**Rapamune®**
**(sirolimus)**
**Oral Solution and Tablets**

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* WARNING: *
* Increased susceptibility to infection and the possible *
* development of lymphoma may result from immunosuppression. *
* Only physicians experienced in immunosuppressive therapy and *
* management of renal transplant patients should use Rapamune®. *
* Patients receiving the drug should be managed in facilities *
* equipped and staffed with adequate laboratory and supportive *
* medical resources. The physician responsible for maintenance *
* therapy should have complete information requisite for the *
* follow-up of the patient. *
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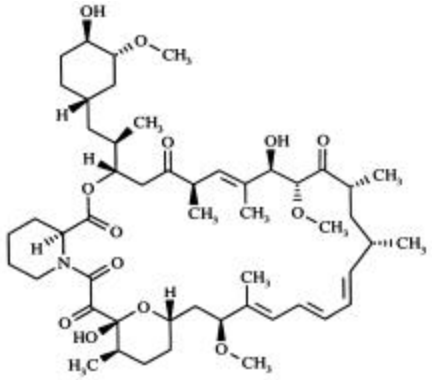
## DESCRIPTION

Rapamune® (sirolimus) is an immunosuppressive agent. Sirolimus is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. The chemical name of sirolimus (also known as rapamycin) is (3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[(1*R*)-2-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-*c*][1,4] oxaazacyclohentriacontine-1,5,11,28,29 (4*H*,6*H*,31*H*)-pentone. Its molecular formula is $C_{51}H_{79}NO_{13}$ and its molecular weight is 914.2. The structural formula of sirolimus is shown below.



Sirolimus is a white to off-white powder and is insoluble in water, but freely soluble in benzyl alcohol, chloroform, acetone, and acetonitrile.

Rapamune® is available for administration as an oral solution containing 1 mg/mL sirolimus and as a white, triangular-shaped tablet containing 1 mg sirolimus.

The inactive ingredients in Rapamune® Oral Solution are Phosal 50 PG® (phosphatidylcholine, propylene glycol, monodiglycerides, ethanol, soy fatty acids, and ascorbyl palmitate) and polysorbate 80. Rapamune Oral Solution contains 1.5% - 2.5% ethanol.

The inactive ingredients in Rapamune® Tablets include sucrose, lactose, polyethylene glycol 8000, calcium sulfate, microcrystalline cellulose, pharmaceutical glaze, talc, titanium dioxide, magnesium stearate, povidone, poloxamer 188, polyethylene glycol 20,000, glyceryl monooleate, carnauba wax, and other ingredients.

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Sirolimus inhibits T lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (Interleukin [IL]-2, IL-4, and IL-15) stimulation by a mechanism that is distinct from that of other immunosuppressants. Sirolimus also inhibits antibody production. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. The sirolimus:FKBP-12 complex has no effect on calcineurin activity. This complex binds to and inhibits the activation of the mammalian Target Of Rapamycin (mTOR), a key regulatory kinase. This inhibition suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the $G_1$ to the S phase of the cell cycle.

Studies in experimental models show that sirolimus prolongs allograft (kidney, heart, skin, islet, small bowel, pancreatico-duodenal, and bone marrow) survival in mice, rats, pigs, and/or primates. Sirolimus reverses acute rejection of heart and kidney allografts in rats and prolonged the graft survival in presensitized rats. In some studies, the immunosuppressive effect of sirolimus lasted up to 6 months after discontinuation of therapy. This tolerization effect is alloantigen specific.

In rodent models of autoimmune disease, sirolimus suppresses immune-mediated events associated with systemic lupus erythematosus, collagen-induced arthritis, autoimmune type I diabetes, autoimmune myocarditis, experimental allergic encephalomyelitis, graft-versus-host disease, and autoimmune uveoretinitis.

### Pharmacokinetics

Sirolimus pharmacokinetic activity has been determined following oral administration in healthy subjects, pediatric dialysis patients, hepatically-impaired patients, and renal transplant patients.

### Absorption

Following administration of Rapamune® Oral Solution, sirolimus is rapidly absorbed, with a mean time-to-peak concentration ($t_{max}$) of approximately 1 hour after a single dose in healthy subjects and approximately 2 hours after multiple oral doses in renal transplant recipients. The systemic

availability of sirolimus was estimated to be approximately 14% after the administration of Rapamune Oral Solution. The mean bioavailability of sirolimus after administration of the tablet is about 27% higher relative to the oral solution. Sirolimus oral tablets are not bioequivalent to the oral solution; however, clinical equivalence has been demonstrated at the 2-mg dose level. (See Clinical Studies and Dosage and Administration). Sirolimus concentrations, following the administration of Rapamune Oral Solution to stable renal transplant patients, are dose proportional between 3 and 12 $mg/m^2$.

***Food effects:*** In 22 healthy volunteers receiving Rapamune Oral Solution, a high-fat meal (1.88 kcal, 54.7% fat) altered the bioavailability characteristics of sirolimus. Compared to fasting, a 34% decrease in the peak blood sirolimus concentration ($C_{max}$), a 3.5-fold increase in the time-to-peak concentration ($t_{max}$), and a 35% increase in total exposure (AUC) was observed. After administration of Rapamune Tablets and a high-fat meal in 24 healthy volunteers, $C_{max}$, $t_{max}$, and AUC showed increases of 65%, 32%, and 23%, respectively. To minimize variability, both Rapamune Oral Solution and Tablets should be taken consistently with or without food (See DOSAGE AND ADMINISTRATION).

**Distribution**

The mean (± SD) blood-to-plasma ratio of sirolimus was 36 (± 17.9) in stable renal allograft recipients, indicating that sirolimus is extensively partitioned into formed blood elements. The mean volume of distribution ($V_{ss}/F$) of sirolimus is 12 ± 7.52 L/kg. Sirolimus is extensively bound (approximately 92%) to human plasma proteins. In man, the binding of sirolimus was shown mainly to be associated with serum albumin (97%), $\alpha_1$-acid glycoprotein, and lipoproteins.

**Metabolism**

Sirolimus is a substrate for both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein. Sirolimus is extensively metabolized by O-demethylation and/or hydroxylation. Seven (7) major metabolites, including hydroxy, demethyl, and hydroxydemethyl, are identifiable in whole blood. Some of these metabolites are also detectable in plasma, fecal, and urine samples. Glucuronide and sulfate conjugates are not present in any of the biologic matrices. Sirolimus is the major component in human whole blood and contributes to more than 90% of the immunosuppressive activity.

**Excretion**

After a single dose of [$^{14}$C]sirolimus in healthy volunteers, the majority (91%) of radioactivity was recovered from the feces, and only a minor amount (2.2%) was excreted in urine.

**Pharmacokinetics in renal transplant patients**

Rapamune Oral Solution: Pharmacokinetic parameters for sirolimus oral solution given daily in combination with cyclosporine and corticosteroids in renal transplant patients are summarized below based on data collected at months 1, 3, and 6 after transplantation. There were no significant differences in any of these parameters with respect to treatment group or month.

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN RENAL TRANSPLANT PATIENTS ( MULTIPLE DOSE ORAL SOLUTION) [a,b]

| n | Dose | $C_{max,ss}$ [c] (ng/mL) | $t_{max,ss}$ (h) | $AUC_{\tau,ss}$ [c] (ng•h/mL) | CL/F/WT [d] (mL/h/kg) |
|---|---|---|---|---|---|
| 19 | 2 mg | 12.2 ± 6.2 | 3.01 ± 2.40 | 158 ± 70 | 182 ± 72 |
| 23 | 5 mg | 37.4 ± 21 | 1.84 ± 1.30 | 396 ± 193 | 221 ± 143 |

a: Sirolimus administered four hours after cyclosporine oral solution (MODIFIED) (e.g., Neoral® Oral Solution) and/or cyclosporine capsules (MODIFIED) (e.g., Neoral® Soft Gelatin Capsules).

b: As measured by the Liquid Chromatographic/Tandem Mass Spectrometric Method (LC/MS/MS).

c: These parameters were dose normalized prior to the statistical comparison.

d: CL/F/WT = oral dose clearance.

Whole blood sirolimus trough concentrations, as measured by immunoassay, (mean ± SD) for the 2 mg/day and 5 mg/day dose groups were 8.59 ± 4.01 ng/mL (n = 226) and 17.3 ± 7.4 ng/mL (n = 219), respectively. Whole blood trough sirolimus concentrations, as measured by LC/MS/MS, were significantly correlated ($r^2 = 0.96$) with $AUC_{\tau,ss}$. Upon repeated twice daily administration without an initial loading dose in a multiple-dose study, the average trough concentration of sirolimus increases approximately 2 to 3-fold over the initial 6 days of therapy at which time steady state is reached. A loading dose of 3 times the maintenance dose will provide near steady-state concentrations within 1 day in most patients. The mean ± SD terminal elimination half life ($t_2$) of sirolimus after multiple dosing in stable renal transplant patients was estimated to be about 62 ± 16 hours.

Rapamune Tablets: Pharmacokinetic parameters for sirolimus tablets administered daily in combination with cyclosporine and corticosteroids in renal transplant patients are summarized below based on data collected at months 1 and 3 after transplantation.

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN RENAL TRANSPLANT PATIENTS (MULTIPLE DOSE TABLETS) [a,b]

| n | Dose (2 mg/day) | $C_{max,ss}$ [c] (ng/mL) | $t_{max,ss}$ (h) | $AUC_{\tau,ss}$ [c] (ng•h/mL) | CL/F/WT [d] (mL/h/kg) |
|---|---|---|---|---|---|
| 17 | Oral solution | 14.4 ± 5.3 | 2.12 ± 0.84 | 194 ± 78 | 173 ± 50 |
| 13 | Tablets | 15.0 ± 4.9 | 3.46 ± 2.40 | 230 ± 67 | 139 ± 63 |

a: Sirolimus administered four hours after cyclosporine oral solution (MODIFIED) (e.g., Neoral® Oral Solution) and/or cyclosporine capsules (MODIFIED) (e.g., Neoral® Soft Gelatin Capsules).

b: As measured by the Liquid Chromatographic/Tandem Mass Spectrometric Method (LC/MS/MS).

c: These parameters were dose normalized prior to the statistical comparison.

d: CL/F/WT = weight-normalized oral dose clearance.

Whole blood sirolimus trough concentrations (mean ± SD), as measured by immunoassay, for the 2 mg oral solution and 2 mg tablets over 6 months, were 8.94 ± 4.36 ng/mL (n = 172) and 9.48 ± 3.85 ng/mL (n = 179), respectively. Whole blood trough sirolimus concentrations, as measured by

LC/MS/MS, were significantly correlated ($r^2 = 0.85$) with $AUC_{\tau,ss}$. Mean whole blood sirolimus trough concentrations in patients receiving either Rapamune Oral Solution or Rapamune Tablets with a loading dose of three times the maintenance dose achieved steady-state concentrations within 24 hours after the start of dose administration.

**Special Populations**

***Hepatic impairment:*** Sirolimus (15 mg) was administered as a single oral dose to 18 subjects with normal hepatic function and to 18 patients with Child-Pugh classification A or B hepatic impairment, in which hepatic impairment was primary and not related to an underlying systemic disease. Shown below are the mean ± SD pharmacokinetic parameters following the administration of sirolimus oral solution.

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN 18 HEALTHY SUBJECTS AND 18 PATIENTS WITH HEPATIC IMPAIRMENT (15 MG SINGLE DOSE – ORAL SOLUTION)

| Population | $C_{max,ss}$[a] (ng/mL) | $t_{max}$ (h) | $AUC_{0-\infty}$ (ng•h/mL) | CL/F/WT (mL/h/kg) |
|---|---|---|---|---|
| Healthy subjects | 78.2 ± 18.3 | 0.82 ± 0.17 | 970 ± 272 | 215 ± 76 |
| Hepatic impairment | 77.9 ± 23.1 | 0.84 ± 0.17 | 1567 ± 616 | 144 ± 62 |

a: As measured by LC/MS/MS.

Compared with the values in the normal hepatic group, the hepatic impairment group had higher mean values for sirolimus AUC (61%) and $t_{1/2}$ (43%) and had lower mean values for sirolimus CL/F/WT (33%). The mean $t_{1/2}$ increased from 79 ± 12 hours in subjects with normal hepatic function to 113 ± 41 hours in patients with impaired hepatic function. The rate of absorption of sirolimus was not altered by hepatic disease, as evidenced by $C_{max}$ and $t_{max}$ values. However, hepatic diseases with varying etiologies may show different effects and the pharmacokinetics of sirolimus in patients with severe hepatic dysfunction is unknown. Dosage adjustment is recommended for patients with mild to moderate hepatic impairment (**see DOSAGE AND ADMINISTRATION**).

***Renal impairment:*** The effect of renal impairment on the pharmacokinetics of sirolimus is not known. However, there is minimal (2.2%) renal excretion of the drug or its metabolites.

***Pediatric:*** Limited pharmacokinetic data are available in pediatric patients. The table below summarizes pharmacokinetic data obtained in pediatric dialysis patients with chronically impaired renal function.

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN PEDIATRIC PATIENTS WITH STABLE CHRONIC RENAL FAILURE MAINTAINED ON HEMODIALYSIS OR PERITONEAL DIALYSIS (1, 3, 9, 15 MG/M$^2$ SINGLE DOSE)

| Age Group (y) | n | $t_{max}$ (h) | $t_{1/2}$ (h) | CL/F/WT (mL/h/kg) |
|---|---|---|---|---|
| 5-11 | 9 | 1.1 ± 0.5 | 71 ± 40 | 580 ± 450 |
| 12-18 | 11 | 0.79 ± 0.17 | 55 ± 18 | 450 ± 232 |

***Geriatric:*** Clinical studies of Rapamune did not include a sufficient number of patients > 65 years of age to determine whether they will respond differently than younger patients. After the administration of Rapamune Oral Solution, sirolimus trough concentration data in 35 renal transplant patients > 65 years of age were similar to those in the adult population (n=822) 18 to 65 years of age. Similar results were obtained after the administration of Rapamune Tablets to 12 renal transplant patients > 65 years of age compared with adults (n=167) 18 to 65 years of age.

***Gender:*** After the administration of Rapamune Oral Solution, sirolimus oral dose clearance in males was 12% lower than that in females; male subjects had a significantly longer $t_{1/2}$ than did female subjects (72.3 hours versus 61.3 hours). A similar trend in the effect of gender on sirolimus oral dose clearance and $t_{½}$ was observed after the administration of Rapamune Tablets. Dose adjustments based on gender are not recommended.

***Race:*** In large phase III trials using Rapamune Oral Solution and cyclosporine oral solution (MODIFIED) (eg, Neoral® Oral Solution) and/or cyclosporine capsules (MODIFIED) (e.g., Neoral® Soft Gelatin Capsules), there were no significant differences in mean trough sirolimus concentrations over time between black (n = 139) and non-black (n = 724) patients during the first 6 months after transplantation at sirolimus doses of 2 mg/day and 5 mg/day. Similarly, after administration of Rapamune Tablets (2 mg/day) in a phase III trial, mean sirolimus trough concentrations over 6 months were not significantly different among black (n = 51) and non-black (n = 128) patients.

**CLINICAL STUDIES**

Rapamune® Oral Solution: The safety and efficacy of Rapamune® Oral Solution for the prevention of organ rejection following renal transplantation were assessed in two randomized, double-blind, multicenter, controlled trials. These studies compared two dose levels of Rapamune Oral Solution (2 mg and 5 mg, once daily) with azathioprine (Study 1) or placebo (Study 2) when administered in combination with cyclosporine and corticosteroids. Study 1 was conducted in the United States at 38 sites. Seven hundred nineteen (719) patients were enrolled in this trial and randomized following transplantation; 284 were randomized to receive Rapamune Oral Solution 2 mg/day, 274 were randomized to receive Rapamune Oral Solution 5 mg/day, and 161 to receive azathioprine 2-3 mg/kg/day. Study 2 was conducted in Australia, Canada, Europe, and the United States, at a total of 34 sites. Five hundred seventy-six (576) patients were enrolled in this trial and randomized before transplantation; 227 were randomized to receive Rapamune Oral Solution 2 mg/day, 219 were randomized to receive Rapamune Oral Solution 5 mg/day, and 130 to receive placebo. In both studies, the use of antilymphocyte antibody induction therapy was prohibited. In both studies, the primary efficacy endpoint was the rate of efficacy failure in the first 6 months after transplantation. Efficacy failure was defined as the first occurrence of an acute rejection episode (confirmed by biopsy), graft loss, or death.

The tables below summarize the results of the primary efficacy analyses from these trials. Rapamune Oral Solution, at doses of 2 mg/day and 5 mg/day, significantly reduced the incidence of efficacy failure (statistically significant at the <0.025 level; nominal significance level adjusted for

multiple [2] dose comparisons) at 6 months following transplantation compared to both azathioprine and placebo.

INCIDENCE (%) OF THE PRIMARY ENDPOINT AT 6 MONTHS: STUDY 1[a]

| Parameter | Rapamune® Oral Solution 2 mg/day (n = 284) | Rapamune® Oral Solution 5 mg/day (n = 274) | Azathioprine 2-3 mg/kg/day (n = 161) |
|---|---|---|---|
| Efficacy failure at 6 months | 18.7 | 16.8 | 32.3 |
| *Components of efficacy failure* | | | |
| Biopsy-proven acute rejection | 16.5 | 11.3 | 29.2 |
| Graft loss | 1.1 | 2.9 | 2.5 |
| Death | 0.7 | 1.8 | 0 |
| Lost to follow-up | 0.4 | 0.7 | 0.6 |

a: Patients received cyclosporine and corticosteroids.

INCIDENCE (%) OF THE PRIMARY ENDPOINT AT 6 MONTHS: STUDY 2[a]

| Parameter | Rapamune® Oral Solution 2 mg/day (n = 227) | Rapamune® Oral Solution 5 mg/day (n = 219) | Placebo (n = 130) |
|---|---|---|---|
| Efficacy failure at 6 months | 30.0 | 25.6 | 47.7 |
| *Components of efficacy failure* | | | |
| Biopsy-proven acute rejection | 24.7 | 19.2 | 41.5 |
| Graft loss | 3.1 | 3.7 | 3.9 |
| Death | 2.2 | 2.7 | 2.3 |
| Lost to follow-up | 0 | 0 | 0 |

a: Patients received cyclosporine and corticosteroids.

Patient and graft survival at 1 year were co-primary endpoints. The table below shows graft and patient survival at 1 year in Study 1 and Study 2. The graft and patient survival rates at 1 year were similar in the Rapamune- and comparator-treated patients.

1-YEAR GRAFT AND PATIENT SURVIVAL (%)[a]

| Parameter | Rapamune® Oral Solution 2 mg/day | Rapamune® Oral Solution 5 mg/day | Azathioprine 2-3 mg/kg/day | Placebo |
|---|---|---|---|---|
| Study 1 | (n = 284) | (n = 274) | (n = 161) | |
| Graft survival | 94.7 | 92.7 | 93.8 | |
| Patient survival | 97.2 | 96.0 | 98.1 | |
| Study 2 | (n = 227) | (n = 219) | | (n = 130) |
| Graft survival | 89.9 | 90.9 | | 87.7 |
| Patient survival | 96.5 | 95.0 | | 94.6 |

a: Patients received cyclosporine and corticosteroids.

The reduction in the incidence of first biopsy-confirmed acute rejection episodes in Rapamune-treated patients compared to the control groups included a reduction in all grades of rejection.

PERCENTAGE OF EFFICACY FAILURE BY RACE AT 6 MONTHS

| Parameter | Rapamune® Oral Solution 2 mg/day | Rapamune® Oral Solution 5 mg/day | Azathioprine 2-3 mg/kg/day | Placebo |
|---|---|---|---|---|
| Study 1 | | | | |
| Black (n=166) | 34.9 (n=63) | 18.0 (n=61) | 33.3 (n=42) | |
| Nonblack (n=553) | 14.0 (n=221) | 16.4 ( n=213) | 31.9 (n=119) | |
| Study 2 | | | | |
| Black (n=66) | 30.8 (n=26) | 33.7 (n=27) | | 38.5 (n=13) |
| Non-black (n=510) | 29.9 (n=201) | 24.5 (n=192) | | 48.7 (n=117) |

In Study 1, which was prospectively stratified by race within center, efficacy failure was similar for Rapamune Oral Solution 2 mg/day and lower for Rapamune Oral Solution 5 mg/day compared to azathioprine in black patients. In Study 2, which was not prospectively stratified by race, efficacy failure was similar for both Rapamune Oral Solution doses compared to placebo in black patients. The decision to use the higher dose of Rapamune Oral Solution in black patients must be weighed against the increased risk of dose-dependent adverse events that were observed with the Rapamune Oral Solution 5 mg dose (see ADVERSE REACTIONS).

OVERALL CALCULATED GLOMERULAR FILTRATION RATES (CC/MIN) BY NANKIVELL EQUATION AT 12 MONTHS POST TRANSPLANT

| Parameter | Rapamune® Oral Solution 2 mg/day | Rapamune® Oral Solution 5 mg/day | Azathioprine 2-3 mg/kg/day | Placebo |
|---|---|---|---|---|
| Study 1 | (n=233) | (n=226) | (n=127) | |
| Mean (SE) | 57.4 (1.28) | 55.1 (1.28) | 65.9 (1.69) | |
| Study 2 | (n=190) | (n=175) | | (n=101) |
| Mean (SE) | 54.9 (1.26) | 52.9 (1.46) | | 61.7 (1.81) |

Mean glomerular filtration rates (GFR) at one year post transplant were calculated by using the Nankivell equation for all subjects in Studies 1 and 2 who had serum creatinine measured at 12 months. In Studies 1 and 2 mean GFR, at 12 months, were lower in patients treated with cyclosporine and Rapamune Oral Solution compared to those treated with cyclosporine and the respective azathioprine or placebo control.

Within each treatment group in Studies 1 and 2, mean GFR at one year post transplant was lower in patients who experienced at least 1 episode of biopsy-proven acute rejection, compared to those who did not.

Renal function should be monitored and appropriate adjustment of the immunosuppression regimen should be considered in patients with elevated serum creatinine levels (see PRECAUTIONS).

**Rapamune® Tablets**: The safety and efficacy of Rapamune Oral Solution and Rapamune Tablets for the prevention of organ rejection following renal transplantation were compared in a randomized multicenter controlled trial (Study 3). This study compared a single dose level (2 mg, once daily) of Rapamune Oral Solution and Rapamune Tablets when administered in combination with cyclosporine and corticosteroids. The study was conducted at 30 centers in Australia, Canada, and the United States. Four hundred seventy-seven (477) patients were enrolled in this study and randomized before transplantation; 238 patients were randomized to receive Rapamune Oral Solution 2 mg/day and 239 patients were randomized to receive Rapamune Tablets 2 mg/day. In this study, the use of antilymphocyte antibody induction therapy was prohibited. The primary efficacy endpoint was the rate of efficacy failure in the first 3 months after transplantation. Efficacy failure was defined as the first occurrence of an acute rejection episode (confirmed by biopsy), graft loss, or death.

The table below summarizes the result of the primary efficacy analysis at 3 months from this trial. The overall rate of efficacy failure in the tablet treatment group was equivalent to the rate in the oral solution treatment group.

INCIDENCE (%) OF THE PRIMARY ENDPOINT AT 3 MONTHS: STUDY 3[a]

| | Rapamune® Oral Solution (n = 238) | Rapamune® Tablets (n = 239) |
|---|---|---|
| Efficacy Failure at 3 months | 23.5 | 24.7 |
| *Components of efficacy failure* | | |
| Biopsy-proven acute rejection | 18.9 | 17.6 |
| Graft loss | 3.4 | 6.3 |
| Death | 1.3 | 0.8 |

a: Patients received cyclosporine and corticosteroids.

The table below summarizes the results of the primary efficacy analysis at 6 months after transplantation.

INCIDENCE (%) OF THE PRIMARY ENDPOINT AT 6 MONTHS: STUDY 3[a]

| | Rapamune® Oral Solution (n = 238) | Rapamune® Tablets (n = 239) |
|---|---|---|
| Efficacy Failure at 6 months | 26.1 | 27.2 |
| *Components of efficacy failure* | | |
| Biopsy-proven acute rejection | 21.0 | 19.2 |
| Graft loss | 3.4 | 6.3 |
| Death | 1.7 | 1.7 |

a: Patients received cyclosporine and corticosteroids.

Graft and patient survival at 12 months were co-primary efficacy endpoints. There was no significant difference between the oral solution and tablet formulations for both graft and patient

survival. Graft survival was 92.0% and 88.7% for the oral solution and tablet treatment groups, respectively. The patient survival rates in the oral solution and tablet treatment groups were 95.8% and 96.2%, respectively.

The mean GFR at 12 months, calculated by the Nankivell equation, were not significantly different for the oral solution group and for the tablet group.

The table below summarizes the mean GFR at one-year post-transplantation for all subjects in Study 3 who had serum creatinine measured at 12 months.

OVERALL CALCULATED GLOMERULAR FILTRATION RATES (CC/MIN) BY NANKIVELL EQUATION AT 12 MONTHS POST TRANSPLANT: STUDY 3

| | Rapamune® Oral Solution | Rapamune® Tablets |
|---|---|---|
| Mean (SE) | 58.3 (1.64) n=166 | 58.5 (1.44) n=162 |

## INDICATIONS AND USAGE

Rapamune is indicated for the prophylaxis of organ rejection in patients receiving renal transplants. It is recommended that Rapamune be used in a regimen with cyclosporine and corticosteroids.

## CONTRAINDICATIONS

Rapamune is contraindicated in patients with a hypersensitivity to sirolimus or its derivatives or any component of the drug product.

## WARNINGS

Increased susceptibility to infection and the possible development of lymphoma and other malignancies, particularly of the skin, may result from immunosuppression (see ADVERSE REACTIONS). Oversuppression of the immune system can also increase susceptibility to infection including opportunistic infections, fatal infections, and sepsis. Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should use Rapamune. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Increased serum cholesterol and triglycerides, that may require treatment, occurred more frequently in patients treated with Rapamune compared to azathioprine or placebo controls. (see PRECAUTIONS).

In phase III studies, mean serum creatinine was increased and mean glomerular filtration rate was decreased in patients treated with Rapamune and cyclosporine compared to those treated with cyclosporine and placebo or azathioprine controls (see CLINICAL STUDIES). Renal function should be monitored during the administration of maintenance immunosuppression regimens including Rapamune in combination with cyclosporine, and appropriate adjustment of the immunosuppression regimen should be considered in patients with elevated serum creatinine levels. Caution should be exercised when using agents which are known to impair renal function (see PRECAUTIONS).

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

Sandimmune® Injection (cyclosporine injection)
Sandimmune® Oral Solution (cyclosporine oral solution)
Sandimmune® Soft Gelatin Capsules (cyclosporine capsules)
Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED])
Neoral® Oral Solution (cyclosporine oral solution [MODIFIED])

The efficacy and safety of the use of Rapamune in combination with other immunosuppressive agents has not been determined.

## PRECAUTIONS

### General

Rapamune is intended for oral administration only.

Lymphocele, a known surgical complication of renal transplantation, occurred significantly more often in a dose-related fashion in Rapamune-treated patients. Appropriate post-operative measures should be considered to minimize this complication.

#### *Lipids*

The use of Rapamune® in renal transplant patients was associated with increased serum cholesterol and triglycerides that may require treatment.

In phase III clinical trials, in *de novo* renal transplant recipients who began the study with normal, fasting, total serum cholesterol (fasting serum cholesterol < 200 mg/dL), there was an increased incidence of hypercholesterolemia (fasting serum cholesterol > 240 mg/dL) in patients receiving both Rapamune® 2 mg and Rapamune® 5 mg compared to azathioprine and placebo controls.

In phase III clinical trials, in *de novo* renal transplant recipients who began the study with normal, fasting, total serum triglycerides (fasting serum triglycerides < 200 mg/dL), there was an increased

incidence of hypertriglyceridemia (fasting serum triglycerides > 500 mg/dL) in patients receiving Rapamune® 2 mg and Rapamune® 5 mg compared to azathioprine and placebo controls.

Treatment of new-onset hypercholesterolemia with lipid-lowering agents was required in 42 -52% of patients enrolled in the Rapamune arms of the study compared to 16% of patients in the placebo arm and 22% of patients in the azathioprine arm.

Renal transplant patients have a higher prevalence of clinically significant hyperlipidemia. Accordingly, the risk/benefit should be carefully considered in patients with established hyperlipidemia before initiating an immunosuppressive regimen including Rapamune.

Any patient who is administered Rapamune should be monitored for hyperlipidemia using laboratory tests and if hyperlipidemia is detected, subsequent interventions such as diet, exercise, and lipid-lowering agents, as outlined by the National Cholesterol Education Program guidelines, should be initiated.

In the limited number of patients studied, the concomitant administration of Rapamune and HMG-CoA reductase inhibitors and/or fibrates appeared to be well tolerated. Nevertheless, all patients administered Rapamune with cyclosporine, in conjunction with an HMG-CoA reductase inhibitor, should be monitored for the development of rhabdomyolysis.

***Renal Function***

Patients treated with cyclosporine and Rapamune were noted to have higher serum creatinine levels and lower glomerular filtration rates compared to patients treated with cyclosporine and placebo or azathioprine controls. Renal function should be monitored during the administration of maintenance immunosuppression regimens including Rapamune in combination with cyclosporine, and appropriate adjustment of the immunosuppression regimen should be considered in patients with elevated serum creatinine levels. Caution should be exercised when using agents (eg, aminoglycosides, and amphotericin B) that are known to have a deleterious effect on renal function.

***Antimicrobial Prophylaxis***

Cases of *Pneumocystis carinii* pneumonia have been reported in patients not receiving antimicrobial prophylaxis. Therefore, antimicrobial prophylaxis for *Pneumocystis carinii* pneumonia should be administered for 1 year following transplantation.

Cytomegalovirus (CMV) prophylaxis is recommended for 3 months after transplantation, particularly for patients at increased risk for CMV disease.

**Information for Patients**

Patients should be given complete dosage instructions (see Patient Instructions). Women of childbearing potential should be informed of the potential risks during pregnancy and that they should use effective contraception prior to initiation of Rapamune therapy, during Rapamune

therapy and for 12 weeks after Rapamune therapy has been stopped (see PRECAUTIONS: Pregnancy).

Patients should be told that exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor because of the increased risk for skin cancer (see WARNINGS).

**Laboratory Tests**

It is prudent to monitor blood sirolimus levels in patients likely to have altered drug metabolism, in patients $13 years who weigh less than 40 kg, in patients with hepatic impairment, and during concurrent administration of potent CYP3A4 inducers and inhibitors (see PRECAUTIONS: Drug Interactions).

**Drug Interactions**

Sirolimus is known to be a substrate for both cytochrome CYP3A4 and P-glycoprotein. The pharmacokinetic interaction between sirolimus and concomitantly administered drugs is discussed below. Drug interaction studies have not been conducted with drugs other than those described below.

**Cyclosporine capsules MODIFIED:**

**Rapamune Oral Solution:** In a single dose drug-drug interaction study, 24 healthy volunteers were administered 10 mg sirolimus either simultaneously or 4 hours after a 300 mg dose of Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). For simultaneous administration, the mean $C_{max}$ and AUC of sirolimus were increased by 116% and 230%, respectively, relative to administration of sirolimus alone. However, when given 4 hours after Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]) administration, sirolimus $C_{max}$ and AUC were increased by 37% and 80%, respectively, compared to administration of sirolimus alone.

Mean cyclosporine $C_{max}$ and AUC were not significantly affected when sirolimus was given simultaneously or when administered 4 hours after Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). However, after multiple-dose administration of sirolimus given 4 hours after Neoral® in renal post-transplant patients over 6 months, cyclosporine oral-dose clearance was reduced, and lower doses of Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]) were needed to maintain target cyclosporine concentration.

**Rapamune Tablets**: In a single-dose drug-drug interaction study, 24 healthy volunteers were administered 10 mg sirolimus (Rapamune Tablets) either simultaneously or 4 hours after a 300 mg dose of Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). For simultaneous administration, mean $C_{max}$ and AUC were increased by 512% and 148%, respectively, relative to administration of sirolimus alone. However, when given 4 hours after cyclosporine administration, sirolimus $C_{max}$ and AUC were both increased by only 33% compared with administration of sirolimus alone.

**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).**

**Cyclosporine oral solution:** In a multiple-dose study in 150 psoriasis patients, sirolimus 0.5, 1.5, and 3 mg/m$^2$/day was administered simultaneously with Sandimmune® Oral Solution (cyclosporine Oral Solution) 1.25 mg/kg/day. The increase in average sirolimus trough concentrations ranged between 67% to 86% relative to when sirolimus was administered without cyclosporine. The intersubject variability (%CV) for sirolimus trough concentrations ranged from 39.7% to 68.7%. There was no significant effect of multiple-dose sirolimus on cyclosporine trough concentrations following Sandimmune® Oral Solution (cyclosporine oral solution) administration. However, the %CV was higher (range 85.9% - 165%) than those from previous studies.

Sandimmune® Oral Solution (cyclosporine oral solution) is not bioequivalent to Neoral® Oral Solution (cyclosporine oral solution MODIFIED), and should not be used interchangeably. Although there is no published data comparing Sandimmune® Oral Solution (cyclosporine oral solution) to SangCya® Oral Solution (cyclosporine oral solution [MODIFIED]), they should not be used interchangeably. Likewise, Sandimmune® Soft Gelatin Capsules (cyclosporine capsules) are not bioequivalent to Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]) and should not be used interchangeably.

**Diltiazem:** 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.

**Ketoconazole:** Multiple-dose ketoconazole administration significantly affected the rate and extent of absorption and sirolimus exposure after administration of Rapamune 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 oral tablets should not be administered with ketoconazole.

**Rifampin:** 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, 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.

***Drugs which may be coadministered without dose adjustment***

Clinically significant pharmacokinetic drug-drug interactions were not observed in studies of drugs listed below. A synopsis of the type of study performed for each drug is provided. Sirolimus and these drugs may be coadministered without dose adjustments.

**Acyclovir:** Acyclovir, 200 mg, was administered once daily for 3 days followed by a single 10-mg dose of sirolimus oral solution on day 3 in 20 adult healthy volunteers.

**Digoxin:** Digoxin, 0.25 mg, was administered daily for 8 days and a single 10-mg dose of sirolimus oral solution was given on day 8 to 24 healthy volunteers.

**Glyburide:** A single 5-mg dose of glyburide and a single 10-mg dose of sirolimus oral solution were administered to 24 healthy volunteers. Sirolimus did not affect the hypoglycemic action of glyburide.

**Nifedipine:** A single 60-mg dose of nifedipine and a single 10-mg dose of sirolimus oral solution were administered to 24 healthy volunteers.

**Norgestrel/ethinyl estradiol (Lo/Ovral®):** Sirolimus oral solution, 2 mg, was given daily for 7 days to 21 healthy female volunteers on norgestrel/ethinyl estradiol.

**Prednisolone:** Pharmacokinetic information was obtained from 42 stable renal transplant patients receiving daily doses of prednisone (5-20 mg/day) and either single or multiple doses of sirolimus oral solution (0.5-5 mg/m$^2$ q 12h).

**Sulfamethoxazole/trimethoprim (Bactrim®):** A single oral dose of sulfamethoxazole (400 mg)/trimethoprim, (80 mg) was given to 15 renal transplant patients receiving daily oral doses of sirolimus (8 to 25 mg/m$^2$).

**Other drug interactions**

Sirolimus is extensively metabolized by the CYP3A4 isoenzyme in the gut wall and liver. Therefore, absorption and the subsequent elimination of systemically absorbed sirolimus may be influenced by drugs that affect this isoenzyme. Inhibitors of CYP3A4 may decrease the metabolism of sirolimus and increase sirolimus levels, while inducers of CYP3A4 may increase the metabolism of sirolimus and decrease sirolimus levels.

Drugs that may increase sirolimus blood concentrations include:

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

Drugs that may decrease sirolimus levels include:

Anticonvulsants: carbamazepine, phenobarbital, phenytoin.

Antibiotics: rifabutin, rifapentine.

This list is not all inclusive.

Care should be exercised when drugs that are metabolized by CYP3A4 are administered concomitantly with Rapamune. Grapefruit juice reduces CYP3A4-mediated metabolism of Rapamune and must not be used for dilution (see DOSAGE AND ADMINISTRATION).

*Vaccination*

Immunosuppressants may affect response to vaccination. Therefore, during treatment with Rapamune, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid.

**Drug-Laboratory Test Interactions**

There are no studies on the interactions of sirolimus in commonly employed clinical laboratory tests.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility**

Sirolimus was not genotoxic in the *in vitro* bacterial reverse mutation assay, the Chinese hamster ovary cell chromosomal aberration assay, the mouse lymphoma cell forward mutation assay, or the *in vivo* mouse micronucleus assay.

Carcinogenicity studies were conducted in mice and rats. In an 86-week female mouse study at dosages of 0, 12.5, 25 and 50/6 (dosage lowered from 50 to 6 mg/kg/day at week 31 due to infection secondary to immunosuppression) there was a statistically significant increase in malignant lymphoma at all dose levels (approximately 16 to 135 times the clinical doses adjusted for body surface area) compared to controls. In a second mouse study at dosages of 0, 1, 3 and 6 mg/kg (approximately 3 to 16 times the clinical dose adjusted for body surface area), hepatocellular adenoma and carcinoma (males), were considered Rapamune related. In the 104-week rat study at dosages of 0, 0.05, 0.1, and 0.2 mg/kg/day (approximately 0.4 to 1 times the clinical dose adjusted for body surface area), there was a statistically significant increased incidence of testicular adenoma in the 0.2 mg/kg/day group.

There was no effect on fertility in female rats following the administration of sirolimus at dosages up to 0.5 mg/kg (approximately 1 to 3 times the clinical doses adjusted for body surface area). In male rats, there was no significant difference in fertility rate compared to controls at a dosage of 2 mg/kg (approximately 4 to 11 times the clinical doses adjusted for body surface area). Reductions in testicular weights and/or histological lesions (e.g., tubular atrophy and tubular giant cells) were observed in rats following dosages of 0.65 mg/kg (approximately 1 to 3 times the clinical doses adjusted for body surface area) and above and in a monkey study at 0.1 mg/kg (approximately 0.4

to 1 times the clinical doses adjusted for body surface area) and above. Sperm counts were reduced in male rats following the administration of sirolimus for 13 weeks at a dosage of 6 mg/kg (approximately 12 to 32 times the clinical doses adjusted for body surface area), but showed improvement by 3 months after dosing was stopped.

**Pregnancy**

*Pregnancy Category C:* Sirolimus was embryo/feto toxic in rats at dosages of 0.1 mg/kg and above (approximately 0.2 to 0.5 the clinical doses adjusted for body surface area). Embryo/feto toxicity was manifested as mortality and reduced fetal weights (with associated delays in skeletal ossification). However, no teratogenesis was evident. In combination with cyclosporine, rats had increased embryo/feto mortality compared to Rapamune alone. There were no effects on rabbit development at the maternally toxic dosage of 0.05 mg/kg (approximately 0.3 to 0.8 times the clinical doses adjusted for body surface area). There are no adequate and well controlled studies in pregnant women. Effective contraception must be initiated before Rapamune therapy, during Rapamune therapy, and for 12 weeks after Rapamune therapy has been stopped. Rapamune should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo/fetus.

**Use during lactation**

Sirolimus is excreted in trace amounts in milk of lactating rats. It is not known whether sirolimus is excreted in human milk. The pharmacokinetic and safety profiles of sirolimus in infants are not known. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from sirolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric use**

The safety and efficacy of Rapamune in pediatric patients below the age of 13 years have not been established.

**Geriatric use**

Clinical studies of Rapamune Oral Solution or Tablets did not include sufficient numbers of patients aged 65 and over to determine whether safety and efficacy differ in this population from younger patients. Data pertaining to sirolimus trough concentrations suggest that dose adjustments based upon age in geriatric renal patients are not necessary.

## ADVERSE REACTIONS

**Rapamune® Oral Solution:** The incidence of adverse reactions was determined in two randomized, double-blind, multicenter controlled trials in which 499 renal transplant patients received Rapamune Oral Solution 2 mg/day, 477 received Rapamune Oral Solution 5 mg/day, 160 received azathioprine, and 124 received placebo. All patients were treated with cyclosporine and corticosteroids. Data (≥ 12 months post-transplant) presented in the table below show the adverse reactions that occurred in any treatment group with an incidence of ≥ 20%.

Specific adverse reactions associated with the administration of Rapamune Oral Solution occurred at a significantly higher frequency than in the respective control group. For both Rapamune Oral Solution 2 mg/day and 5 mg/day these include hypercholesterolemia, hyperlipemia, hypertension, and rash; for Rapamune Oral Solution 2 mg/day acne; and for Rapamune Oral Solution 5 mg/day anemia, arthralgia, diarrhea, hypokalemia, and thrombocytopenia. The elevations of triglycerides and cholesterol and decreases in platelets and hemoglobin occurred in a dose related manner in patients receiving Rapamune.

Patients maintained on Rapamune Oral Solution 5 mg/day, when compared to patients on Rapamune Oral Solution 2 mg/day, demonstrated an increased incidence of the following adverse events: anemia, leukopenia, thrombocytopenia, hypokalemia, hyperlipemia, fever, and diarrhea.

ADVERSE EVENTS OCCURRING AT A FREQUENCY OF ≥ 20% IN ANY TREATMENT GROUP IN PREVENTION OF ACUTE RENAL REJECTION TRIALS (%)[a] AT ≥ 12 MONTHS POST-TRANSPLANTATION FOR STUDIES 1 AND 2

| Body System | Rapamune® Oral Solution ------2 mg/day------ | | Rapamune® Oral Solution -----5 mg/day----- | | Azathioprine 2-3 mg/kg/day | Placebo |
|---|---|---|---|---|---|---|
| Adverse Event | Study 1 (n = 281) | Study 2 (n = 218) | Study 1 (n = 269) | Study 2 (n = 208) | Study 1 (n = 160) | Study 2 (n = 124) |
| **Body As A Whole** | | | | | | |
| Abdominal pain | 28 | 29 | 30 | 36 | 29 | 30 |
| Asthenia | 38 | 22 | 40 | 28 | 37 | 28 |
| Back pain | 16 | 23 | 26 | 22 | 23 | 20 |
| Chest pain | 16 | 18 | 19 | 24 | 16 | 19 |
| Fever | 27 | 23 | 33 | 34 | 33 | 35 |
| Headache | 23 | 34 | 27 | 34 | 21 | 31 |
| Pain | 24 | 33 | 29 | 29 | 30 | 25 |
| **Cardiovascular System** | | | | | | |
| Hypertension | 43 | 45 | 39 | 49 | 29 | 48 |
| **Digestive System** | | | | | | |
| Constipation | 28 | 36 | 34 | 38 | 37 | 31 |
| Diarrhea | 32 | 25 | 42 | 35 | 28 | 27 |
| Dyspepsia | 17 | 23 | 23 | 25 | 24 | 34 |
| Nausea | 31 | 25 | 36 | 31 | 39 | 29 |
| Vomiting | 21 | 19 | 25 | 25 | 31 | 21 |
| **Hemic And Lymphatic System** | | | | | | |
| Anemia | 27 | 23 | 37 | 33 | 29 | 21 |
| Leukopenia | 9 | 9 | 15 | 13 | 20 | 8 |
| Thrombocytopenia | 13 | 14 | 20 | 30 | 9 | 9 |
| **Metabolic And Nutritional** | | | | | | |
| Creatinine increased | 35 | 39 | 37 | 40 | 28 | 38 |
| Edema | 24 | 20 | 16 | 18 | 23 | 15 |
| Hypercholesteremia (See WARNINGS and PRECAUTIONS) | 38 | 43 | 42 | 46 | 33 | 23 |
| Hyperkalemia | 15 | 17 | 12 | 14 | 24 | 27 |
| Hyperlipemia (See WARNINGS and PRECAUTIONS) | 38 | 45 | 44 | 57 | 28 | 23 |
| Hypokalemia | 17 | 11 | 21 | 17 | 11 | 9 |
| Hypophosphatemia | 20 | 15 | 23 | 19 | 20 | 19 |
| Peripheral edema | 60 | 54 | 64 | 58 | 58 | 48 |
| Weight gain | 21 | 11 | 15 | 8 | 19 | 15 |
| **Musculoskeletal System** | | | | | | |
| Arthralgia | 25 | 25 | 27 | 31 | 21 | 18 |
| **Nervous System** | | | | | | |
| Insomnia | 14 | 13 | 22 | 14 | 18 | 8 |
| Tremor | 31 | 21 | 30 | 22 | 28 | 19 |
| **Respiratory System** | | | | | | |
| Dyspnea | 22 | 24 | 28 | 30 | 23 | 30 |
| Pharyngitis | 17 | 16 | 16 | 21 | 17 | 22 |
| Upper respiratory infection | 20 | 26 | 24 | 23 | 13 | 23 |

ADVERSE EVENTS OCCURRING AT A FREQUENCY OF ≥ 20% IN ANY TREATMENT GROUP IN PREVENTION OF ACUTE RENAL REJECTION TRIALS (%)[a] AT ≥ 12 MONTHS POST-TRANSPLANTATION FOR STUDIES 1 AND 2

| **Body System** | Rapamune® Oral Solution ------2 mg/day------ | | Rapamune® Oral Solution -----5 mg/day----- | | Azathioprine 2-3 mg/kg/day | Placebo |
|---|---|---|---|---|---|---|
| Adverse Event | Study 1 (n = 281) | Study 2 (n = 218) | Study 1 (n = 269) | Study 2 (n = 208) | Study 1 (n = 160) | Study 2 (n = 124) |
| **Skin And Appendages** | | | | | | |
| Acne | 31 | 22 | 20 | 22 | 17 | 19 |
| Rash | 12 | 10 | 13 | 20 | 6 | 6 |
| **Urogenital System** | | | | | | |
| Urinary tract infection | 20 | 26 | 23 | 33 | 31 | 26 |

a: Patients received cyclosporine and corticosteroids.

At 12 months, there were no significant differences in incidence rates for clinically important opportunistic or common transplant-related infections across treatment groups, with the exception of mucosal infections with *Herpes simplex*, which occurred at a significantly greater rate in patients treated with Rapamune 5 mg/day than in both of the comparator groups.

The table below summarizes the incidence of malignancies in the two controlled trials for the prevention of acute rejection. At 12 months following transplantation, there was a very low incidence of malignancies and there were no significant differences among treatment groups.

INCIDENCE (%) OF MALIGNANCIES IN PREVENTION OF ACUTE RENAL REJECTION TRIALS: AT 12 MONTHS POST-TRANSPLANT [a]

| Malignancy | Rapamune® Oral Solution 2 mg/day (n = 511) | Rapamune® Oral Solution 5 mg/day (n = 493) | Azathioprine 2-3 mg/kg/day (n = 161) | Placebo (n = 130) |
|---|---|---|---|---|
| Lymphoma/lymphoproliferative disease | 0.4 | 1.4 | 0.6 | 0 |
| Non-melanoma skin carcinoma | 0.4 | 1.4 | 1.2 | 3.1 |
| Other malignancy | 0.6 | 0.6 | 0 | 0 |

a: Patients received cyclosporine and corticosteroids

Among the adverse events that were reported at a rate of ≥3% and <20%, the following were more prominent in patients maintained on Rapamune 5 mg/day, when compared to patients on Rapamune 2 mg/day: epistaxis, lymphocele, insomnia, thrombotic thrombocytopenic purpura (hemolytic-uremic syndrome), skin ulcer, increased LDH, hypotension, facial edema.

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; 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, SGOT increased, 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.

Less frequently occurring adverse events included: mycobacterial infections, Epstein-Barr virus infections, and pancreatitis.

**Rapamune® Tablets:** The safety profile of the tablet did not differ from that of the oral solution formulation. The incidence of adverse reactions up to 12 months was determined in a randomized, multicenter controlled trial (Study 3) in which 229 renal transplant patients received Rapamune Oral Solution 2 mg once daily and 228 patients received Rapamune Tablets 2 mg once daily. All patients were treated with cyclosporine and corticosteroids. The adverse reactions that occurred in either treatment group with an incidence of ≥20% in Study 3 are similar to those reported for Studies 1 & 2. There was no notable difference in the incidence of these adverse events between treatment groups (oral solution versus tablets) in Study 3, with the exception of acne, which occurred more frequently in the oral solution group, and tremor which occurred more frequently in the tablet group, particularly in Black patients.

The adverse events that occurred in patients with an incidence of ≥3% and <20% in either treatment group in Study 3 were similar to those reported in Studies 1 & 2. There was no notable difference in the incidence of these adverse events between treatment groups (oral solution versus tablets) in Study 3, with the exception of hypertonia, which occurred more frequently in the oral solution group and diabetes mellitus which occurred more frequently in the tablet group. Hispanic patients in the tablet group experienced hyperglycemia more frequently than Hispanic patients in the oral solution group. In Study 3 alone, menorrhagia, metrorrhagia, and polyuria occurred with an incidence of ≥3% and <20%.

The clinically important opportunistic or common transplant-related infections were identical in all three studies and the incidences of these infections were similar in Study 3 compared with Studies 1&2. The incidence rates of these infections were not significantly different between the oral solution and tablet treatment groups in Study 3.

In Study 3 (at 12 months), there were two cases of lymphoma/lymphoproliferative disorder in the oral solution treatment group (0.8%) and two reported cases of lymphoma/lymphoproliferative disorder in the tablet treatment group (0.8%). These differences were not statistically significant and were similar to the incidences observed in Studies 1 & 2.

**Other clinical experience:** Cases of pneumonitis with no identified infectious etiology, sometimes with an interstitial pattern, have occurred in patients receiving immunosuppressive regimens including Rapamune. In some cases, the pneumonitis has resolved upon discontinuation of Rapamune.

## OVERDOSAGE

There is minimal experience with overdose. During clinical trials, there were two accidental Rapamune ingestions, of 120 mg and 150 mg. One patient, receiving 150 mg, experienced an episode of transient atrial fibrillation. The other patient experienced no adverse effects. General supportive measures should be followed in all cases of overdose. Based on the poor aqueous solubility and high erythrocyte binding of Rapamune, it is anticipated that Rapamune is not dialyzable to any significant extent.

In mice and rats, the acute oral lethal dose was greater than 800 mg/kg.

## DOSAGE AND ADMINISTRATION

It is recommended that Rapamune Oral Solution and Tablets be used in a regimen with cyclosporine and corticosteroids. Two-mg Rapamune oral solution has been demonstrated to be clinically equivalent to 2-mg Rapamune oral tablets; 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. 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.

To minimize the variability of exposure to Rapamune, this drug should be taken consistently with or without food. Grapefruit juice reduces CYP3A4-mediated metabolism of Rapamune and must not be administered with Rapamune or used for dilution.

**It is recommended that sirolimus be taken 4 hours after administration of cyclosporine oral solution (MODIFIED) and/or cyclosporine capsules (MODIFIED).**

**Dosage Adjustments**

The initial dosage in patients $13 years who weigh less than 40 kg should be adjusted, based on body surface area, to 1 mg/m$^2$/day. The loading dose should be 3 mg/m$^2$.

It is recommended that the maintenance dose of Rapamune be reduced by approximately one third in patients with hepatic impairment. It is not necessary to modify the Rapamune loading dose**.** Dosage need not be adjusted because of impaired renal function.

**Blood Concentration Monitoring**

Routine therapeutic drug level monitoring is not required in most patients. Blood sirolimus levels should be monitored in pediatric patients, in patients with hepatic impairment, during concurrent administration of strong CYP3A4 inducers and inhibitors, and/or if cyclosporine dosing is markedly reduced or discontinued. In controlled clinical trials with concomitant cyclosporine, mean sirolimus whole blood trough levels, as measured by immunoassay, were 9 ng/mL (range 4.5 – 14 ng/mL [10$^{th}$ to 90$^{th}$ percentile]) for the 2 mg/day treatment group, and 17 ng/mL (range 10 - 28 ng/mL [10$^{th}$ to 90$^{th}$ percentile]) for the 5 mg/day dose.

Results from other assays may differ from those with an immunoassay. On average, chromatographic methods (HPLC UV or LC/MS/MS) yield results that are approximately 20% lower than the immunoassay for whole blood concentration determinations. Adjustments to the targeted range should be made according to the assay ultilized to determine sirolimus trough concentrations. Therefore, comparison between concentrations in the published literature and an individual patient concentration using current assays must be made with detailed knowledge of the assay methods employed. A discussion of the different assay methods is contained in *Clinical Therapeutics*, Volume 22, Supplement B, April 2000.

**Instructions for Dilution and Administration of Rapamune® Oral Solution Bottles**

The amber oral dose syringe should be used to withdraw the prescribed amount of Rapamune® Oral Solution from the bottle. Empty the correct amount of Rapamune from the syringe into only a glass or plastic container holding at least two (2) ounces (¼ 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 (½ cup, 120 mL)) of water or orange juice, stir vigorously, and drink at once.

**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 (½ cup, 120 mL)) of water or orange juice, stir vigorously, and drink at once.

**Handling and Disposal**

Since Rapamune is not absorbed through the skin, there are no special precautions. However, if direct contact with the skin or mucous membranes occurs, wash thoroughly with soap and water; rinse eyes with plain water.

**HOW SUPPLIED**

Rapamune® 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.

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.

Rapamune® Tablets are available as follows: 1 mg, white, triangular-shaped tablets marked "RAPAMUNE 1 mg" on one side.

NDC # 0008-1031-05, bottle of 100 tablets.
NDC # 0008-1031-10, Redipak® cartons of 100 tablets (10 blister cards of 10 tablets each).

**Storage**

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., several days, but not longer than 30 days).

An amber syringe and cap are provided for dosing and the product may be kept in the syringe for a maximum of 24 hours at room temperatures up to 25°C (77°F) or refrigerated at 2°C to 8°C (36°F to 46°F). The syringe should be discarded after one use. After dilution, the preparation should be used immediately.

Rapamune Oral Solution provided in bottles may develop a slight haze when refrigerated. If such a haze occurs allow the product to stand at room temperature and shake gently until the haze disappears. The presence of this haze does not affect the quality of the product.

Rapamune® Tablets should be stored at 20° to 25°C (USP Controlled Room Temperature) (68° - 77°F). Use cartons to protect blister cards and strips from light. Dispense in a tight, light-resistant container as defined in the USP.

**$R_x$ only.**

US Pat. Nos.: 5,100,899; 5,212,155; 5, 308,847; 5,403,833; 5,536,729.

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Division of Wyeth-Ayerst Pharmaceuticals Inc.
Philadelphia, PA 19101

25 August 2000

# PATIENT INSTRUCTIONS FOR RAPAMUNE® ORAL SOLUTION ADMINISTRATION

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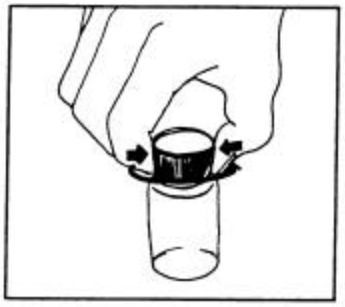
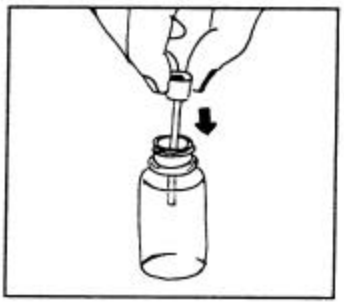
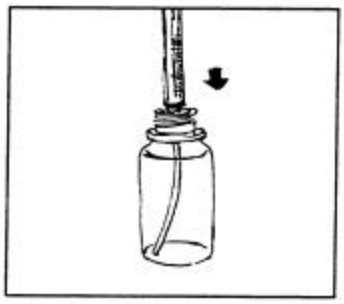


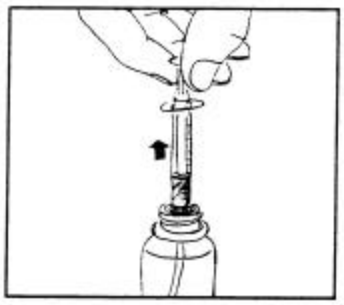
1. Open the solution bottle. Remove the safety cap by squeezing the tabs on the cap and twisting counterclockwise.



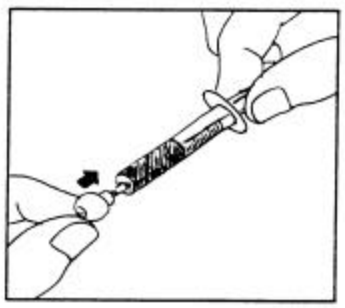
2. On first use, insert the adapter assembly (plastic tube with stopper) tightly into the bottle until it is even with the top of the bottle. Do not remove the adapter assembly from the bottle once inserted.



3. For each use, tightly insert one of the amber syringes with the plunger fully depressed into the opening in the adapter.

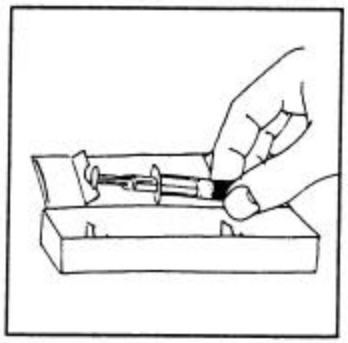


4. Withdraw the prescribed amount of Rapamune® Oral Solution by gently pulling out the plunger of the syringe until the bottom of the black line of the plunger is even with the appropriate mark on the syringe. Always keep the bottle in an upright position. If bubbles form in the syringe, empty the syringe into the bottle and repeat the procedure.



5. You may have been instructed to carry your medication with you. If it is necessary to carry the filled syringe, place a cap securely on the syringe — the cap should snap into place.

6



6. Then place the capped syringe in the enclosedcarrying case. Once in the syringe, the medication may be kept at room temperature or refrigerated and should be used within 24 hours. Extreme temperatures (below 36°F and above 86°F) should be avoided. Remember to keep this medication out of the reach of children.

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7. Empty the syringe into a glass or plastic cup containing at least 2 ounces (1/4 cup; 60 mL) of water or orange juice, stir vigorously for one (1) minute and drink immediately. Refill the container with at least 4 ounces (1/2 cup; 120 mL) of water or orange juice, stir vigorously again and drink the rinse solution. Apple juice, grapefruit juice or other liquids are NOT to be used. Only glass or plastic cups should be used to dilute Rapamune® Oral Solution. The syringe and cap should be used once and then discarded.

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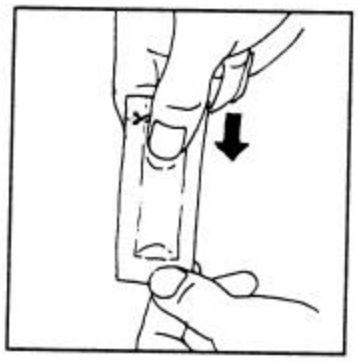
8. Always store the bottles of medication in the refrigerator. When refrigerated, a slight haze may develop in the solution. The presence of a haze does not affect the quality of the product. If this happens, bring the Rapamune® Oral Solution to room temperature and shake until the haze disappears. If it is necessary to wipe clean the mouth of the bottle before returning the product to the refrigerator, wipe with a dry cloth to avoid introducing water, or any other liquid, into the bottle.

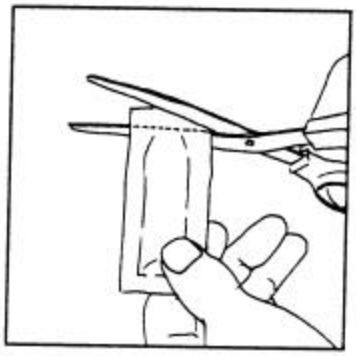
## PATIENT INSTRUCTIONS FOR RAPAMUNE® ORAL SOLUTION ADMINISTRATION

1



1. Before opening the pouch, squeeze the pouch from the neck area to push the contents into the lower part of the pouch.

2



2. Carefully open the pouch by folding the marked area and then cutting with a scissors along the marked line near the top of the pouch.

3

3. Squeeze the entire contents of the pouch into a glass or plastic cup containing at least 2 ounces (1/4 cup; 60 mL) of water or orange juice, stir vigorously for one (1) minute and drink immediately. Refill the container with at least 4 ounces (1/2 cup, 120 mL) of water or orange juice, stir vigorously again and drink the rinse solution. Apple juice, grapefruit juice or other liquids are NOT to be used. Only glass or plastic cups should be used to dilute Rapamune® Oral Solution.

4. Unused pouches should be stored in the refrigerator.

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