1. NAME OF THE MEDICINAL PRODUCT

Rapamune

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sirolimus (INN)

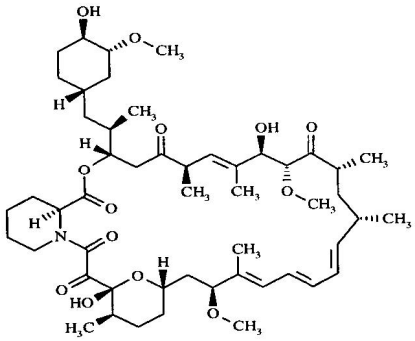
Rapamune (sirolimus) is an immunosuppressive agent. Sirolimus is a macrocyclic lactone produced by *Streptomyces hygroscopicus*.

Chemical Name

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.

Structure

The structural formula of sirolimus is shown below.



Molecular Formula

Its molecular formula is $C_{51}H_{79}NO_{13}$

Molecular Weight

Its molecular weight is 914.2.

Physical Characteristics

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

Composition and Pharmaceutical Characteristics

Rapamune is available for administration as an oral solution containing 1 mg/mL sirolimus and

as a tan, triangular-shaped tablet containing 0.5 mg sirolimus, as a white, triangular-shaped tablet containing 1 mg, and as a yellow-to-beige triangular-shaped tablet containing 2 mg sirolimus.

Excipients: see **Section 6.1 List of excipients**.

3. PHARMACEUTICAL FORM

Oral solution and tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Rapamune (sirolimus) is indicated for the prophylaxis of organ rejection in patients receiving renal transplants.

In patients at low to moderate immunologic risk, it is recommended that Rapamune be used initially in a regimen with cyclosporine and corticosteroids.

Cyclosporine should be withdrawn 2 to 4 months after transplantation and the Rapamune dose should be increased to reach recommended blood concentrations (see **Section 4.2 Posology and method of administration**). Cyclosporine withdrawal has not been studied in patients with Banff 93 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, renal re-transplants, multi-organ transplants, or patients with high-panel reactive antibodies (see **Section 5 PHARMACOLOGICAL PROPERTIES - Clinical trials data on efficacy**).

4.2. Posology and method of administration

4.2.1. Dosage

Bioavailability has not been determined for tablets after they have been crushed, chewed, or split and therefore, this cannot be recommended.

Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe 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.

Patients at low to moderate immunologic risk

It is recommended that Rapamune oral solution and tablets be used initially in a regimen with cyclosporine and corticosteroids. Cyclosporine should be withdrawn 2 to 4 months after renal transplantation in patients at low to moderate immunological risk, and the Rapamune dose should be increased to reach recommended blood concentrations. Cyclosporine withdrawal has not been studied in patients with Banff 93 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 **Section 4.1 Therapeutic indications** and **Section 5 PHARMACOLOGICAL PROPERTIES - Clinical trials data on efficacy**).

Adults

Rapamune with cyclosporine therapy
The usual dosage regimen for Rapamune is a 6 mg oral loading dose, administered as soon as possible after transplantation, followed by 2 mg once daily. The Rapamune dose should then be individualized, to obtain whole blood trough levels of 4 to 12 ng/mL.

2 mg of Rapamune oral solution has been demonstrated to be clinically equivalent to 2 mg of 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 Rapamune tablets on a mg to mg basis. (See **Section 5 PHARMACOLOGICAL PROPERTIES – 5.2 Pharmacokinetics, Absorption**.) Rapamune is to be administered orally once daily.

Rapamune maintenance regimen with cyclosporine withdrawal
Initially, patients 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 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 at year 1 and 5 (see below) were close to these ranges (see **Section 4.2.2 Sirolimus whole blood trough level 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).

Patients at high immunologic risk

It is recommended that Rapamune be taken 4 hours after cyclosporine microemulsion [cyclosporine, USP] administration.

Use in Children

Safety and efficacy of Rapamune in pediatric patients below the age of 13 years have not been established. It is recommended that sirolimus whole blood trough levels be monitored if used in pediatric patients <13 years of age.

Use in Elderly Patient

No dose adjustment is required in elderly patients.

Clinical studies of Rapamune did not include sufficient number of patients aged 65 and over to determine whether they will respond differently than younger patients. Sirolimus trough concentration data in 35 renal transplant patients >65 years of age were similar to those in the adult population (n=822) from 18 to 65 years of age.

Patients with Renal Impairment

No dosage adjustment is required.

Patients with Hepatic Impairment

In patients with hepatic impairment, it is recommended that the maintenance dose of Rapamune be reduced by approximately one-third to one-half. It is not necessary to modify the Rapamune loading dose.

The pharmacokinetics of Rapamune has not been studied in patients with severe hepatic impairment.

In patients with hepatic impairment, it is recommended that sirolimus whole blood trough levels be monitored.

4.2.2. Sirolimus whole blood trough level monitoring

Blood sirolimus trough levels should be monitored:

(1) in patients with hepatic impairment
(2) in patients receiving concentration-controlled Rapamune
(3) in pediatric patients
(4) during concurrent administration of inhibitors and inducers of CYP3A4 and P-glycoprotein (P-gp)
(5) if cyclosporine dosing is markedly reduced, or if cyclosporine is discontinued.

Therapeutic drug monitoring should not be the sole basis for adjusting sirolimus therapy. Careful attention should be made to clinical signs/symptoms, tissue biopsies, and laboratory parameters.

It is recommended that patients switched from the solution to the tablet formulation on a mg per mg basis have a trough concentration taken 1 or 2 weeks after switching formulations to confirm that the trough concentration is within the recommended target range.

Assay Methodology
The recommended 24-hour trough concentration ranges for sirolimus are based on chromatographic methods. Several assay methodologies have been used to measure the whole blood concentrations of sirolimus. Currently in clinical practice, sirolimus whole blood concentrations are being measured by both chromatographic and immunoassay methodologies. The concentration values obtained by these different methodologies are not interchangeable. Adjustments to the targeted range should be made according to the assay being utilized to determine the sirolimus trough concentration. Since results are assay and laboratory dependent, and the results may change over time, adjustments to the target therapeutic range must be made

with a detailed knowledge of the site-specific assay used. A discussion of the different assay methods is contained in Clinical Therapeutics, Volume 22, Supplement B, April 2000.

4.2.3. Mode of administration

Rapamune is intended for oral administration only.

Rapamune must be taken consistently with or without food to minimize variation in drug absorption.

Only water or orange juice should be used for Rapamune oral solution dilution, using only glass or plastic cups. Do not dilute Rapamune with grapefruit juice (see **Section 4.5 Interaction with other medicinal products and other forms of interaction**) or any other liquids.

Rapamune oral solution contains polysorbate-80, which is known to increase the rate of di-(2-ethylhexyl)phthalate (DEHP) extraction from polyvinyl chloride (PVC). This should be considered during the preparation and administration of Rapamune oral solution. It is important that the recommendations in **Section 4.2 Posology and method of administration** be followed closely.

4.3. Contraindications

Rapamune is contraindicated in patients with a hypersensitivity to sirolimus or its derivatives or any excipients in the formulation.

4.4. Special warnings and precautions for use

Immunosuppression increases the susceptibility to infection and the development of lymphoma and other malignancies, particularly of the skin, (see **Section 4.8 Undesirable effects**). Oversuppression of the immune system can also increase susceptibility to opportunistic infections, sepsis, and fatal infections. 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.

Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, exfoliative dermatitis, and hypersensitivity vasculitis, have been associated with the administration of sirolimus (see **Section 4.8 Undesirable effects**).

The safety and efficacy of Rapamune as immunosuppressive therapy have not been established in liver or lung transplant patients, and therefore, such use is not recommended.

<u>Liver Transplantation</u>
Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis (HAT): The use of Rapamune in combination with tacrolimus was associated with excess mortality and graft loss in a study in *de novo* liver transplant recipients. Many of these patients had evidence of infection at or near the time of death. In this and another study in *de novo* liver transplant recipients, the use of Rapamune in combination with cyclosporine or tacrolimus was associated with an increase

in HAT; most cases of HAT occurred within 30 days post-transplantation and most led to graft loss or death.

A clinical study in liver transplant patients randomised to conversion to a sirolimus-based regimen versus continuation of a calcineurin inhibitors (CNI)-based regimen 6-144 months post-liver transplantation demonstrated an increased number of deaths in the sirolimus conversion group compared to the CNI continuation group, although the difference was not statistically significant (see **Section 5 PHARMACOLOGICAL PROPERTIES - Clinical trials data on efficacy**).

Lung Transplantation

Bronchial Anastomotic Dehiscence: Cases of bronchial anastomotic dehiscence, most fatal, have been reported in *de novo* lung transplant patients when Rapamune has been used as part of an immunosuppressive regimen.

Co-administration of Rapamune with strong inhibitors of CYP3A4 and/or P-gp (such as ketoconazole, voriconazole, itraconazole, erythromycin, telithromycin, or clarithromycin) or strong inducers of CYP3A4 and/or P-gp (such as rifampin or rifabutin) is not recommended. Sirolimus is extensively metabolised by the CYP3A4 isozyme in the intestinal wall and liver. Inhibitors of CYP3A4 decrease the metabolism of sirolimus and increase sirolimus levels. Inducers of CYP3A4 increase the metabolism of sirolimus and decrease sirolimus levels (see **Section 4.5 Interaction with other medicinal products and other forms of interaction**).

Renal Function

In Studies 1 and 2, from month 6 through months 24 and 36, respectively, mean serum creatinine was increased and mean glomerular filtration rate was decreased in patients treated with Rapamune and cyclosporine compared with those treated with cyclosporine and placebo or azathioprine controls. The rate of decline in renal function was greater in patients receiving Rapamune and cyclosporine compared with control therapies (see **Section 5 PHARMACOLOGICAL PROPERTIES - Clinical trials data on efficacy**). Renal function should be closely monitored during the co-administration of Rapamune with cyclosporine because long-term administration of the combination has been associated with deterioration of renal function. Renal function should also be closely monitored during the co-administration of Rapamune with tacrolimus. Appropriate adjustment of the immunosuppression regimen, including discontinuation of Rapamune and/or cyclosporine and/or tacrolimus, 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 clinical trials, Rapamune has been administered concurrently with corticosteroids and with cyclosporine. The formulations of cyclosporine include:

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

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

General

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.

Wound Healing and Fluid Accumulation

Mammalian Target Of Rapamycin (mTOR) inhibitors such as sirolimus have been shown *in vitro* to inhibit production of certain growth factors that may affect angiogenesis, fibroblast proliferation, and vascular permeability. There have been reports of impaired or delayed wound healing in patients receiving Rapamune, including lymphocele and wound dehiscence. Patients with a body mass index (BMI) greater than 30 kg/m^2 may be at increased risk of abnormal wound healing based on data from the medical literature.

There have also been reports of fluid accumulation, including peripheral edema, lymphedema, pleural effusion and pericardial effusions (including hemodynamically significant effusions in children and adults), in patients receiving Rapamune.

Skin Malignancies

Immunosuppression increases the susceptibility to the development of lymphoma and other malignancies, particularly of the skin. Therefore, patients taking Rapamune should limit exposure to sunlight and UV light by wearing protective clothing and using a sunscreen with a high protective factor (see **Section 4.8 Undesirable effects**).

Hyperlipidemia

The use of Rapamune may lead to more frequently increased serum cholesterol and triglycerides that may require treatment compared with azathioprine or placebo controls. Patients must be monitored for hyperlipidemia.

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.

Rhabdomyolysis

In clinical trials, the concomitant administration of Rapamune and HMG-CoA reductase inhibitors and/or fibrates was well tolerated. During Rapamune therapy with or without cyclosporine, patients should be monitored for elevated lipids, and patients administered an

HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects as described in the respective labeling for these agents.

Rapamune following Cyclosporine Withdrawal

In a study that compared a regimen of Rapamune and cyclosporine to one in which cyclosporine was withdrawn 2-4 months post-transplantation, those in whom cyclosporine was not withdrawn had significantly higher serum creatinine levels and significantly lower glomerular filtration rates at 12 months through 60 months, and significantly lower graft survival at 48 months, the point at which it was decided by the sponsor to discontinue subjects from assigned therapy in the Rapamune and cyclosporine arm. When the protocol was amended all subjects had reached 48 months and some completed the 60 months of the study.

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 individual patients.

In patients with delayed graft function, Rapamune may delay recovery of renal function.

Proteinuria

Periodic quantitative monitoring of urinary protein excretion is recommended. In a study evaluation conversion from CNI to Rapamune in maintenance renal transplant patients 6 – 120 months post-transplant, increased urinary protein excretion was commonly observed from the 6 through 24 month after conversion of Rapamune compared with CNI continuation (23.6% versus 12.8%, respectively) (see **Section 4.8 Undesirable effects** and **Section 5 PHARMACOLOGICAL PROPERTIES - Clinical trials data on efficacy**). Those patients in the highest quartile of urinary protein excretion prior to Rapamune conversion (urinary protein to creatinine ratio ≥0.27) were those whose protein excretion increased the most after conversion. New-onset nephrosis (nephrotic syndrome) was also reported in 2% of the patients in the study. Reduction in the degree of urinary protein excretion was observed for individual patients following discontinuation of Rapamune. The safety and efficacy of conversion from calcineurin inhibitors to sirolimus in maintenance renal transplant patients have not been established.

Conversion to Rapamune in Patients with Glomerular Filtration Rate <40 mL/min

In a study evaluating conversion from CNI to Rapamune in maintenance renal transplant patients 6-120 months post-transplant (see **Section 5 PHARMACOLOGICAL PROPERTIES - Clinical trials data on efficacy**), in a stratum of the Rapamune treatment arm with a calculated glomerular filtration rate of less than 40 mL/min, there was a higher rate of serious adverse events, including pneumonia, acute rejection, graft loss and death. The safety and efficacy of conversion from calcineurin inhibitors to Rapamune in maintenance renal transplant patients have not been established.

De Novo Use without Calcineurin Inhibitor (CNI)

The safety and efficacy of *de novo* use of Rapamune without a calcineurin inhibitor (CNI) is not established in renal transplant patients. In two multi-center clinical studies, *de novo* renal transplant patients treated with Rapamune, MMF, steroids, and an IL-2 receptor antagonist had significantly higher acute rejection rates and numerically higher death rates compared to patients treated with a calcineurin inhibitor, MMF, steroids, and IL-2 receptor antagonist. A benefit, in terms of better renal function, was not apparent in the treatment arms with *de novo* use of Rapamune without a CNI. It should be noted that an abbreviated schedule of administration of daclizumab was employed in one of the studies.

Calcineurin Inhibitor-induced Hemolytic Uremic Syndrome/Thrombotic Thrombocytopenic Purpura/Thrombotic Microangiopathy (HUS/TTP/TMA)
The concomitant use of sirolimus with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced HUS/TTP/TMA.

Angioedema
The concomitant administration of Rapamune and angiotensin-converting enzyme (ACE) inhibitors has resulted in angioneurotic edema-type reactions.

Elevated sirolimus levels (with/without concomitant ACE inhibitors) may also potentiate angioedema (see **Section 4.5.1 Inhibitors of Cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp)**). In some cases, the angioedema has resolved upon discontinuation or dose reduction of Rapamune.

Interstitial Lung Disease
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 trough sirolimus levels increases (see **Section 4.8 Undesirable effects**, Interstitial Lung Disease).

Latent Viral Infections
Patients treated with immunosuppressants, including Rapamune, are at increased risk for opportunistic infections, including activation of latent viral infections. Among these conditions is BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal outcomes, including graft loss. Physicians should consider latent viral infections in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms (see **Section 4.8 Undesirable effects**, Latent Viral Infections).

Antimicrobial Prophylaxis
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 infection.

Contraception
Women of childbearing potential should be informed of the potential risks during pregnancy

and that effective contraception must be initiated before Rapamune therapy, and maintained during Rapamune therapy and for 12 weeks after Rapamune therapy has been stopped.

Use in High-Risk Patients
The safety and efficacy of cyclosporine withdrawal in high-risk renal transplant patients have not been adequately studied and such use is therefore, not recommended. This includes patients with Banff 93 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, renal re-transplants, multi-organ transplants, and patients with a high panel of reactive antibodies (see **Section 4.1 Therapeutic indications** and **Section 5 PHARMACOLOGICAL PROPERTIES - Clinical trials data on efficacy**).

Laboratory Tests
Whole blood sirolimus levels should be monitored in all patients. 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 **Section 4.5 Interaction with other medicinal products and other forms of interaction**).

4.5. Interaction with other medicinal products and other forms of interaction

Sirolimus is known to be a substrate for both cytochrome CYP3A4 and P-glycoprotein (P-gp). 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.

4.5.1. Inhibitors and inducers of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp)

Co-administration of Rapamune with strong inhibitors of CYP3A4 (such as ketoconazole, voriconazole, itraconazole, telithromycin, or clarithromycin) or inducers of CYP3A4 (such as rifampin or rifabutin) is not recommended. Sirolimus is extensively metabolised by the CYP3A4 isoenzyme intestinal wall and liver and undergoes counter-transport from enterocytes of the small intestine by the P-glycoprotein (P-gp) drug-efflux pump. Therefore, absorption and the subsequent elimination of systemically absorbed sirolimus may be influenced by drugs that affect these proteins. Inhibitors of CYP3A4 and P-gp may increase sirolimus levels. Inducers of CYP3A4 and P-gp may decrease sirolimus levels. In patients in whom strong inhibitors or inducers of CYP3A4 and P-gp are indicated, alternative therapeutic agents with less potential for inhibition or induction of CYP3A4 and P-gp should be considered.

Substances that inhibit CYP3A4 include but are not limited to:
- Calcium channel blockers: diltiazem, nicardipine, verapamil
- Antifungal agents: clotrimazole, fluconazole, itraconazole, ketoconazole, voriconazole
- Antibiotics: clarithromycin, erythromycin, telithromycin, troleandomycin
- Gastrointestinal prokinetic agents: cisapride, metoclopramide
- Other drugs: bromocriptine, cimetidine, cyclosporine, danazol, protease inhibitors (e.g., for HIV and hepatitis C that include drugs such as ritonavir, indinavir, boceprevir, and telaprevir)
- Grapefruit juice

Substances that induce CYP3A4 include but are not limited to:

- Anticonvulsants: carbamazepine, phenobarbital, phenytoin
- Antibiotics: rifabutin, rifampicin, rifapentine
- Herbal preparations: St. John's Wort (*Hypericum perforatum*, hypericin)

The pharmacokinetic interaction between sirolimus and concomitantly administered drugs is discussed below. Drug interaction studies have been conducted with the following:

Diltiazem

Diltiazem is a substrate and inhibitor of CYP3A4 and P-gp. Sirolimus levels should be monitored and a dose reduction may be necessary if diltiazem is co-administered.

The simultaneous oral administration of 10 mg of sirolimus oral solution and 120 mg of diltiazem to 18 healthy volunteers significantly increased 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.

Verapamil

Verapamil is an inhibitor of CYP3A4 and P-gp. Sirolimus levels should be monitored and appropriate dose reduction of both medications should be considered.

Multiple-dose administration of verapamil and Rapamune oral solution significantly affected the rate and extent of absorption of both drugs. In a study of 25 healthy volunteers, whole blood sirolimus C_{max}, t_{max}, and AUC were increased 2.3-fold, 1.1-fold, and 2.2-fold, respectively. Plasma S-(-) verapamil C_{max} and AUC were both increased 1.5-fold, and t_{max} was decreased 24%.

Erythromycin

Erythromycin is an inhibitor of CYP3A4 and P-gp. Sirolimus levels should be monitored and appropriate dose reductions of both medications should be considered.

Multiple-dose administration of erythromycin ethylsuccinate and Rapamune oral solution significantly increased the rate and extent of absorption of both drugs. In a study of 24 healthy volunteers, whole blood sirolimus C_{max}, t_{max}, and AUC were increased 4.4-fold, 1.4-fold, and 4.2-fold, respectively. The C_{max}, t_{max}, and AUC of plasma erythromycin base were increased 1.6-fold, 1.3-fold, and 1.7-fold, respectively.

Ketoconazole

Ketoconazole is a strong inhibitor of CYP3A4 and P-gp. Co-administration of Rapamune and ketoconazole is not recommended.

In a study of 24 healthy volunteers, it was found that 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 4.4-fold, 1.4-fold, and 10.9-fold, respectively. However, the terminal $t_{1/2}$ of sirolimus was not changed. Single-dose Rapamune did not affect steady-state 12-hour plasma ketoconazole concentrations.

Rifampicin

Rifampin is a strong inducer of CYP3A4 and P-gp. Co-administration of Rapamune and rifampin is not recommended.

Pretreatment of 14 healthy volunteers with multiple doses of rifampicin (600 mg daily for 14 days) followed by a single 20 mg-dose of Rapamune oral solution, greatly increased sirolimus oral-dose clearance by 5.5-fold (range = 2.8 to 10), which represents mean decreases in AUC and C_{max} of about 82% and 71%, respectively.

4.5.2. Non-interactions

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 co-administered 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.

- **Atorvastatin:** Atorvastatin, 20 mg, was given daily for 10 days to 23 healthy volunteers, followed by a combined regimen of sirolimus oral solution, 2 mg, and atorvastatin, 20 mg, for 5 days.

- **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.

- **Prednisone:** 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).

4.5.3. Cyclosporine

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

Patients administered sirolimus with cyclosporine together with HMG-CoA reductase inhibitor and/or fibrate should be monitored for the development of rhabdomyolysis (see **Section 4.4 Special warnings and precautions for use**).

Cyclosporine microemulsion (cyclosporine, USP)

It is recommended that Rapamune be taken 4 hours after cyclosporine microemulsion (cyclosporine, USP) administration.

In a single-dose drug-drug interaction study, 24 healthy volunteers were administered 10 mg Rapamune oral solution either simultaneously or 4 hours after a 300 mg dose of cyclosporine microemulsion (cyclosporine, USP). 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 cyclosporine microemulsion (cyclosporine, USP) administration, sirolimus C_{max} and AUC were increased by 37% and 80%, respectively, compared to administration of Rapamune alone.

In an otherwise identical study, Rapamune was administered as a 10 mg dose by tablet. For simultaneous administration, mean C_{max} and AUC were increased by 6.1-fold and 2.5-fold, respectively, relative to administration of Rapamune alone. However, when given 4 hours after cyclosporine microemulsion (cyclosporine, USP) administration, sirolimus C_{max} and AUC were both increased by only 33% compared with administration of Rapamune alone.

After multiple-dose administration of Rapamune by oral solution given 4 hours after cyclosporine microemulsion (cyclosporine, USP) in renal post-transplant patients over 6 months, cyclosporine oral-dose clearance was reduced, and lower doses of cyclosporine microemulsion (cyclosporine, USP) were needed to maintain target cyclosporine concentrations.

Rapamune Oral Solution: In a single dose drug-drug interaction study, 24 healthy volunteers were administered 5 mg Rapamune either simultaneously or 2 hours before and after a 300 mg dose of cyclosporine microemulsion (cyclosporine, USP). For simultaneous administration, the mean C_{max} and AUC of sirolimus were increased by 117% and 183%, respectively, relative to administration of Rapamune alone. When given 2 hours after cyclosporine microemulsion (cyclosporine, USP) administration, sirolimus C_{max} and AUC were increased by 126% and 141%, respectively, compared to administration of Rapamune alone. When given 2 hours before cyclosporine microemulsion (cyclosporine, USP) administration, sirolimus C_{max} and AUC were not affected.

Sandimmune® Soft Gelatin Capsules (cyclosporine capsules) are not bioequivalent to Neoral® Soft Gelatin Capsules (cyclosporine capsules) and should not be used interchangeably.

- **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), and should not be used interchangeably. Although there

is no published data comparing Sandimmune® Oral Solution (cyclosporine oral solution) to SandCya® Oral Solution (cyclosporine oral solution), they should not be used interchangeably.

4.5.4. HMG-CoA reductase inhibitors, fibrates

Patients administered Rapamune with HMG-CoA reductase inhibitors and/or fibrates should be monitored for the development of rhabdomyolysis (see **Section 4.4 Special warnings and precautions for use**).

4.5.5. Calcineurin inhibitors

Calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA) has been reported in patients receiving sirolimus with a calcineurin inhibitor (see **Section 4.4 Special warnings and precautions for use**).

4.5.6. Vaccination

Immunosuppressants may affect response to vaccination. During treatment with immunosuppressants, including Rapamune, vaccination may be less effective. The use of live vaccines should be avoided during treatment with Rapamune.

4.5.7. Food

The bioavailability of sirolimus is affected by concomitant food intake after administration by either Rapamune oral solution or tablet. Rapamune® should be taken consistently with or without food to minimize blood level variability.

Grapefruit juice reduces CYP3A4-mediated drug metabolism and potentially enhances P-gp-mediated drug counter-transport from enterocytes of the small intestines. This juice must not be taken with Rapamune tablets or oral solution or be used for oral solution dilution (see **Section 4.2 Posology and method of administration - Mode of Administration**).

4.5.8. Interference with laboratory and other diagnostic tests

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

4.6. Pregnancy and lactation

Pregnancy

There are no studies of Rapamune use in pregnant women. In animal studies, embryo/fetal toxicity was manifested as mortality and reduced fetal weights (with associated delays in skeletal ossification) (see **Section 5.3 Preclinical safety data**).

Rapamune should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo/fetus (see **Section 4.4 Special warnings and precautions for use**).

Lactation

Rapamune is excreted in trace amounts in milk of lactating rats. It is not known whether sirolimus is excreted in human milk. Because many drugs are excreted into 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.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8. Undesirable effects

Rapamune Oral Solution: The incidence of adverse reactions was determined in two randomised, 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 with 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.

In general, adverse events related to the administration of Rapamune were dependent on dose/concentration.

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
Hypercholesterolemia	38	43	42	46	33	23
(See **Section 4.4. Special warnings and precautions for use**)						
Hyperkalemia	15	17	12	14	24	27
Hyperlipidemia	38	45	44	57	28	23
(See **Section 4.4. Special warnings and precautions for use**)						
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						

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)
Dyspnea	22	24	28	30	23	30
Pharyngitis	17	16	16	21	17	22
Upper respiratory infection	20	26	24	23	13	23
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.

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 frequency of adverse reactions listed in the following table includes reactions reported in patients treated with Rapamune-based regimens.

In general, adverse events related to administration of Rapamune were dependent on dose/concentration.

The adverse reactions in the table below are listed in the MedDRA frequency categories.

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1000	Very Rare <1/10,000	Frequency Not Known (Cannot be estimated from available data)
Blood and Lymphatic System Disorders	Thrombocytopenia; anaemia; leukopenia	Haemolytic uraemic syndrome; neutropenia	Pancytopenia; thrombotic thrombocytopenic purpura			
Cardiac Disorders	Tachycardia	Pericardial effusion				
Gastrointestinal Disorders	Abdominal pain; constipation; diarrhoea; nausea	Pancreatitis; stomatitis; ascites				

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10, 000 to <1/1 000	Very Rare <1/10,000	Frequency Not Known (Cannot be estimated from available data)
General Disorders and Administration Site Conditions	Oedema; oedema peripheral; pyrexia; pain; impaired healing					
Immune System Disorders		Hypersensitivity (including angioedema, anaphylactic reaction, and anaphylactoid reaction)				
Infections and Infestations	Pneumonia; fungal infection; viral infection; bacterial infection; herpes simplex; urinary tract infection	Sepsis; pyelonephritis; cytomegalovirus infection; herpes zoster	Mycobacterial infection (including tuberculosis); Epstein-Barr virus infection			
Investigations	Blood lactate dehydrogenase increased; blood creatinine increased; liver function test abnormal (including alanine aminotransferase increased and aspartate aminotransferase increased)					

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10, 000 to <1/1 000	Very Rare <1/10,000	Frequency Not Known (Cannot be estimated from available data)
Metabolism and Nutrition Disorders	Hypokalaemia; hypophosphataemia; hyperlipidaemia (including hypercholesterolaemia); hyperglycaemia; hypertriglyceridaemia; fluid retention; diabetes mellitus					
Musculoskeletal, Connective Tissue and Bone Disorders	Arthralgia	Osteonecrosis				
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)		Squamous cell carcinoma of skin; basal cell carcinoma	Lymphoma; post-transplant lymphoproliferative disorder; malignant melanoma			Neuroendocrine carcinoma of the skin
Nervous System Disorders	Headache					Posterior reversible encephalopathy syndrome*
Renal and Urinary Disorders	Proteinuria		Nephrotic syndrome; focal segmental glomerulosclerosis			
Reproductive System and Breast Disorders	Menstrual disorder (including amenorrhoea and menorrhagia)	Ovarian cyst				
Respiratory, Thoracic and Mediastinal Disorders		Pulmonary embolism; pneumonitis; pleural effusion; epistaxis	Pulmonary haemorrhage	Alveolar proteinosis		

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10, 000 to <1/1 000	Very Rare <1/10,000	Frequency Not Known (Cannot be estimated from available data)
Skin and Subcutaneous Tissue Disorders	Rash; acne		Dermatitis exfoliative	Hypersensitivity vasculitis		
Vascular Disorders	Hypertension; lymphocele	Venous thrombosis (including deep vein thrombosis)	Lymphoedema			

*ADR identified post-marketing

Rapamune following cyclosporine withdrawal: The incidence of adverse reactions was determined through 60 months in a randomised, multicenter controlled trial 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 randomisation (start of cyclosporine withdrawal) was similar to that of the 2-mg Rapamune groups in studies of Rapamune in combination with cyclosporine. Following randomisation (at 3 months), patients who had cyclosporine eliminated from their therapy experienced significantly higher incidences of increased AST/SGOT and increased ALT/SGPT, liver damage, hypokalemia, thrombocytopenia, abnormal healing, acne, ileus, and joint disorder. Conversely, the incidence of acidosis, hypertension, cyclosporine toxicity, increased creatinine, abnormal kidney function, toxic nephropathy, edema, hyperuricemia, gout, 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.

Following cyclosporine withdrawal, (at 60 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 following cyclosporine withdrawal, based upon distinct categories, is presented in the following table. The incidence of lymphoma/lymphoproliferative disease was similar in all treatment groups. The overall incidence of malignancy, based upon the number of patients who had one or more malignancy, was lower in patients who had cyclosporine withdrawn than in patients receiving Rapamune plus cyclosporine (10.7% versus 15.8%, respectively).

INCIDENCE (%) OF MALIGNANCIES FOLLOWING CYCLOSPORINE WITHDRAWAL AT 60 MONTHS POST-TRANSPLANT[a]

Malignancy[d]	Non-randomised[b] (n = 95)	Rapamune with Cyclosporine Therapy[b] (n = 215)	Rapamune Following Cyclosporine Withdrawal[c] (n = 215)
Lymphoma/lymphoproliferative disease	1.1	1.4	0.5

Skin Carcinoma			
Non-melanoma skin carcinoma	5.3	8.8	7.0
Melanoma	0.0	0.5	0.5
Other Malignancy	5.3	7.0	3.3

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

By 60 months, the incidence of non-skin malignancies (lymphoma/lymphoproliferative disease plus other malignancy from the table above) was significantly higher in the cohort who continued cyclosporine as compared with the cohort who had cyclosporine withdrawn (8.4% versus 3.8%, respectively). For skin cancer, the median time to first occurrence was significantly delayed (491 versus 1126 days) and when taking into account that a patient may have multiple skin cancers the relative risk (RR = 0.346) for developing skin cancer was significantly lowered in the cyclosporine withdrawal group as compared with the group that continued cyclosporine.

Safety was assessed in a controlled trial (see **Section 5 PHARMACOLOGICAL PROPERTIES - Clinical trials data on efficacy**) involving 448 patients who received at least one dose of study drug (safety population): 224 patients received at least one dose of sirolimus with tacrolimus, and 224 patients 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. Diarrhea and herpes simplex occurred significantly more frequently in patients who received sirolimus and tacrolimus, whereas, hypertension, cardiomegaly, lymphocele, increased creatinine, acne, urinary tract disorder, ovarian cyst, and calcineurin inhibitor toxicity occurred at a significantly higher rate in patients who received sirolimus and cyclosporine. The incidence of malignancy was low (1.3% in each group).

The safety and efficacy of conversion from calcineurin inhibitors to Rapamune in maintenance renal transplant patients has not been established. In a study evaluating the safety and efficacy of conversion (6 to 120 months after transplantation) from calcineurin inhibitors to Rapamune (sirolimus target levels of 12-20 ng/mL by chromatographic assay) in maintenance renal transplant patients, enrollment was stopped in the subset of patients (n=90) with a baseline glomerular filtration rate of less than 40 mL/min. There was a higher rate of serious adverse events including pneumonia, acute rejection, graft loss and death in this Rapamune treatment arm (n=60, median time post-transplant 36 months).

In a study evaluating the safety and efficacy of conversion from tacrolimus to Rapamune 3 to 5 months post renal transplant, a higher rate of acute rejection and new onset diabetes mellitus was observed following conversion to Rapamune (see **Section 5.1 Pharmacodynamic properties**).

The concomitant use of sirolimus with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced HUS/TTP/TMA (see **Section 4.4 Special warnings and precaution for use**).

In patients with delayed graft function, Rapamune may delay recovery of renal function (see **Section 4.4 Special warnings and precaution for use**, Renal Function).

Other Clinical Experience
Azoospermia has been reported with the use of Rapamune and has been reversible upon discontinuation of Rapamune in most cases (see **Section 5.3 Preclinical safety data**).

Clostridium difficile enterocolitis has been reported in patients receiving sirolimus.

Interstitial Lung Disease
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 trough sirolimus level increases. (see **Section 4.4 Special warnings and precaution for use**, Interstitial Lung Disease).

Latent Viral Infections
BK virus associated nephropathy and progressive multifocal leukoencephalopathy (PML) have been observed in patients receiving immunosuppressants, including Rapamune. These infection may be associated with serious or fatal outcomes, including renal graft loss (see **Section 4.4 Special warnings and precautions for use**, Latent Viral Infections).

Hepatotoxicity
Hepatotoxicity has been reported, including fatal hepatic necrosis with elevated trough sirolimus levels (i.e., exceeding therapeutic levels).

Abnormal Healing
Abnormal healing following transplant surgery has been reported, including fascial dehiscence, incisional hernia and anastomosis disruption (e.g., wound, vascular, airway, ureteral, biliary).

4.9. Overdose

There is limited experience with overdose. In general, the adverse effects of overdose are consistent with those listed in the **Section 4.8 Undesirable effects**. General supportive measures should be followed in all cases of overdose. Based on the poor aqueous solubility and high erythrocyte and plasma protein binding of sirolimus, it is anticipated that sirolimus is not dialyzable to any significant extent.

In mice and rats, the acute oral lethal dose (LD_{50}) was greater than 800 mg/kg.

4.10. Abuse and dependence

Rapamune has no potential for abuse. There is no evidence of dependence on Rapamune.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Immunosuppressant
ATC code: L04AA10

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 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, dogs, and/or primates. Sirolimus reverses acute rejection of heart and kidney allografts in rats and prolongs the graft survival in presensitized rats. In some studies, the immunosuppressive effect of sirolimus lasts 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.

Clinical Trials Data on Efficacy

Rapamune Oral Solution with cyclosporine: The safety and efficacy of Rapamune Oral Solution for the prevention of organ rejection following renal transplantation were assessed in two randomised, 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 randomised following transplantation; 284 were randomised to receive Rapamune Oral Solution 2 mg/day, 274 were randomised 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 randomised before transplantation; 227 were randomised to receive Rapamune Oral Solution 2 mg/day, 219 were randomised 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 dose comparisons) at 6 months following transplantation compared with both azathioprine and placebo.

INCIDENCE (%) OF THE PRIMARY ENDPOINT AT 6 AND 24 MONTHS FOR STUDY 1[a,b]

	Rapamune	Rapamune	Azathioprine

Parameter	Oral Solution 2 mg/day (n = 284)	Oral Solution 5 mg/day (n = 274)	2-3 mg/kg/day (n = 161)
Efficacy failure at 6 months[c]	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
Efficacy failure at 24 months	32.8	25.9	36.0
Components of efficacy failure			
Biopsy-proven acute rejection	23.6	17.5	32.3
Graft loss	3.9	4.7	3.1
Death	4.2	3.3	0
Lost to follow-up	1.1	0.4	0.6

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.
c: Primary endpoint.

INCIDENCE (%) OF THE PRIMARY ENDPOINT AT 6 AND 36 MONTHS FOR STUDY 2[a,b]

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[c]	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
Efficacy failure at 36 months	44.1	41.6	54.6
Components of efficacy failure			
Biopsy-proven acute rejection	32.2	27.4	43.9
Graft loss	6.2	7.3	4.6
Death	5.7	5.9	5.4
Lost to follow-up	0	0.9	0.8

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.
c: Primary endpoint.

Patient and graft survival at 1 year were co-primary endpoints. The table below shows graft and patient survival at 1 and 2 years in Study 1, and 1 and 3 years in Study 2. The graft and patient survival rates were similar in patients treated with Rapamune and comparator-treated patients.

GRAFT AND PATIENT SURVIVAL (%) FOR STUDY 1 (12 AND 24 MONTHS) AND STUDY 2 (12 AND 36 MONTHS)[a,b]

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				
Month 12	94.7	92.7	93.8	
Month 24	85.2	89.1	90.1	
Patient survival				
Month 12	97.2	96.0	98.1	
Month 24	92.6	94.9	96.3	
Study 2	(n = 227)	(n = 219)		(n = 130)
Graft survival				
Month 12	89.9	90.9		87.7
Month 36	81.1	79.9		80.8
Patient survival				
Month 12	96.5	95.0		94.6
Month 36	90.3	89.5		90.8

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.

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

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 with 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 with 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 **Section 4.8 Undesirable effects**).

PERCENTAGE OF EFFICACY FAILURE BY RACE AT 6 MONTHS[a,b]

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)	
Non-black (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)

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.

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 with those treated with cyclosporine and the respective azathioprine or placebo control. Within each treatment group in both of these studies, mean GFR at one year post transplant was lower in patients who experienced at least one episode of biopsy-proven acute rejection, compared to those who did not.

OVERALL CALCULATED GLOMERULAR FILTRATION RATES (CC/MIN) BY NANKIVELL EQUATION AT 12 MONTHS POST TRANSPLANT[a,b]

Parameter	Rapamune Oral Solution 2 mg/day	Rapamune Oral Solution 5 mg/day	Azathioprine 2-3 mg/kg/day	Placebo
Study 1				
Month 12	57.4 ± 1.3 (n = 269)	54.6 ± 1.3 (n = 248)	64.1 ± 1.6 (n = 149)	
Month 24	58.4 ± 1.5 (n = 221)	52.6 ± 1.5 (n = 222)	62.4 ± 1.9 (n = 132)	
Study 2				
Month 12	52.4 ± 1.5 (n = 211)	51.5 ± 1.5 (n = 199)		58.0 ± 2.1 (n = 117)
Month 36	48.1 ± 1.8 (n = 183)	46.1 ± 2.0 (n = 177)		53.4 ± 2.7 (n = 102)

a: Includes patients who prematurely discontinued treatment.
b: Patients who has a graft loss were included in the analysis with GFR set to 0.0.

These findings suggest that sirolimus potentiates the renal toxicity of cyclosporine. Therefore, cyclosporine withdrawal, 2 to 4 months after transplantation in patients with low to moderate immunological risk should be individualized and the decision to withdraw cyclosporine should be on the discretion of the clinician based on individual risk versus benefit profile of the patient.

Renal function should be monitored and appropriate adjustment of the immunosuppression regimen should be considered in patients with elevated or increasing serum creatinine levels (see **Section 4.4 Special warnings and precaution for use**).

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 randomised 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 randomised before transplantation; 238 patients were randomised to receive Rapamune Oral Solution 2 mg/day and 239 patients were randomised 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 efficacy failure analysis at 3 and 6 months from this trial. The overall rate of efficacy failure at 3 months, the primary endpoint, in the tablet treatment group was equivalent to the rate in the oral solution treatment group.

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

	Rapamune Oral Solution (n = 238)	Rapamune Tablets (n = 239)
Efficacy Failure at 3 months[c]	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
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.
b: Includes patients who prematurely discontinued treatment.
c: Efficacy failure at 3 months was the primary endpoint.

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 patients 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[a,b]

	Rapamune Oral Solution	Rapamune Tablets
Mean ± SEM	58.88 ± 1.68 (n = 150)	59.05 ± 1.47 (n = 147)

a: Includes patients who prematurely discontinued treatment.
b: Patients who had a graft loss were included in the analysis with GFR set to 0.0.

Rapamune maintenance regimen with cyclosporine withdrawal: The safety and efficacy of Rapamune as a maintenance regimen were assessed following cyclosporine withdrawal at 3 to 4 months post-renal transplantation. In a randomised multi-centre 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 (pre-randomisation period) followed by the withdrawal of cyclosporine. During cyclosporine withdrawal the Rapamune dosages were adjusted to achieve targeted sirolimus whole blood trough concentration ranges (16 to 24 ng/mL until month 12, then 12 to 20 ng/mL thereafter through month 60). At 3 months, 430 patients were equally randomised to either Rapamune with cyclosporine therapy or Rapamune as a maintenance regimen following cyclosporine withdrawal. Eligibility for randomisation included no Banff 93 Grade III 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-confirmed acute rejection, graft loss or death) and treatment failure (defined as the first occurrence of either discontinuation, acute rejection, graft loss or death).

The following table summarizes the resulting graft and patient survival at 12, 24, 36, 48 and 60 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]	95.3[c]	97.2
Month 24	91.6	94.0
Month 36[d]	87.0	91.6
Patient Survival		
Month 12	97.2	98.1
Month 24	94.4	95.8
Month 36[d]	91.6	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 summarizes the results of first biopsy-proven acute rejection at 12 and 36 months. There was a significant difference in first biopsy-proven acute rejection between the two groups during post-randomisation through 12 months. Most of the post-randomisation acute rejections occurred in the first 3 months following randomisation.

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)
Pre-randomisation[c]	9.3	10.2
Post-randomisation through 12 months[c]	4.2	9.8
Post-randomisation from 12 to 36 months	1.4	0.5
Post-randomisation 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.
c: Randomisation occurred at 3 months ± 2 weeks.

Patients receiving renal allografts with ≥4 HLA mismatches experienced significantly higher rates of acute rejection following randomisation to the cyclosporine withdrawal group compared with patients who continued cyclosporine (15.3% versus 3.0%). Patients receiving renal allografts with ≤3 HLA mismatches, demonstrated similar rates of acute rejection between treatment groups (6.8% versus 7.7%) following randomisation.
The following table 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 n = 208	59.3 ± 1.5 n = 203

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 24		
Mean ± SEM	48.4 ± 1.7 n = 203	58.4 ± 1.6 n = 201
Month 36		
Mean ± SEM	47.0 ± 1.8 (n = 196)	58.5 ± 1.9 (n = 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 randomisation 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 post-randomisation.

Although the initial protocol was designed for 36 months, there was a subsequent amendment to extend this study. The results for the cyclosporine withdrawal 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.

In an open-label, randomized, comparative, multicenter study where renal transplant patients were either converted from tacrolimus to sirolimus 3 to 5 months post-transplant or remained on tacrolimus, there was no significant difference in renal function at 2 years. There were more adverse events (99.2% versus 91.1%, p=0.002) and more discontinuations from the treatment due to adverse events (26.7% versus 4.1%, p<0.001) in the group converted to sirolimus compared to the tacrolimus group. The incidence of biopsy confirmed acute rejection was higher (p=0.020) for patients in the sirolimus group (11, 8.4%) compared to the tacrolimus group (2, 1.6%) through 2 years; most rejections were mild in severity (8 of 9 [89%] T-cell BCAR, 2 of 4 [50%] antibody mediated BCAR) in the sirolimus group. Patients who had both antibody-mediated rejection and T-cell-mediated rejection on the same biopsy were counted once for each category. More patients converted to sirolimus developed new onset diabetes mellitus defined as 30 days or longer of continuous or at least 25 days non-stop (without gap) use of any diabetic treatment after randomization, a fasting glucose ≥126 mg/dL or a non-fasting glucose ≥200 mg/dL after randomization (18.3% versus 5.6%, p=0.025). A lower incidence of squamous cell carcinoma of the skin was observed in the sirolimus group (0% versus 4.9%).

5.2. Pharmacokinetics

Sirolimus pharmacokinetic activity has been determined following oral administration in healthy subjects, pediatric 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. Following administration by tablet, sirolimus t_{max} was approximately 3 hours after single doses in healthy volunteers and multiple doses in renal transplant patients. 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 **Section 5 PHARMACOLOGICAL PROPERTIES - Clinical trials data on efficacy** and **Section 4.2 Posology and method of administration**.)

Sirolimus concentrations, are dose proportional between 3 and 12 mg/m^2 after administration of Rapamune oral solution in stable renal transplant patients, and between 5 and 40 mg after administration of Rapamune tablets to healthy volunteers.

Food effects: In 22 healthy volunteers receiving Rapamune Oral Solution, a high-fat meal (860 kcal, 54.7% fat) altered the bioavailability characteristics of sirolimus. Compared with 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. Thus, a high-fat meal produced differences in the two formulations with respect to rate of absorption but not in extent of absorption. Evidence from a large randomised multicenter controlled trial comparing Rapamune oral solution to tablets supports that the differences in absorption rates do not affect the efficacy of the drug.

To minimize variability, both Rapamune Oral Solution and Tablets should be taken consistently with or without food. Bioequivalence testing based on AUC and C_{max} showed that sirolimus administered with orange juice is equivalent to administration with water. Therefore, orange juice and water may be used interchangeably to dilute sirolimus for oral solution. Grapefruit juice reduces CYP3A4 mediated drug metabolism and potentially enhances P-gp mediated drug counter-transport from enterocytes of the small intestine and must not be used for dilution or taken with Rapamune. (See **Section 4.5 Interaction with other medicinal products and other forms of interaction** and **Section 4.2 Posology and method of administration**).

Distribution

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

The 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.

Elimination

After a single dose of [^{14}C] sirolimus by oral solution in healthy subjects, the majority (91%) of radioactivity was recovered from the feces, and only a minor amount (2.2%) was excreted in urine. The mean ± SD terminal elimination half-life ($t_{½}$) of sirolimus after multiple dosing by Rapamune oral solution in stable renal transplant patients was estimated to be about 62 ± 16 hours.

Pharmacokinetics in renal transplant patients

Mean (±SD) pharmacokinetic parameters for sirolimus oral solution given daily in combination with cyclosporine and corticosteroids in renal transplant patients were determined at months 1, 3, and 6 after transplantation. There were no significant differences in C_{max}, t_{max}, AUC, or CL/F with respect to treatment group or month. After daily administration of Rapamune in renal transplant patients by oral solution and tablet, estimates of C_{max}, AUC, and CL/F did not appear to be different; but t_{max} was significantly different.

Upon repeated twice daily administration of Rapamune oral solution without an initial loading dose in a multiple-dose study, the average trough concentration of sirolimus increased approximately 2- to 3-fold over the initial 6 days of therapy at which time steady state was reached. Mean whole blood sirolimus trough concentrations in patients receiving either Rapamune by oral solution or tablet with a loading dose of three times the maintenance dose achieved steady-state concentrations within 24 hours after the start of dose administration.

The pharmacokinetic parameters of sirolimus in adult renal transplant patients following multiple dosing with Rapamune 2 mg daily, in combination with cyclosporine and corticosteroids, is summarized in the following table.

MEAN ± SD STEADY-STATE SIROLIMUS PHARMACOKINETIC PARAMETERS IN ADULT RENAL TRANSPLANT PATIENTS FOLLOWING RAPAMUNE 2 MG DAILY[a,b]

	Multiple Dose (daily dose)	
	Solution	Tablets
C_{max} (ng/mL)	14.4 ± 5.3	15.0 ± 4.9
t_{max} (hr)	2.1 ± 0.8	3.5 ± 2.4
AUC (ng•h/mL)	194 ± 78	230 ± 67
C_{min} (ng/mL)[c]	7.1 ± 3.5	7.6 ± 3.1
CL/F (mL/h/kg)	173 ± 50	139 ± 63

a: In presence of cyclosporine administered 4 hours before Rapamune dosing.
b: Based on data collected at months 1 and 3 post-transplantation.
c: Average C_{min} over 6 months.

Whole blood trough sirolimus concentrations, as measured by LC/MS/MS in renal transplant patients, were significantly correlated 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.

Sirolimus Concentrations (Chromatographic Equivalent) Observed in Phase 3 Clinical Studies

The following sirolimus concentrations (chromatographic equivalent) were observed in phase III clinical studies (see **Section 5 PHARMACOLOGICAL PROPERTIES - Clinical trials data on efficacy**).

SIROLIMUS WHOLE BLOOD TROUGH CONCENTRATIONS OBSERVED IN RENAL TRANSPLANT PATIENTS ENROLLED IN PHASE 3 STUDIES

Patient Population (Study number)	Treatment	Year 1		Year 3	
		Mean (ng/mL)	10^{th} – 90^{th} percentiles (ng/mL)	Mean (ng/mL)	10^{th} – 90^{th} percentiles (ng/mL)
(Studies 1 & 2)	Rapamune (2 mg/day) + Cyclosporine	7.2	3.6 – 11	–	–
	Rapamune (5 mg/day) + Cyclosporine	14	8 – 22	–	–
Low-to-moderate risk (Study 3)	Rapamune + Cyclosporine	8.6	5 – 13[a]	9.1	5.4 – 14
	Rapamune alone	19	14 – 22[a]	16	11 – 22
High risk (Study 4)	Rapamune + Cyclosporine	15.7 11.8 11.5	5.4 – 27.3[b] 6.2 – 16.9[c] 6.3 – 17.3[d]	–	–

a: Months 4 through 12
b: Up to Week 2; observed Cyclosporine C_{min} was 217 (56 – 432) ng/mL
c: Week 2 to Week 26; observed Cyclosporine C_{min} range was 174 (71 – 288) ng/mL
d: Week 26 to Week 52; observed Cyclosporine C_{min} was 136 (54.5 – 218) ng/mL

Average Rapamune doses and sirolimus whole blood trough concentrations for tablets administered daily in combination with cyclosporine or tacrolimus and corticosteroids in high-risk renal transplant patients (Study 5; see **Section 5 PHARMACOLOGICAL PROPERTIES - Clinical trials data on efficacy**) 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 Tacrolimus Therapy	Rapamune with Cyclosporine Therapy
Rapamune Dose (mg/day)		
Months 3 to 6[a]	6.5 ± 3.0	5.1 ± 2.4
Months 9 to 12[b]	6.5 ± 3.0	5.0 ± 2.3
Sirolimus C_{min} (ng/mL)[c]		
Months 3 to 6	11.5 ± 6.2	11.8 ± 4.2
Months 9 to 12	10.7 ± 3.6	11.2 ± 3.8

a: n=110 in Rapamune/Tacrolimus group, n=109 in Rapamune/Cyclosporine Group.
b: n=117 in Rapamune/Tacrolimus group, n=127 in Rapamune/Cyclosporine Group.
c: Expressed by chromatography.

Patients treated with the combination of Rapamune and tacrolimus required larger Rapamune doses to achieve the target sirolimus concentrations than patients treated with the combination of Rapamune and cyclosporine.

Special Populations

Patients with Renal Impairment
There is minimal renal excretion of drug or its metabolites. The pharmacokinetics of sirolimus are very similar in various populations with renal function ranging from normal to absent (dialysis patients).

Patients with Hepatic Impairment
Sirolimus oral solution (15 mg) was administered as a single oral dose to subjects with normal hepatic function and to patients with Child-Pugh classification A (mild), B (moderate), or C (severe) primary hepatic impairment.

Compared with the values in the normal hepatic function group, the patients with mild, moderate, or severe hepatic impairment had 43%, 94%, and 189% higher mean values for sirolimus AUC, respectively, and $t_{1/2}$ with no significant differences in mean C_{max}. As the severity of hepatic impairment increased, there were steady increases in mean sirolimus $t_{1/2}$, and decreases in the mean sirolimus clearance normalized for body weight (CL/F/kg).

The maintenance dose of Rapamune should be reduced by approximately one third in patients with mild to moderate hepatic impairment and by approximately one half in patients with severe hepatic impairment based on decreased clearance (see **Section 4.2 Posology and method of administration**). In patients with hepatic impairment, it is necessary that sirolimus whole blood trough levels be monitored. In patients with severe hepatic impairment, consideration should be given to monitoring every 5 to 7 days for a longer period of time after dose adjustment or after loading dose due to the delay in reaching steady state because of the prolonged half-life.

Children
Sirolimus pharmacokinetic data were collected in concentration-controlled trials of pediatric renal transplant patients who were also receiving cyclosporine and corticosteroids. The target ranges for trough concentrations were either 10-20 ng/mL for the 21 children receiving tablets, or 5-15 ng/mL for the one child receiving oral solution. The children aged 6-11 years (n = 8) received mean ± SD doses of 1.75 ± 0.71 mg/day (0.064 ± 0.018 mg/kg, 1.65 ± 0.43 mg/m^2). The children aged 12-18 years (n = 14) received mean ± SD doses of 2.79 ± 1.25 mg/day (0.053 ± 0.0150 mg/kg, 1.86 ± 0.61 mg/m^2). At the time of sirolimus blood sampling for pharmacokinetic evaluation, the majority (80%) of these pediatric patients received the sirolimus dose at 16 hours after the once daily cyclosporine dose.

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

Age (y)	n	Body weight (kg)	$C_{max,ss}$ (ng/mL)	$t_{max,ss}$ (h)	$C_{min,ss}$ (ng/mL)	$AUC_{\tau,ss}$ (ng•h/mL)	CL/F[c] (mL/h/kg)	CL/F[c] (L/h/m^2)
6-11	8	27 ± 10	22.1 ± 8.9	5.88 ± 4.05	10.6 ± 4.3	356 ± 127	214 ± 129	5.4 ± 2.8
12-18	14	52 ± 15	34.5 ± 12.2	2.7 ± 1.5	14.7 ± 8.6	466 ± 236	136 ± 57	4.7 ± 1.9

a: Sirolimus co-administered with cyclosporine oral solution (e.g., Neoral Oral Solution) and/or cyclosporine capsule (e.g., Neoral Soft Gelatin Capsules).
b: As measured by Liquid Chromatographic/Tandem Mass Spectrometric Method (LC/MS/MS).
c: Oral-dose clearance adjusted by either body weight (kg) or body surface area (m^2).

The Table below summarizes pharmacokinetic data obtained in pediatric dialysis patients with chronically impaired renal function receiving Rapamune by oral solution.

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 (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

* All subjects received sirolimus oral solution.

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) from 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 $t_{1/2}$ 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 (e.g., Neoral® Oral Solution) and/or cyclosporine capsules (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.

5.3. Preclinical safety data

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenicity

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 the 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.

Mutagenicity
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.

Reproductive Toxicology
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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

The inactive ingredients in Rapamune Oral Solution are Phosal 50 PG® (phosphatidylcholine, propylene glycol, mono-and di-glycerides, 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 monohydrate, polyethylene glycol 8000 powdered, calcium sulfate anhydrous, microcrystalline cellulose, pharmaceutical glaze (shellac solution 4# cut), talc, titanium dioxide, magnesium stearate, povidone (K29/32), poloxamer 188, polyethylene glycol (macrogol) type 20,000, glyceryl monooleate (60%), carnauba wax, vitamin E (*dl-alpha* tocopherol), alcohol denatured 23A*, water purified*, mineral spirits odorless, ink-red opacode S-1-15095, yellow iron (ferric) oxide [0.5 mg and 2 mg only], brown iron (ferric) oxide [0.5 mg and 2 mg only] and water for injection*.

*Removed during processing. Does not appear in the finished dosage form.

6.2. Incompatibilities

A glass or plastic container should be used for dilution of Rapamune oral solution before administration.

6.3. 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 2 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 aluminium pouches of 1 mL.
NDC # 0008-1030-07, containing 30 unit-of-use laminated aluminium pouches of 2 mL.
NDC # 0008-1030-08, containing 30 unit-of-use laminated aluminium pouches of 5 mL.

Rapamune Tablets are available as follows:

0.5 mg, tan, triangular, sugar coated tablets branded "RAPAMUNE 0.5 mg" in red ink on one side;
1 mg, white, triangular-shaped tablets marked "RAPAMUNE 1 mg" on one side;
2 mg, yellow-to-beige triangular-shaped tablets marked "RAPAMUNE 2 mg" on one side.

Packaged in Polyvinyl chloride (PVC), polyethylene (PE) and Aclar blister with aluminium foil lidding.

NDC # 0008-1041 -05, bottle of 100 tablets.
NDC # 0008-1041 -10, Redipak® cartons of 100 tablets (10 blister cards of 10 tablets each).
Item # 66894 unit carton 3 x 10's: Rapamune 1 mg and Rapamune 2 mg.
Item # 66948 unit carton 10 x 10's: Rapamune 0.5 mg, Rapamune 1 mg and Rapamune 2 mg.

Not all products may be marketed

6.4. Storage and shelf-life

Shelf-life: Refer to outer carton.

Store Rapamune Oral Solution bottles protected from light and refrigerated at 2°C to 8°C (36°F to 46°F).

Use the contents of the bottle within one month after opening. If necessary, the patient may store 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).

Amber syringes and caps are provided for dosing and the product may be kept in the syringe for a maximum of 24 hours at room temperature up to 25°C (77°F) or refrigerated at 2°C to 8°C (36°F to 46°F). Discard the syringe after one use.

After dilution, use the preparation immediately.

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

Rapamune Tablet 0.5 mg should be stored at or below 30°C. Rapamune Tablet 1 mg should be

stored below 30°C. Rapamune Tablet 2 mg should be stored at 20°C to 25°C (USP Controlled Room Temperature) (68°F – 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; 5,989,591.

6.5. Special precautions for disposal and other handling

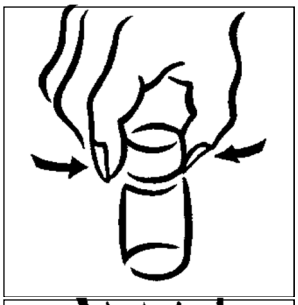
Since Rapamune is not absorbed through the skin, there are no special precautions. However, if direct contact with the skin or mucous membranes occurs, wash thoroughly with soap and water; rinse eyes with plain water.

INSTRUCTIONS FOR DILUTION AND ADMINISTRATION OF RAPAMUNE ORAL SOLUTION

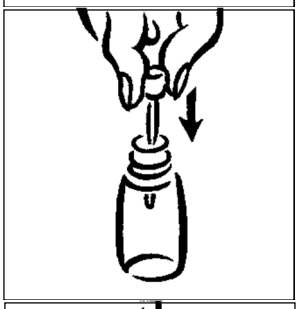
Bottles
The amber oral dose syringe should be used to withdraw the prescribed amount of Rapamune Oral Solution from the bottle. Empty the correct amount of Rapamune from the syringe into a glass or plastic container holding at least two (2) ounces (1/4 cup, 60 mL) of water or orange juice. Grapefruit juice or other liquids must not be used for dilution. Stir vigorously and drink at once. Rinse the glass with an additional 120 mL (four ounces or ½ cup) of water or orange juice, stir vigorously, and drink immediately.

PATIENT INSTRUCTIONS FOR RAPAMUNE ORAL SOLUTION ADMINISTRATION

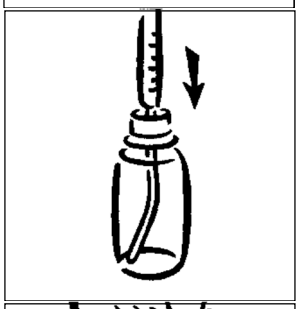
Bottles



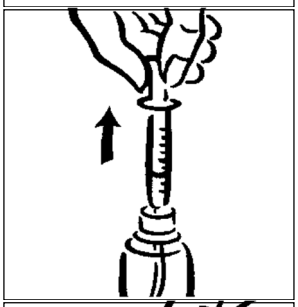
1. Open the solution bottle. Remove the safety cap by squeezing the tabs on the cap and twisting counterclockwise.



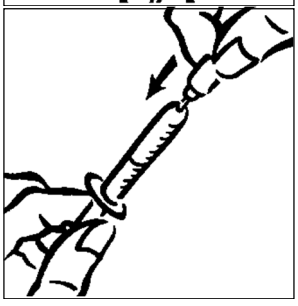
2. On the first use, insert the adapter assembly (plastic tube with stopper) tightly into the bottle until it is even with the top of the bottle. Do not remove the adapter assembly from the bottle once inserted.



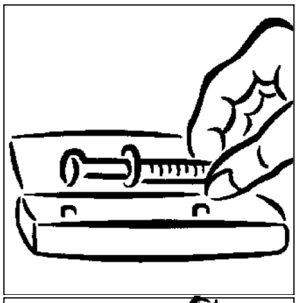
3. For each use, tightly insert one of the amber syringes with the plunger fully depressed into the opening in the adapter.



4. Withdraw the prescribed amount of Rapamune Oral Solution by gently pulling out the plunger of the syringe until the level of the solution 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. Then place the capped syringe in the enclosed carrying 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 reach of children.

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.

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.

7. PRODUCT OWNER

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