**WARNING: IMMUNOSUPPRESSION, USE IS NOT RECOMMENDED IN LIVER OR LUNG TRANSPLANT PATIENTS**

- **Increased susceptibility to infection and the possible development of lymphoma and other malignancies may result from immunosuppression**

**Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of renal transplant patients should use Rapamune for prophylaxis of organ rejection in patients receiving renal transplants. 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**.

- **The safety and efficacy of Rapamune (sirolimus) as immunosuppressive therapy have not been established in liver or lung transplant patients, and therefore, such use is not recommended**.
- **Liver Transplantation – 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 patients. 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 patients, 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.**

- **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.**

## 1. NAME OF THE MEDICINAL PRODUCT

Rapamune

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each tablet contains sirolimus equivalent to 1 mg of sirolimus.

## 3. PHARMACEUTICAL FORM

Sirolimus 1 mg tablets are white triangular-shaped sugar coated tablet, branded ‘RAPAMUNE 1 mg’ in red ink.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Prophylaxis of Organ Rejection in Renal Transplantation

Rapamune is indicated for the prophylaxis of organ rejection in patients receiving a renal transplant.

**In patients at low to moderate immunological 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 5.1 Pharmacodynamic properties).

**In patients at high immunologic risk** (defined as Black transplant recipients and/or repeat renal transplant recipients who lost a previous allograft for immunologic reason and/or patients with high-panel reactive antibodies (PRA; peak PRA level >80%), it is recommended that Rapamune be used in a combination of tacrolimus and corticosteroids or cyclosporine and corticosteroids for the first year following transplantation (see Sections 4.2 Posology and method of administration and 5.1 Pharmacodynamic properties). The safety and efficacy of these combinations in high-risk renal transplant patients have not been studied beyond one year. Therefore, after the first year following transplantation, any adjustments to the immunosuppressive regimen should be considered on the basis of the clinical status of the patient.

### 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.

Therapeutic drug monitoring is recommended for all patients receiving Rapamune (see details on drug monitoring in different patient populations below and Section 4.2.2 Sirolimus whole blood trough level monitoring).

**Prophylaxis of organ rejection in renal transplantation**

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**

Rapamune and Cyclosporine Combination Therapy:
For *de novo* transplant recipients, a loading dose of Rapamune corresponding to 3 times the maintenance dose should be given. A daily maintenance dose of 2 mg is recommended for use in renal transplant patients,

with a loading dose of 6 mg.

It is recommended that Rapamune 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 immunologic 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 Sections 4.1 Therapeutic indications and 5.1 Pharmacodynamic properties).

Rapamune following Cyclosporine withdrawal (Referred to as Rapamune Maintenance Regimen, RMR)
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**

Rapamune Combination Therapy:
It is recommended that Rapamune be used in a combination of cyclosporine and corticosteroids for the first year following transplantation in patients at high immunologic risk (defined as Black transplant recipients and/or repeat renal transplant recipients who lost a previous allograft for immunologic reason and/or patients with high-panel reactive antibodies [PRA; peak PRA level >80%]) (see Section 5.1 Pharmacodynamic properties). The safety and efficacy of these combinations in high-risk patients have not been studied beyond one year. Therefore, after the first year following transplantation, any adjustments to the immunosuppressive regimen should be considered on the basis of the clinical status of the patient.

For patients receiving Rapamune with cyclosporine, Rapamune therapy should be initiated with a loading dose of up to 15 mg on day 1 post-transplantation. Beginning on day 2, an initial maintenance dose of 5 mg/day should be given. A trough level should be obtained between days 5 and 7, and the daily dose of Rapamune should thereafter be adjusted to achieve whole blood trough sirolimus concentrations of 10-15 ng/mL.

The starting dose of cyclosporine should be up to 7 mg/kg/day in divided doses, and the dose should subsequently be adjusted to achieve whole blood trough concentrations of 200-300 ng/mL for 14 days, 150-200 ng/mL from day 15 to the end of week 26, and 100-150 ng/mL from week 27 to the end of week 52. Prednisone should be administered at a minimum of 5 mg/day.

Antibody induction therapy may be used (see Section 5.1 Pharmacodynamic properties).

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

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

It is recommended that Rapamune be taken 4 hours after cyclosporine microemulsion [(cyclosporine, USP) MODIFIED]* administration (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

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

Safety and efficacy information from a controlled clinical trial in pediatric and adolescent (<18 years of age) renal transplant recipients judged to be at high immunologic risk, defined as a history of one or more acute rejection episodes and/or the presence of chronic allograft nephropathy, do not support the chronic use of Rapamune in combination with calcineurin inhibitors and corticosteroids, due to the increased risk of lipid abnormalities and deterioration of renal function associated with these immunosuppressive regimens, without increased benefit with respect to acute rejection, graft survival, or patient survival (see Section 5.1 Pharmacodynamic properties).

Use in Elderly Patients
No dose adjustment is required in elderly patients.

Clinical studies of Rapamune did not include sufficient numbers of patients aged 65 and over to determine whether safety and efficacy differ in this population from 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 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.

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

Patients with Renal Impairment
Based on clinical pharmacokinetics data, the Rapamune dosage need not be adjusted because of impaired renal function.

### 4.2.2 Sirolimus whole blood trough level monitoring

Blood sirolimus trough levels should be monitored: (See Assay Methodology section below)
- in patients receiving concentration-controlled Rapamune
- in pediatric patients
- in patients with hepatic impairment
- during concurrent administration of inhibitors and inducers of CYP3A4 and P-glycoprotein (P-gp)
- if the cyclosporine dose is markedly reduced, or if cyclosporine is discontinued.

Therapeutic drug monitoring should not be the sole basis for adjusting sirolimus therapy. Careful attention should also be paid 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.

In controlled clinical trials with concomitant cyclosporine, mean sirolimus whole blood trough levels through Month 6 following transplantation, expressed as chromatographic assay value, were approximately 7.2 ng/mL (range 3.6 - 11 ng/mL) for the 2 mg/day treatment group (n=226), and 14 ng/mL (range 8.0 - 22 ng/mL [$10^{th}$ to $90^{th}$ percentile]) for the 5 mg/day dose (n=219; values were obtained using a research immunoassay, but are expressed as chromatographic equivalent values, accounting for immunoassay bias).

In the controlled clinical trial with cyclosporine withdrawal, the mean sirolimus whole blood trough concentrations during months 4 through 12 following transplantation, as measured by chromatography, were 8.6 ng/mL (range 5.0 – 12.7 ng/mL [$10^{th}$ to $90^{th}$ percentile]) in the concomitant Rapamune and cyclosporine treatment group (n=205) and were 18.6 ng/mL (range 13.6 – 22.4 ng/mL [$10^{th}$ to $90^{th}$ percentile]) in the cyclosporine withdrawal treatment group (n=201). By month 60, the mean sirolimus whole blood trough concentrations remained stable in the concomitant Rapamune and cyclosporine group (n=71) at 9.1 ng/mL (range 5.4 to 13.9 ng/mL [$10^{th}$ to $90^{th}$ percentile]). For the cyclosporine withdrawal group (n=104) by month 60, the mean sirolimus whole blood concentration had fallen to 16.3 ng/mL (range 11.2 to 21.9 ng/mL [$10^{th}$ to $90^{th}$ percentile]).

In a concentration-controlled clinical trial in high-risk adult patients, the mean whole blood sirolimus trough concentrations, during months 9 through 12 months following transplantation, as measured by chromatography, in the sirolimus/tacrolimus group, were 10.7 ng/mL (range 5.6 – 15.1 ng/mL [$10^{th}$ to $90^{th}$ percentile]) (n=117), and the mean whole blood trough concentrations of tacrolimus were 5.3 ng/mL (range 3.0 – 8.6 ng/mL [$10^{th}$ to $90^{th}$ percentile]). Additionally, the mean whole blood trough concentrations of sirolimus in the sirolimus/cyclosporine group were 11.2 ng/mL (range 6.8 – 15.9 ng/mL [$10^{th}$ to $90^{th}$ percentile]) (n=127), and the mean whole blood trough concentrations of cyclosporine were 133 ng/mL (range 54 – 215 ng/mL [$10^{th}$ to $90^{th}$ percentile]).

<u>Assay Methodology</u>
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, adjustment to the targeted therapeutic range must be made with a detailed knowledge of the site-specific assay used. A discussion of different assay methods is contained

in *Clinical Therapeutics* 2000; 22 Suppl. B:B1-B132.

### 4.2.3 Mode of Administration

Rapamune is intended for oral administration only.

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

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 Sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects). Oversuppression of the immune system can also increase susceptibility to opportunistic infections, sepsis and fatal infections.

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.

*Liver Transplantation - 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 randomized to conversion to a sirolimus-based regimen versus continuation of a 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 5.1 Pharmacodynamic properties).

*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.

<u>Drug-Drug Interactions</u>
Co-administration of Rapamune with strong inhibitors of CYP3A4 and/or P-gp (such as ketoconazole, voriconazole, itraconazole, telithromycin, or clarithromycin) or strong inducers of CYP3A4 and/or P-gp (such as rifampin or rifabutin) is not recommended. Sirolimus is extensively metabolized 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).

There have been reports of increased blood levels of sirolimus during concomitant use with cannabidiol. Caution should be used when cannabidiol and Rapamune are co-administered, closely monitor sirolimus blood levels and for adverse events suggestive of sirolimus toxicity (see Sections 4.2.2 Sirolimus whole blood trough level monitoring and 4.5.4 Cannabidiol).

Wound Healing and Fluid Accumulation

There have been reports of impaired or delayed wound healing in patients receiving Rapamune, including lymphocele and wound dehiscence. Lymphocele, a known surgical complication of renal transplantation, occurred significantly more often in a dose-related fashion in patients treated with Rapamune. Appropriate measures should be considered to minimize such complications. Patients with a BMI greater than 30 $kg/m^2$ may be at increased risk of abnormal wound healing based on data from the medical literature (see Section 4.8 Undesirable effects).

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 Sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects).

Hyperlipidemia

The use of Rapamune may lead to increased serum cholesterol and triglycerides that may require treatment. Patients must be monitored for hyperlipidemia.

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.

Renal Function

Patients treated with cyclosporine and Rapamune had higher serum creatinine levels and lower glomerular filtration rates compared to patients 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 5.1 Pharmacodynamic properties). Therefore, renal function should be monitored during the co-administration of Rapamune with cyclosporine. Renal function should also be closely monitored during the co-administration of Rapamune with tacrolimus. Appropriate adjustments of the immunosuppressive regimen, including discontinuation of Rapamune and/or cyclosporine and/or tacrolimus, should be considered in patients with elevated serum creatinine levels.

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 (see Section 4.4 Special warnings and precautions for use).

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 evaluating conversion from calcineurin inhibitors (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 months after conversion to Rapamune compared with CNI continuation (23.6% versus 12.8%, respectively) [see Sections 4.8 Undesirable effects and 5.1 Pharmacodynamic properties]. 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 calcineurin inhibitors (CNI) to Rapamune in maintenance renal transplant patients 6-120 months post-transplant (see Section 5.1 Pharmacodynamic properties), 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 with 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 4.8 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 are 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
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 Sections 4.1 Therapeutic indications and 5.1 Pharmacodynamic properties).

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

### 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 metabolized by the CYP3A4 isozyme in the 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, letermovir, 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.

Verapamil
Verapamil is an inhibitor of CYP3A4. Sirolimus levels should be monitored and appropriate dose reductions of both medications should be considered.

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

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

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

### 4.5.2 Non-Interactions

No clinically significant pharmacokinetic drug-drug interactions were observed in studies of the following drugs: acyclovir, atorvastatin, digoxin, glibenclamide (glyburide), nifedipine, norgestrel 0.3 mg/ethinyl estradiol 0.03 mg, methylprednisolone, sulfamethoxazole/trimethoprim and tacrolimus.

### 4.5.3 Cyclosporine

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

Patients administered sirolimus with cyclosporine should be monitored for the development of rhabdomyolysis (see Section 4.4 Special warnings and precautions for use).

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

### 4.5.4 Cannabidiol

There have been reports of increased blood levels of sirolimus during concomitant use with cannabidiol. Caution should be used when cannabidiol and Rapamune are co-administered, closely monitor sirolimus blood levels and for adverse events suggestive of sirolimus toxicity (see Sections 4.2.2 Sirolimus whole blood trough level monitoring and 4.4 Special warnings and precautions for use).

### 4.5.5 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).

### 4.5.6 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).

### 4.5.7 Vaccinations

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.

### 4.5.8 Food

The bioavailability of sirolimus is affected by concomitant food intake after administration by Rapamune 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 intestine. This juice must not be taken with Rapamune tablets (see Section 4.2.3 Mode of Administration).

### 4.5.9 Interference with laboratory and other diagnostic tests

Not applicable

## 4.6 Fertility, 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).

[Need for effective contraception: see statement in Section 4.4 Special warnings and precautions for use.]

**Lactation**
Sirolimus is excreted in trace amounts in milk in lactating rats. It is not known whether sirolimus is excreted into human milk. A decision should be made whether to discontinue breast feeding or to discontinue Rapamune therapy.

## 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

### 4.8.1 Undesirable effects observed with Prophylaxis of Organ Rejection in Renal Transplantation

The adverse reactions listed in the following table includes reactions reported in patients treated with Rapamune in combination with cyclosporine and corticosteroids.

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

Adverse Drug Reactions (ADR) by System Organ Class (SOC) and Council for International Organizations of Medical Sciences (CIOMS) frequency categories listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC

| **ADVERSE REACTIONS - PROPHYLAXIS OF ORGAN REJECTION IN RENAL TRANSPLANTATION (N=1501)** | | | | | | |
|---|---|---|---|---|---|---|
| **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)** |
| 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 | | | |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | | Squamous cell carcinoma of skin; basal cell carcinoma | Lymphoma; malignant melanoma post transplant lympho-proliferative disorder | | | Neuroendocrine carcinoma of the skin |
| Blood and lymphatic system disorders | Thrombocytopenia; anaemia; leukopenia | Haemolytic uraemic syndrome; neutropenia | Pancytopenia; thrombotic thrombo-cytopenic purpura | | | |

| ADVERSE REACTIONS - PROPHYLAXIS OF ORGAN REJECTION IN RENAL TRANSPLANTATION (N=1501) | | | | | | |
|---|---|---|---|---|---|---|
| **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)** |
| Immune system disorders | | Hypersensitivity (including angioedema, anaphylactic reaction, and anaphylactoid reaction) | | | | |
| Metabolism and nutrition disorders | Hypokalaemia; hypophosphataemia; hyperlipidaemia (including hyper-cholesterolaemia); hyperglycaemia; hyper-triglyceridaemia; fluid retention; diabetes mellitus | | | | | |
| Nervous system disorders | Headache | | | | | Posterior reversible encephalopathy syndrome* |
| Cardiac disorders | Tachycardia | Pericardial effusion | | | | |
| Vascular disorders | Hypertension; Lymphocele | Venous thrombosis (including deep vein thrombosis) | Lymphoedema | | | |
| Respiratory, thoracic and mediastinal disorders | | Pulmonary embolism; pneumonitis; pleural effusion; epistaxis | Pulmonary haemorrhage | Alveolar proteinosis | | |
| Gastrointestinal disorders | Abdominal pain; constipation; diarrhoea; nausea | Pancreatitis; stomatitis; ascites | | | | |
| Skin and subcutaneous tissue disorders | Rash; Acne | | Dermatitis exfoliative | Hypersensitivity vasculitis | | |
| Musculoskeletal and connective tissue disorders | Arthralgia | Osteonecrosis | | | | |

| ADVERSE REACTIONS - PROPHYLAXIS OF ORGAN REJECTION IN RENAL TRANSPLANTATION (N=1501) | | | | | | |
|---|---|---|---|---|---|---|
| **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)** |
| Renal and urinary disorders | Proteinuria | | Nephrotic syndrome; focal segmental glomerulo-sclerosis | | | |
| Reproductive system and breast disorders | Menstrual disorder (including amenorrhoea and menorrhagia) | Ovarian cyst | | | | |
| General disorders and administration site conditions | Impaired healing oedema; oedema peripheral; pyrexia; pain; | | | | | |
| Investigations | Liver function test abnormal (including alanine aminotransferase increased and aspartate aminotransferase increased); blood creatinine increased; blood lactate dehydrogenase increased | | | | | |

*ADR identified post-marketing

*Rapamune following cyclosporine withdrawal:* The incidence of adverse reactions was determined through 60 months in a randomized, multi-center 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 randomization (start of cyclosporine withdrawal) was similar to that of the 2 mg Rapamune groups in studies of Rapamune in combination with cyclosporine. Following randomization (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 AT 60 MONTHS POST-TRANSPLANT[a]** | | | |
|---|---|---|---|
| **Malignancy[d]** | **Non-randomized[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 5.1 Pharmacodynamic properties) 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).

Safety was assessed in a controlled clinical trial in pediatric (<18 years of age) renal transplant patients considered high immunologic risk, defined as a history of one or more acute allograft rejection episodes and/or the presence of chronic allograft nephropathy on a renal biopsy (see Section 5.1 Pharmacodynamic properties). The use of Rapamune in combination with calcineurin inhibitors and corticosteroids was associated with an increased risk of deterioration of renal function, serum lipid abnormalities (including but not limited to increased serum triglycerides and cholesterol), and urinary tract infections.

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 precautions for use).

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

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 precautions 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 infections 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).

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.

## 4.9 Overdose

There is limited experience with overdose. In general, the adverse effects of overdose are consistent with those listed in the Undesirable effects section. 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 $LD_{50}$ 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: L04AH01

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

Studies in experimental models show that sirolimus prolongs allograft (kidney, heart, skin, islet, small bowel, pancreatico-duodenal, or 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

*Prophylaxis of Organ Rejection*
The safety and efficacy of Rapamune for the prevention of organ rejection following renal transplantation were assessed in two randomized, double-blind, multicenter, controlled trials. These studies compared two dose levels of Rapamune (2 mg and 5 mg, once daily) with azathioprine or placebo when administered in combination with cyclosporine and corticosteroids. The study of Rapamune (2 mg and 5 mg, once daily) compared to azathioprine was conducted in the United States at 38 sites. Seven hundred nineteen (719) patients were enrolled in this trial and randomized following transplantation; 284 were randomized to receive Rapamune 2 mg/day, 274 were randomized to receive Rapamune 5 mg/day, and 161 to receive azathioprine 2-3 mg/kg/day. The study of Rapamune (2 mg and 5 mg, once daily) compared to placebo control was conducted in Australia, Canada, Europe, and the United States, at a total of 34 sites. Five hundred seventy-six (576) patients were enrolled in this trial and randomized before transplantation; 227 were randomized to receive Rapamune 2 mg/day, 219 were randomized to receive Rapamune 5 mg/day, and 130 to receive placebo. Efficacy failure was defined as the first occurrence of an acute rejection episode (confirmed by biopsy), graft loss, or death.

The primary efficacy analyses from these trials determined that Rapamune, at doses of 2 mg/day and 5 mg/day, significantly reduced the incidence of efficacy failure at 6 months following transplantation

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

The graft and patient survival rates, which were co-primary endpoints, were similar in the Rapamune-treated and comparator-treated patients at 1 year.

The tables below summarize the results of the primary efficacy analyses from these trials. Rapamune Oral Solution, at doses of 2 mg/day and 5 mg/day, significantly reduced the incidence of efficacy failure (statistically significant at the <0.025 level; nominal significance level adjusted for multiple [2] dose comparisons) at 6 months following transplantation compared with both azathioprine and placebo.

**INCIDENCE (%) OF EFFICACY FAILURE AT 6 AND 24 MONTHS FOR STUDY 1[a,b]**

| **Parameter** | **Rapamune Oral Solution 2 mg/day (n = 284)** | **Rapamune Oral Solution 5 mg/day (n = 274)** | **Azathioprine 2-3 mg/kg/day (n = 161)** |
|---|---|---|---|
| Efficacy failure at 6 months [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 EFFICACY FAILURE 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 |

| INCIDENCE (%) OF EFFICACY FAILURE 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 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 following table 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 episodes in patients treated with Rapamune compared with the control groups included a reduction in all grades of rejection.

In the study of Rapamune (2 mg and 5 mg, once daily) with azathioprine comparator, which was prospectively stratified by race within center, efficacy failure was similar for Rapamune 2 mg/day and lower for Rapamune 5 mg/day compared to azathioprine in black patients. In the placebo-controlled study of Rapamune (2 mg and 5 mg, once daily), which was not prospectively stratified by race, efficacy failure was

similar for both Rapamune doses compared to placebo in black patients.

| **PERCENTAGE OF EFFICACY FAILURE BY RACE AT 6 MONTHS[a]** | | | | | |
|---|---|---|---|---|---|
| | | **Rapamune 2 mg/day** | **Rapamune 5 mg/day** | **Azathioprine 2-3 mg/kg/day** | **Placebo** |
| Rapamune (2 mg and 5 mg, once daily) versus azathioprine comparator | | | | | |
| 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) | |
| | | | | | |
| Rapamune (2 mg and 5 mg, once daily) versus placebo comparator | | | | | |
| 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: All patients received CsA and corticosteroids. | | | | | |

Mean glomerular filtration rates (GFR) at one year post-transplant were calculated using the Nankivell equation for all subjects in each study who had serum creatinine measured at 12 months. In both studies, mean GFR at one year was lower in patients treated with cyclosporine and Rapamune compared to 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.

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 randomized, multicenter, controlled trial conducted at 57 centers in Australia, Canada, and Europe, five hundred twenty-five (525) patients were enrolled. All patients in this study received the tablet formulation. This study compared patients who were administered Rapamune, cyclosporine, and corticosteroids continuously, with patients who received the same standardized therapy for the first 3 months after transplantation (pre-randomization 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 randomized to either Rapamune with cyclosporine therapy, or Rapamune as a maintenance regimen following cyclosporine withdrawal. Eligibility for randomization included no Banff Grade 3 acute rejection episode or vascular rejection in the 4 weeks before random assignment; serum creatinine ≤4.5 mg/dL; and adequate renal function to support cyclosporine withdrawal (in the opinion of the investigator). The primary efficacy endpoint was graft survival at 12 months after transplantation. Secondary efficacy endpoints were the rate of biopsy-confirmed acute rejection, patient survival, incidence of efficacy failure (defined as the first occurrence of either biopsy-proven acute rejection, graft loss, or death), and treatment failure (defined as the first occurrence of either discontinuation, acute rejection, graft loss, or death).

Based upon the analysis of data from 36 months and beyond, which showed a growing difference in graft survival and renal function, as well as significantly lower blood pressure in the cyclosporine withdrawal group, it was decided by the sponsor to discontinue subjects from the Rapamune with cyclosporine group. When the protocol was amended all subjects had reached 48 months and some completed the 60 months of the study.

The following table summarizes the resulting graft and patient survival at 12, 24, 36, 48 and 60 months for this trial. At 48 months, there was a statistically significant difference in graft survival between the two groups for both analyses (including and excluding loss to follow-up).

| **GRAFT AND PATIENT SURVIVAL (%): AFTER CYCLOSPORINE WITHDRAWAL[a]** | | |
|---|---|---|
| **Parameter** | **Rapamune with Cyclosporine Therapy (n = 215)** | **Rapamune Following Cyclosporine Withdrawal (n = 215)** |
| Graft Survival | | |
| Month 12[b] | 95.3[c] [95.3][d] | 97.2 [97.2] |
| Month 24 | 91.6 [91.6] | 94.0 [94.0] |
| Month 36[e] | 87.0 [88.4] | 91.6 [92.6] |
| Month 48 | 75.3 [84.2] | 86.0 [91.2] |
| Month 60 | 67.9 [83.3] | 80.0 [88.4] |
| Patient Survival | | |
| Month 12 | 97.2 [97.2] | 98.1 [98.1] |
| Month 24 | 94.4 [94.9] | 95.8 [96.3] |
| Month 36[e] | 91.6 [94.4] | 94.0 [96.3] |
| Month 48 | 78.6 [91.6] | 86.5 [95.3] |
| Month 60 | 68.8 [90.2] | 80.9 [93.0] |

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

The following table summarizes the results of first biopsy-proven acute rejection at 12 and 60 months. There was a significant difference in first biopsy-proven rejection between the two groups during post-randomization through 12 months. However, at month 60, the difference between the two groups was not significant (6.5% versus 10.2%, respectively). Most of the post-randomization acute rejections occurred in the first 3 months following randomization.

| INCIDENCE OF FIRST BIOPSY-PROVEN ACUTE REJECTION (%) BY TREATMENT GROUP AT 60 MONTHS: AFTER CYCLOSPORINE WITHDRAWAL[a,b] | | |
|---|---|---|
| **Period** | **Rapamune with Cyclosporine Therapy (n = 215)** | **Rapamune Following Cyclosporine withdrawal (n = 215)** |
| Pre-randomization[c] | 9.3 | 10.2 |
| Post-randomization through 12 months[c] | 4.2 | 9.8 |
| Post-randomization from 12 to 60 months | 2.3 | 0.4 |
| Post-randomization through 60 months | 6.5 | 10.2 |
| Total at 60 months | 15.8 | 20.5 |

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

The following table summarizes the mean calculated GFR after cyclosporine withdrawal.

| CALCULATED GLOMERULAR FILTRATION RATES (mL/min) BY NANKIVELL EQUATION AT 12, 24, 36, 48 and 60 MONTHS POST TRANSPLANT: AFTER CYCLOSPORINE WITHDRAWAL[a,b,c] | | |
|---|---|---|
| **Parameter** | **Rapamune with Cyclosporine Therapy** | **Rapamune Following Cyclosporine Withdrawal** |
| Month 12 | | |
| Mean ± SEM | 53.2 ± 1.5<br>n = 208 | 59.3 ± 1.5<br>n = 203 |
| Month 24 | | |
| Mean ± SEM | 48.4 ± 1.7<br>n = 203 | 58.4 ± 1.6<br>n = 201 |
| Month 36 | | |
| Mean ± SEM | 47.0 ± 1.8<br>(n = 196) | 58.5 ± 1.9<br>(n = 199) |
| Month 48 | | |
| Mean ± SEM | 43.5 ± 2.0<br>n = 185 | 58.1 ± 2.0<br>(n = 187) |
| Month 60 | | |
| Mean ± SEM | 42.7 ± 2.2<br>n = 176 | 58.0 ± 2.1<br>n = 193 |

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, 36, 48 and 60 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. At month 60, patients with an acute rejection at any time after transplantation had a significantly higher mean calculated GFR for patients receiving Rapamune as a maintenance regimen following cyclosporine withdrawal than for those in the Rapamune with cyclosporine therapy group.

The safety and efficacy of conversion from calcineurin inhibitors (CNI) to Rapamune were assessed in maintenance renal transplant patients. This study was a randomized, multicenter, controlled trial conducted at 111 centers globally, including US and Europe. Eight hundred thirty (830) patients were enrolled and stratified by baseline calculated glomerular filtration rate (GFR, 20-40 mL/min versus greater than 40 mL/min). Enrollment in the patient stratum with baseline calculated GFR less than 40 mL/min was discontinued due to an imbalance in safety events (see Sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects).

This study compared renal transplant patients (6-120 months after transplantation) who were converted from calcineurin inhibitors to Rapamune, with patients who continued to receive calcineurin inhibitors. Concomitant immunosuppressive medications included mycophenolate mofetil (MMF), azathioprine (AZA), and corticosteroids. Rapamune was initiated with a single loading dose of 12-20 mg, after which dosing was adjusted to achieve a target sirolimus whole blood trough concentration of 8-20 ng/mL (chromatographic method). The primary efficacy endpoint was calculated GFR at 12 months post-randomization. Secondary endpoints included biopsy-confirmed acute rejection, graft loss, and death. Enrollment in the patient stratum with baseline calculated GFR less than 40 mL/min was discontinued due to an imbalance in safety events (see Sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects). Findings in the patient stratum with baseline calculated GFR greater than 40 mL/min (Rapamune conversion, n = 497; CNI continuation, n = 246) are summarized below: There was no clinically or statistically significant improvement in Nankivell GFR compared to baseline.

**RENAL FUNCTION IN STABLE RENAL TRANSPLANT PATIENTS IN PATIENTS WITH BASELINE GFR >40 mL/min THE RAPAMUNE CONVERSION STUDY (STUDY 5)**

| **Parameter** | **Rapamune conversion N=496** | **CNI continuation N=245** | **Difference (95% CI)** |
|---|---|---|---|
| GFR mL/min (Nankivell) at 1 year | 59.0 | 57.7 | 1.3 (-1.1, 3.7) |
| GFR mL/min (Nankivell) at 2 year | 53.7 | 52.1 | 1.6 (-1.4, 4.6) |

In the patient stratum with baseline calculated GFR greater than 40 mL/min (Rapamune conversion, n = 497; CNI continuation, n = 246), renal function and the rates of acute rejection, graft loss, and death were similar at 1 and 2 years. Treatment-emergent adverse events occurred more frequently during the first 6 months after Rapamune conversion. The rates of pneumonia were significantly higher for the sirolimus conversion group.

While the mean and median values for urinary protein to creatinine ratio were similar between treatment groups at baseline, significantly higher mean and median levels of urinary protein excretion were seen in the Rapamune conversion arm at 1 year and at 2 years, as shown in the table below. In addition, when compared to patients who continued to receive calcineurin inhibitors, a higher percentage of patients had urinary protein to creatinine ratios >1 at 1 and 2 years after sirolimus conversion. This difference was seen in both patients who had a urinary protein to creatinine ratio ≤1 and those who had a protein to creatinine ratio >1 at baseline. More patients in the sirolimus conversion group developed nephrotic range proteinuria, as defined by a urinary protein to creatinine ratio >3.5 (46/482 [9.5%] versus 9/239 [3.8%]), even when the patients with baseline nephrotic range proteinuria were excluded. The rate of nephrotic range proteinuria was significantly higher in the sirolimus conversion group compared to the calcineurin inhibitor continuation group with

baseline urinary protein to creatinine ratio >1 (13/29 *versus* 1/14), excluding patients with baseline nephrotic range proteinuria.

**MEAN AND MEDIAN VALUES FOR URINARY PROTEIN TO CREATININE RATIO (mg/mg) BETWEEN TREATMENT GROUPS AT BASELINE, 1 AND 2 YEARS IN THE STRATUM WITH BASELINE CALCULATED GFR >40 mL/min**

| Study period | Sirolimus Conversion | | | CNI Continuation | | | |
|---|---|---|---|---|---|---|---|
| | N | Mean ± SD | Median | N | Mean ± SD | Median | p-value |
| Baseline | 410 | 0.35 ± 0.76 | 0.13 | 207 | 0.28 ± 0.61 | 0.11 | 0.381 |
| 1 year | 423 | 0.88 ± 1.61 | 0.31 | 203 | 0.37 ± 0.88 | 0.14 | <0.001 |
| 2 years | 373 | 0.86 ± 1.48 | 0.32 | 190 | 0.47 ± 0.98 | 0.13 | <0.001 |

The above information should be taken into account when considering conversion from calcineurin inhibitors to Rapamune in stable renal transplant patients due to the lack of evidence showing that renal function improves following conversion, and the finding of a greater increment in urinary protein excretion, and an increased incidence of treatment-emergent nephrotic range proteinuria following conversion to Rapamune. This was particularly true among patients with existing abnormal urinary protein excretion prior to conversion.

In the stratum with baseline calculated GFR greater than 40 mL/min, the mean and median values for urinary protein to creatinine ratio were similar between treatment groups at baseline (mean: 0.35 and 0.28; median: 0.13 and 0.11 for the Rapamune conversion and CNI continuation groups, respectively). At 24 months, the mean and median urinary protein to creatinine ratios were significantly higher in the Rapamune conversion group as compared to those of the (CNI) continuation group (mean: 0.87 and 0.48, $p<0.002$; median: 0.33 and 0.13, $p<0.001$, for the Rapamune conversion and CNI continuation groups, respectively) (see Section 4.4 Special warnings and precautions for use). New-onset nephrosis (nephrotic syndrome) was also reported (see Section 4.8 Undesirable effects).

At 2 years, the rate of non-melanoma skin malignancies was significantly lower in the Rapamune conversion group as compared to the CNI continuation group (1.8% and 6.9%, respectively, $p<0.001$). This difference in skin malignancy rates persisted after exclusion of patients with a prior history of skin malignancies (0.7% and 4.1% for the Rapamune conversion and CNI continuation groups, respectively, $p<0.002$). It should be noted that Study 4 was not designed to consider malignancy risk factors or systematically screen subjects for malignancy.

In a subset of study patients with a baseline GFR greater than 40 mL/min and normal urinary protein excretion, calculated GFR was higher at 1 and 2 years in patients converted to Rapamune (n = 197) than for the corresponding subset of CNI continuation patients (n = 102). The rates of acute rejection, graft loss, and death were similar, but urinary protein excretion was increased in the Rapamune treatment arm of the subset.

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%).

Rapamune was studied in a one-year, randomized, open-label, controlled clinical trial in high risk patients who were defined as Black transplant recipients and/or repeat renal transplant recipients who lost a previous allograft for immunologic reason and/or patients with high-panel reactive antibodies (PRA; peak PRA level >80%). Patients were randomized 1:1 to concentration-controlled sirolimus and tacrolimus or concentration-controlled sirolimus and cyclosporine (MODIFIED), and both groups received corticosteroids per local practice. Antibody induction was allowed per protocol as prospectively defined at each transplant center, and was used in 85.3% of patients. The study was conducted at 35 centers in the United States. Baseline demography was well-balanced in both groups; 77.7% of those receiving sirolimus and tacrolimus were Black, and 77.2% of those receiving sirolimus and cyclosporine were Black. The evaluable intention-to-treat population (defined as all patients who were randomized and received a transplant, and at least one dose of study medication) included 224 patients who received sirolimus and tacrolimus and 224 patients who received sirolimus and cyclosporine. The co-primary endpoints, all measured at 12 months in the evaluable ITT population, were efficacy failure (defined as the first occurrence of biopsy-confirmed acute rejection, graft loss, or death), first occurrence of graft loss or death, and renal function as measured by the calculated GFR using the Nankivell formula. The table below summarizes the co-primary endpoints. The overall rates of efficacy failure and the first occurrence of graft loss or death were similar in both groups.

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

| Parameter | Rapamune with Tacrolimus, Corticosteroids (n = 224) | Rapamune with Cyclosporine, Corticosteroids (n = 224) |
|---|---|---|
| Efficacy Failure (%) | 21.9 | 23.2 |
| | | |
| Graft Loss or Death (%) | 10.3 | 9.8 |
| | | |
| Renal Function (mean ± SEM)[a,b] | 54.5 ± 1.7 | 52.6 ± 1.6 |
| | (n = 224) | (n = 222) |

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

Patient survival at 12 months was 95.1% in patients who received sirolimus and tacrolimus versus 94.6% in patients who received sirolimus and cyclosporine. The incidence of biopsy-confirmed acute rejection was 13.8% in patients who received sirolimus and tacrolimus versus 17.4% in patients who received sirolimus and cyclosporine. Although acute rejection was numerically lower in patients who received sirolimus and tacrolimus, the severity of rejection was statistically greater compared with those who received sirolimus and cyclosporine. On-therapy renal function was consistently higher in patients who received sirolimus and tacrolimus as compared with patients who received sirolimus and cyclosporine.

A clinical study in liver transplant patients randomized to conversion from a CNI-based regimen to a sirolimus-based regimen versus continuation of a CNI-based regimen 6-144 months post-liver transplantation failed to demonstrate superiority in baseline-adjusted GFR at 12 months (-4.45 mL/min and -3.07 mL/min, respectively). The study also failed to demonstrate non-inferiority of the rate of combined graft loss, missing survival data, or death for the sirolimus conversion group compared to the CNI continuation group. The number of deaths in the sirolimus conversion group was higher than the CNI continuation group, although the difference was not statistically significant. The rates of premature study discontinuation, adverse events overall (and infections, specifically), and biopsy-proven acute liver graft rejection at 12 months were all significantly greater in the sirolimus conversion group compared to the CNI continuation group.

Rapamune was evaluated in a 36-month, open-label, randomized, controlled clinical trial at 14 North American centers in pediatric (aged 3 to <18 years) renal transplant recipients considered to be at high immunologic risk for developing chronic allograft nephropathy, defined as a history of one or more acute allograft rejection episodes and/or the presence of chronic allograft nephropathy on a renal biopsy. Seventy-eight (78) subjects were randomized in a 2:1 ratio to Rapamune (sirolimus target concentrations of 5 to 15 ng/mL, by chromatographic assay, n = 53) in combination with a calcineurin inhibitor and corticosteroids or to continue calcineurin-inhibitor-based immunosuppressive therapy (n = 25). The primary endpoint of the study was efficacy failure as defined by the first occurrence of biopsy confirmed acute rejection, graft loss, or death, and the trial was designed to show superiority of Rapamune added to a calcineurin-inhibitor-based immunosuppressive regimen compared to a calcineurin-inhibitor-based regimen. The cumulative incidence of efficacy failure up to 36 months was 45.3% in the Rapamune group compared to 44.0% in the control group, and did not demonstrate superiority. There was one death in each group. The use of Rapamune in combination with calcineurin inhibitors and corticosteroids was associated with an increased risk of deterioration of renal function, serum lipid abnormalities (including but not limited to increased serum triglycerides and cholesterol), and urinary tract infections. This study does not support the addition of Rapamune to calcineurin-inhibitor-based immunosuppressive therapy in this subpopulation of pediatric renal transplant patients (see Sections 4.2.1 Dosage and 5.2 Pharmacokinetic properties).

**Disclaimer: Data on Rapamune Oral Solution is provided only as a reference and Rapamune Oral Solution is not marketed in Malaysia.**

## 5.2 Pharmacokinetic properties

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 of Rapamune in healthy subjects and approximately 2 hours after multiple oral doses of Rapamune in renal transplant recipients. Following administration of Rapamune tablet, sirolimus $t_{max}$ was approximately 3 hours after single doses in healthy volunteers and multiple doses in renal transplant patients.

The systemic availability (F) of sirolimus from Rapamune oral solution was estimated to be approximately 14%. After Rapamune tablet administration, F was estimated to be approximately 17%. Bioequivalence

between 1 mg, 2 mg, and 5 mg tablets has been generally shown in healthy volunteers. The exception was that $t_{max}$ was longer for the 5 mg tablets compared with the other tablets.

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 in healthy volunteers.

Distribution

The mean (± SD) blood-to-plasma ratio of sirolimus was 36 (± 17.9) in stable renal allograft recipients after administration of Rapamune oral solution, indicating that sirolimus is extensively partitioned into formed blood elements. The mean volume of distribution (Vss/F) of sirolimus by Rapamune oral solution 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%), α1-acid glycoprotein, and lipoproteins.

Metabolism

Sirolimus is a substrate for both CYP3A4 and P-glycoprotein. Sirolimus is extensively metabolized by O-demethylation and/or hydroxylation. Seven 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 greater 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 ($t_{1/2}$) of sirolimus after multiple dosing by Rapamune oral solution in stable renal transplant patients was estimated to be about 62 ± 16 hours.

Effect of Food

In 22 healthy subjects, a high fat breakfast (860 kcal, 55% kcal from fat) altered the bioavailability characteristics of sirolimus after administration. by Rapamune oral solution. Compared to fasting, a 34% decrease in the peak blood sirolimus concentration ($C_{max}$), a 3.5-fold increase in the time to peak concentration ($t_{max}$), and a 35% increase in mean total exposure (AUC) was observed. In an otherwise identical study, Rapamune was administered by tablet to 24 healthy subjects. The values for $C_{max}$, $t_{max}$, 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 randomized multicenter controlled trial comparing Rapamune oral solution to tablets supports that the differences in absorption rates do not effect the efficacy of the drug.

Rapamune should be taken consistently with or without food to minimize blood level variability. Bioequivalence testing based on AUC and $C_{max}$ showed that Rapamune administered with orange juice is equivalent to administration with water. Therefore, orange juice and water may be used interchangeably to dilute Rapamune 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 taken with Rapamune (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Renal transplant patients

Mean (± SD) pharmacokinetic parameters for sirolimus given daily by Rapamune oral solution 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 Rapamune by tablet with a loading dose of three times the maintenance dose achieved steady-state concentrations within 24 hours after the start of dose administration.

High-risk patients

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 (see Section 5.1 Pharmacodynamic properties) 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.

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] | 5.2 ± 2.7 | 7.6 ± 3.1 |
| CL/F (mL/h/kg) | 173 ± 50 | 139 ± 63 |
| a: In presence of cyclosporine administered 4 hours before Rapamune dosing.<br>b: Based on data collected at months 1 and 3 post-transplantation.<br>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 3 clinical studies (see Section 5.1 Pharmacodynamic properties).

| SIROLIMUS WHOLE BLOOD TROUGH CONCENTRATIONS OBSERVED IN RENAL TRANSPLANT PATIENTS ENROLLED IN PHASE 3 STUDIES | | | | | |
|---|---|---|---|---|---|
| **Patient Population (Study number)** | **Treatment** | | | **Year 3** | |
| | | **Mean (ng/mL)** | **$10^{th}$ – $90^{th}$ percentiles (ng/mL)** | **Mean (ng/mL)** | **$10^{th}$ – $90^{th}$ percentiles (ng/mL)** |
| Study 301 | Rapamune (2 mg/day) + Cyclosporine | 7.2 | 3.6 – 11[a] | – | – |
| | Rapamune (5 mg/day) + Cyclosporine | 14 | 8 – 22[a] | – | – |
| Low-to-moderate risk Study 310 | Rapamune + Cyclosporine | 8.6 | 5 – 13[b] | 9.1 | 5.4 – 14 |
| | Rapamune alone | 19 | 14 – 22[b] | 16 | 11 – 22 |
| High risk Study 903 | Rapamune + Cyclosporine | 15.7<br>11.8<br>11.5 | 5.4 – 27.3[c]<br>6.2 – 16.9[d]<br>6.3 – 17.3[e] | – | – |
| a: Month 6<br>b: Months 4 through 12<br>c: Up to Week 2; observed Cyclosporine $C_{min}$ was 217 (56 – 432) ng/mL<br>d: Week 2 to Week 26; observed Cyclosporine $C_{min}$ range was 174 (71 – 288) ng/mL<br>e: Week 26 to Week 52; observed Cyclosporine $C_{min}$ was 136 (54.5 – 218) ng/mL | | | | | |

The withdrawal of cyclosporine and concurrent increases in sirolimus trough concentrations to steady-state required approximately 6 weeks. Following cyclosporine withdrawal, larger Rapamune doses were required due to the absence of the inhibition of sirolimus metabolism and transport by cyclosporine and to achieve higher target sirolimus trough concentrations during concentration-controlled administration.

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

Patients with Hepatic Impairment
The rate of absorption of sirolimus was not altered by hepatic disease, as evidenced by no changes in $C_{max}$ and $t_{max}$ values. 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 (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 10 - 20 ng/mL for the 21 children receiving tablets. 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) | $AUC_{t,ss}$ (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 (MODIFIED) (e.g., Neoral Oral Solution) and/or cyclosporine capsules (MODIFIED) (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$^2$).

Elderly
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.

Gender
Rapamune oral dose clearance after Rapamune oral solution 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).). Similar gender effects on oral-dose clearance and t1/2 were obtained after administration of Rapamune by tablets. These pharmacokinetic differences do not require dose adjustment based on gender.

Race
In large phase III trials using Rapamune and cyclosporine microemulsion [(cyclosporine, USP) MODIFIED], there were no significant differences in mean trough sirolimus concentrations or AUC over time between black (n = 139) and non-black (n = 724) patients during the first 6 months after transplantation at Rapamune doses of 2 mg/day.

**Disclaimer: Data on Rapamune Oral Solution is provided only as a reference and Rapamune Oral Solution is not marketed in Malaysia.**

## 5.3 Preclinical safety data

Carcinogenicity
Carcinogenicity studies were conducted in mice and rats. In an 86-week female mouse study at 4 dosages that were approximately 16 to 135 times the clinical doses (adjusted for body surface area) there was a statistically significant increase in malignant lymphoma at all dose levels compared with controls. In a second mouse study at dosages that were approximately 3 to 16 times the clinical doses (adjusted for body surface area), hepatocellular adenoma and carcinoma (males) were considered sirolimus related. In the 104-week rat study at dosages that were approximately 0.4 to 1 times the clinical doses (adjusted for body surface area), there was a statistically significant increased incidence of testicular adenoma in the highest dose 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
Sirolimus was embryo/fetal toxic in rats at dosages of 0.1 mg/kg and above (approximately 0.2 to 0.5 the clinical doses adjusted for body surface area). Embryo/fetal toxicity was manifested as mortality and reduced fetal weights (with associated delays in skeletal ossification). However, no teratogenesis was evident. In combination with cyclosporine, rats had increased embryo/fetal mortality compared to sirolimus alone. There were no effects on rabbit development at the maternally toxic dosage of 0.05 mg/kg (approximately 0.3 to 0.8 times the clinical doses adjusted for body surface area).

There 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 a slight reduction in fertility compared to controls in one study at a dosage of 2 mg/kg (approximately 4 to 11 times the clinical doses adjusted for body surface area). A second study failed to confirm these findings. 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

Lactose monohydrate, Polyethylene glycol 8000 powdered, Magnesium stearate, Talc

## 6.2 Incompatibilities

None

**6.3 Shelf life**

Observe “Expiry date” (month/year) imprinted on outer carton.

**6.4 Special precautions for storage**

Sirolimus tablets should be stored below 30°C. Use cartons to protect blister cards and strips from light. Dispense in a tight, light-resistant container as defined in the USP.

**6.5 Nature and contents of container**

Bottle of 100 tablets. Blister in cartons of 30’s.

Some product strengths or pack sizes may not be available in your country.

**6.6 Instructions for use and handling**

Not applicable.

**7. MANUFACTURER**

Pfizer Ireland Pharmaceuticals Unlimited Company,
Little Connell, Newbridge, Co.
Kildare, Ireland.

**Date of Revision: 02 OCT 2025**

**RAPAMUNE – 1025**