) for the first year following transplantation. Thereafter, the target sirolimus concentrations should be 12 to 20 ng/mL (chromatographic method). The actual observations in Study 4 were close to these ranges (See **DOSAGE AND ADMINISTRATION: Blood Concentration Monitoring**). 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).

6. The third paragraph of the **DOSAGE AND ADMINISTRATION/Blood Concentration Monitoring** section was modified as follows:

   In a controlled clinical trial with cyclosporine withdrawal (Study 4), the mean sirolimus whole blood trough concentrations during months 4 through 12 following transplantation, as measured by immunoassay, were 10.7 ng/mL (range ~~6.3 - 16.0~~6.3 - 15.9 ng/mL [10^{th} to 90^{th} percentile]) in the concomitant Rapamune and cyclosporine treatment group (n = 205) and were 23.3 ng/mL (range ~~17.0 - 29.0~~17.0 - 29.3 ng/mL [10^{th} to 90^{th} percentile]) in the cyclosporine withdrawal treatment group (n = 20~~0~~1). By year 3, the mean sirolimus whole blood trough concentrations remained stable in the concomitant Rapamune and cyclosporine group (n = 135) at 11.4 ng/mL (range 6.7 to 17.4 ng/mL [10^{th} to 90^{th} percentile]). For the cyclosporine withdrawal group (n = 140) by year 3, the mean sirolimus whole blood concentration had fallen to 20.4 ng/mL (range 14.0 to 27.4 ng/mL [10^{th} to 90^{th} percentile]).

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

B. Approval of "Changes Being Effected" Labeling Supplements

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

NDA Number	Name of Drug Product	Supplement Number	Date of Supplement	Date of Receipt
21-083	Rapamune® (sirolimus) Oral Solution, 1 mg/mL	S-025	December 15, 2005	December 16, 2005
21-110	Rapamune® (sirolimus) Tablets, 1 mg, 2 mg, and 5 mg	S-034	December 15, 2005	December 16, 2005

We acknowledge receipt of your submissions dated May 24, 2006 and June 1, 2006.
These supplemental applications, submitted as "Supplements - Changes Being Effected," provide for the addition of "pulmonary embolism," "deep venous thrombosis," "pulmonary hemorrhage" and "proteinuria" to the **ADVERSE REACTIONS** section of the package insert.

These supplemental new drug applications, as amended, provide for the following revisions to the text of the package insert (~~strikethrough~~ = deleted text and double-underlined = added text):

1. The ninth paragraph of the **ADVERSE REACTIONS/Rapamune® Oral Solution** section was revised as follows:

   The following adverse events were reported with ≥3% and <20% incidence in patients in any Rapamune treatment group in the two controlled clinical trials for the prevention of acute rejection, BODY AS A WHOLE: abdomen enlarged, abscess, ascites, cellulitis, chills, face edema, flu syndrome, generalized edema, hernia, *Herpes zoster* infection, lymphocele, malaise, pelvic pain, peritonitis, sepsis; CARDIOVASCULAR SYSTEM: atrial fibrillation, congestive heart failure, hemorrhage, hypervolemia, hypotension, palpitation, peripheral vascular disorder, postural hypotension, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation, venous thromboembolism (including pulmonary embolism, deep venous thrombosis);

DIGESTIVE SYSTEM: anorexia, dysphagia, eructation, esophagitis, flatulence, gastritis, gastroenteritis, gingivitis, gum hyperplasia, ileus, liver function tests abnormal, mouth ulceration, oral moniliasis, stomatitis; ENDOCRINE SYSTEM: Cushing's syndrome, diabetes mellitus, glycosuria; HEMIC AND LYMPHATIC SYSTEM: ecchymosis, leukocytosis, lymphadenopathy, polycythemia, thrombotic thrombocytopenic purpura (hemolytic-uremic syndrome); METABOLIC AND NUTRITIONAL: acidosis, alkaline phosphatase increased, BUN increased, creatine phosphokinase increased, dehydration, healing abnormal, hypercalcemia, hyperglycemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypomagnesemia, hyponatremia, lactic dehydrogenase increased, AST/SGOT increased, ALT/SGPT increased, weight loss; MUSCULOSKELETAL SYSTEM: arthrosis, bone necrosis, leg cramps, myalgia, osteoporosis, tetany; NERVOUS SYSTEM: anxiety, confusion, depression, dizziness, emotional lability, hypertonia, hypesthesia, hypotonia, insomnia, neuropathy, paresthesia, somnolence; RESPIRATORY SYSTEM: asthma, atelectasis, bronchitis, cough increased, epistaxis, hypoxia, lung edema, pleural effusion, pneumonia, rhinitis, sinusitis; SKIN AND APPENDAGES: fungal dermatitis, hirsutism, pruritus, skin hypertrophy, skin ulcer, sweating; SPECIAL SENSES: abnormal vision, cataract, conjunctivitis, deafness, ear pain, otitis media, tinnitus; UROGENITAL SYSTEM: albuminuria, bladder pain, dysuria, hematuria, hydronephrosis, impotence, kidney pain, kidney tubular necrosis, nocturia, oliguria, pyelonephritis, pyuria, scrotal edema, testis disorder, toxic nephropathy, urinary frequency, urinary incontinence, urinary retention.

2. The **ADVERSE REACTIONS/Other clinical experience** section was revised and reorganized as follows:

Other clinical experience: Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, and hypersensitivity vasculitis, have been associated with the administration of sirolimus (see **WARNINGS**). Abnormal healing following transplant surgery has been reported, including fascial dehiscence and anastomotic disruption (e.g., wound, vascular, airway, ureteral, biliary) (see **WARNINGS**).

Cases of interstitial lung disease (including pneumonitis, and infrequently bronchiolitis obliterans organizing pneumonia [BOOP] and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving immunosuppressive regimens including Rapamune. In some cases, the interstitial lung disease has resolved upon discontinuation or dose reduction of Rapamune. The risk may be increased as the sirolimus trough concentration increases (see **PRECAUTIONS**, **General**, **Interstitial Lung Disease**). There have been reports of pulmonary hemorrhage. The concomitant use of sirolimus with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced HUS/TTP/TMA (see **PRECAUTIONS**).

Hepatotoxicity has been reported, including fatal hepatic necrosis, with elevated sirolimus trough concentrations. There have been reports of neutropenia, proteinuria, pancytopenia, joint disorders, and lymphedema.

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

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and patient package insert). Please submit an electronic version of the FPL according to the guidance

for industry titled *Providing Regulatory Submissions in Electronic Format - NDA.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions **"FPL for approved supplements NDA 21-083/S-024 and S-025 and NDA 21-110/S-032 and S-034."** Approval of these submissions by FDA is not required before the labeling is used.

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 the 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 these NDAs and a copy to the following address:

MEDWATCH
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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 Rebecca D. Saville, 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

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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