

AUSTRALIAN PRODUCT INFORMATION - RAPAMUNE® (sirolimus)

1. NAME OF THE MEDICINE

Sirolimus

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RAPAMUNE tablets contain 0.5 mg, 1 mg, 2 mg and 5 mg sirolimus.

RAPAMUNE oral solution contains 1 mg/mL sirolimus.

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

Excipient(s) with known effect:

Rapamune tablets:

- Sucrose
- Lactose monohydrate

Rapamune oral solution:

- Ethanol

For the full list of excipients, see Section 6.1 List of excipients

3. PHARMACEUTICAL FORM

Rapamune oral solution: Pale yellow to yellow solution.

Rapamune 0.5 mg Tablets: 0.5 mg tan triangular-shaped sugar coated tablets branded with "RAPAMUNE 0.5 mg" in red ink.

Rapamune 1 mg Tablets: 1 mg white triangular-shaped coated tablets.

Rapamune 2 mg Tablets: 2 mg yellow triangular-shaped coated tablets.

Rapamune 5 mg Tablets: 5 mg tan triangular-shaped coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rapamune is indicated for the prophylaxis of organ rejection in patients at mild to moderate immunological risk receiving renal transplants. Therapeutic drug monitoring of sirolimus is required.

4.2 Dose and method of administration

Dosage

Bioavailability has not been determined for tablets after they have been crushed, chewed, or split and therefore this cannot be recommended. Patients unable to take the tablets should be prescribed the solution and instructed in its use.

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.

Therapeutic drug monitoring is recommended for all patients receiving Rapamune (see Therapeutic Drug Monitoring subsection below).

Two mg of Rapamune oral solution has been demonstrated to be clinically equivalent to two 1 mg Rapamune tablets and hence are interchangeable on a mg to mg basis. However, it is not known if higher doses of Rapamune oral solution are clinically equivalent to higher doses of tablets on a mg to mg basis.

When switching from 1 mg to 5 mg tablets, sirolimus whole blood steady-state trough concentrations would be expected to be 24% higher on average with 5 mg tablets compared to 1 mg tablets (based on repeat dosing at the recommended dosage interval of 24 hours). When switching from 2 mg to 5 mg tablets, the increase in sirolimus concentration would be expected to be 13% on average and when switching from 1 mg to 2 mg tablets, 10% on average (see Section 5.2 Pharmacokinetic properties, Absorption, Oral Tablets).

It is recommended that a trough level be taken 1 to 2 weeks after switching between different strengths of Rapamune tablets.

It is recommended that Rapamune be taken 4 hours after administration of ciclosporin (CsA) oral solution and/or CsA capsules (see Section 4.5 Interactions with other medicines and other forms of interactions, Inhibitors and Inducers of Cytochrome P450 3A4 (CYP3A4), Ciclosporin (CYP3A4 substrate)). Rapamune should be taken consistently either with or without food. It should not be taken with grapefruit juice.

Adults

Initial Treatment

Rapamune is usually administered as a 6 mg oral loading dose as soon as possible after transplantation followed by 2 mg once daily (in combination with ciclosporin and corticosteroids (see Section 4.4 Special warnings and precautions for use, *De Novo* Use Without Calcineurin Inhibitor (CNI)). The dose should then be individualised to obtain sirolimus whole blood trough concentrations of 4-12 ng/mL (chromatographic assay) (see Therapeutic Drug Monitoring subsection below).

Treatment 2-4 Months after Transplantation

After 2 to 4 months, ciclosporin should be progressively discontinued over a period of 4 to 8 weeks and the Rapamune dose adjusted to obtain sirolimus whole blood trough concentrations of 12-20 ng/mL (chromatographic assay) (see Therapeutic Drug Monitoring subsection below).

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. Treatment with corticosteroids should continue. CsA inhibits the metabolism and transport of sirolimus, and consequently, sirolimus concentrations will decrease when CsA 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 CsA (approximately 2-fold increase).

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.

Adjustments in dose should not be based on a single sirolimus whole blood trough level, unless warranted by clinical signs/symptoms, tissue biopsy, and /or laboratory parameters (see above). Repeating the trough level measurement may in many cases be warranted prior to dose adjustment.

In patients for whom CsA withdrawal is either unsuccessful or cannot be attempted because of the high risk of transplant rejection, Rapamune should be discontinued and an alternative immunosuppressive regimen instituted.

Dosage Adjustment

Use in Children and Adolescents

There is insufficient experience to recommend the use of Rapamune in children and adolescents. Limited pharmacokinetic information is available in children.

Elderly Patients (> 65 years)

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. 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. Rapamune tablets administered to 12 renal transplant patients >65 years of age also gave similar results to adult patients (n = 167) 18 to 65 years of age.

Patients with Renal Impairment

No dosage adjustment is required.

Patients with Hepatic Impairment

In patients with hepatic impairment, it is recommended that the maintenance dose of Rapamune

be reduced by approximately one third in patients with mild to moderate hepatic impairment and by approximately one half in patients with severe hepatic impairment. It is not necessary to modify the Rapamune loading dose (see Section 5.2 Pharmacokinetic properties). It is recommended that sirolimus whole blood trough levels be closely monitored in patients with impaired hepatic function.

Therapeutic Drug Monitoring

Most patients who received 2 mg of Rapamune 4 hours after CsA had whole blood trough concentrations of sirolimus within the 4 to 12 ng/mL target range (chromatographic assay). Optimal therapy requires therapeutic drug concentration monitoring in all patients. Whole blood sirolimus levels should be closely monitored in the following populations:

- in patients receiving concentration-controlled Rapamune
- in patients with hepatic impairment
- when inducers (e.g. rifampicin, rifabutin) or inhibitors (e.g. ketoconazole) of CYP3A4 and P-glycoprotein (P-gp) are concurrently administered and after their discontinuation; and/or
- if CsA dosing is markedly reduced or discontinued, as these populations are most likely to have special dosing requirements.

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.

Assay Methodology

The recommended 24-hour trough concentration ranges for sirolimus are based on chromatographic methods.

Several assay methodologies have been used to measure the whole blood concentrations of sirolimus. Currently in clinical practice, sirolimus whole blood concentrations are being measured by both chromatographic and immunoassay methodologies. The concentration values obtained by these different methodologies are not interchangeable.

Adjustments to the targeted range should be made according to the assay utilised to determine sirolimus trough concentrations. 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.

Monitoring Advice

Monitoring of triglycerides and cholesterol should be included as part of routine post-transplant patient management (see Section 4.4 Special warnings and precautions for use, Hyperlipidaemia).

Method of Administration

Instructions for Dilution and Administration of Rapamune Oral Solution

The dosing syringe should be used to withdraw the prescribed amount of Rapamune oral solution from the bottle. Empty the correct amount of Rapamune oral solution from the syringe into a glass or plastic container holding at least 60 mL of water or orange juice. Only glass or plastic cups should be used to mix Rapamune Oral Solution. Do not use any liquids other than water or orange juice for dilution. Stir vigorously and drink at once. When mixed with water or orange

juice, Rapamune oral solution produces a white to off-white dispersion. Refill the container with an additional volume (minimum of 120 mL) of water or orange juice, stir vigorously, and drink at once. Grapefruit juice must not be taken with sirolimus (see Section 5.2 Pharmacokinetic properties). Discard the syringe after one use.

Influence of Foods, Compatibility with Drugs/Fluids

To minimise the pharmacokinetic effect of CsA (microemulsion) on sirolimus, administration of sirolimus and CsA (microemulsion) should be separated by approximately 4 hours.

Food increases the bioavailability of sirolimus (see Section 5.2 Pharmacokinetic properties). To minimise variability, Rapamune oral solution and Rapamune tablets should be taken consistently with or without food. Grapefruit juice must not be taken with Rapamune.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Wound Healing and Fluid Accumulation

mTOR inhibitors such as sirolimus have been shown *in-vitro* to inhibit production of certain growth factors that may affect angiogenesis, fibroblast proliferation, and vascular permeability. There have been reports of impaired or delayed wound healing in patients receiving Rapamune, including lymphocele and wound dehiscence. 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 minimise such complications. Patients with a BMI greater than 30 kg/m² may be at increased risk of abnormal wound healing based on data from the medical literature (see Section 4.8 Adverse effects (undesirable effects), Other Clinical Experience, *Abnormal Healing*). There have also been reports of fluid accumulation, including peripheral oedema, lymphoedema, pleural effusion and pericardial effusions (including haemodynamically significant effusions in children and adults), in patients receiving Rapamune.

Malignancies

Immunosuppression increases the susceptibility to the development of lymphoma and other malignancies, particularly of the skin (see Section 4.8 Adverse effects (undesirable effects), Other Clinical Experience, *Rapamune Following CsA Withdrawal*). 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.

Hypersensitivity Reactions

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

Infections

Over-suppression of the immune system can also increase susceptibility to opportunistic infections, sepsis and fatal infections.

Hyperlipidaemia

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

Any patient who is administered Rapamune should be monitored for hyperlipidaemia using laboratory tests and, if hyperlipidaemia is detected, subsequent interventions such as diet, exercise and lipid-lowering agents should be initiated (see Section 4.2 Dose and method of administration, Monitoring Advice).

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

Rhabdomyolysis

In the limited number of patients studied, the concomitant administration of Rapamune and HMG-CoA reductase inhibitors and/or fibrates was well tolerated. During Rapamune therapy with or without CsA, patients should be monitored for elevated lipids and patients administered an HMG-CoA reductase inhibitor and/or fibrates should be monitored for the development of rhabdomyolysis and other adverse effects as described in the respective Product Information for these agents.

Renal Function

Renal function should be monitored during concomitant administration of Rapamune and CsA. Appropriate adjustment of the immunosuppression regimen should be considered in patients with elevated serum creatinine levels. Caution should be exercised when co-administering other agents that are known to have a deleterious effect on renal function.

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

Patients treated with CsA and Rapamune beyond 3 months had higher serum creatinine levels and lower calculated glomerular filtration rates compared to patients treated with CsA and placebo or azathioprine controls. The rate of decline in renal function was greater in patients receiving Rapamune and CsA compared with control therapies (see Section 5.1 Pharmacodynamic properties, Clinical Trials, Rapamune Maintenance Regimen with Cyclosporin Withdrawal). Patients who were successfully withdrawn from CsA had lower serum creatinine levels and higher calculated glomerular filtration rates compared to patients remaining on CsA. Therefore, the long-term combination of CsA with sirolimus is not recommended.

Renal function should be closely monitored during the co-administration of Rapamune with tacrolimus.

Conversion to Rapamune

The safety and efficacy of conversion from calcineurin inhibitors in maintenance renal transplant patients have not been established.

Safety of abrupt conversion to Rapamune from calcineurin inhibitors at 6-120 months after renal transplantation was assessed (see Section 5.1 Pharmacodynamic properties, Clinical Trials, Conversion from Calcineurin Inhibitors to Rapamune). Enrolment was ceased in the stratum with baseline GFR < 40 mL/min (n = 87) because of a higher rate of serious adverse events including pneumonia, acute rejection, graft loss and death.

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, Clinical Trials, Conversion from Calcineurin Inhibitors to Rapamune).

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 6th through 24th month after conversion to Rapamune compared with CNI continuation (23.6% versus 12.8%, respectively) (see Section 5.1 Pharmacodynamic properties, Clinical Trials, Conversion from Calcineurin Inhibitors to Rapamune). 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.

***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-centre clinical studies, *de novo* renal transplant patients treated with Rapamune, mycophenolate mofetil (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 an IL-2 receptor antagonist.

A benefit, in terms of better renal function, was not apparent in the treatment arms with *de novo* use in 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 Haemolytic Uraemic 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 oedema-type reactions.

Elevated sirolimus levels (with/without concomitant ACE inhibitors) may also potentiate angioedema (see Section 4.5 Interactions with other medicines and other forms of interactions, Inhibitors and Inducers of Cytochrome P450 3A4 (CYP3A4)). 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 organising pneumonia [BOOP] and pulmonary fibrosis), some fatal, with no identified infectious aetiology 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 Adverse effects (undesirable effects), Other Clinical Experience, *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 Adverse effects (undesirable effects), Other Clinical Experience, *Latent Viral Infections*).

Antimicrobial Prophylaxis

Cases of *Pneumocystis carinii* pneumonia have been reported in patients not receiving antimicrobial prophylaxis. Therefore, antimicrobial prophylaxis for *Pneumocystis carinii* pneumonia should be administered for one year following transplantation (see also Section 4.5 Interactions with other medicines and other forms of interactions).

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

Liver and Lung Transplantation

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

Liver Transplantation – Excess Mortality, Graft Loss and Hepatic Artery Thrombosis (HAT)

The use of sirolimus 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 sirolimus in combination with CsA or tacrolimus was associated with an increase in HAT; most cases of HAT occurred within 30 days post-transplantation and most led to graft loss or death.

A clinical study in liver transplant patients randomised to conversion to a sirolimus-based regimen versus continuation of a 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.

Lung Transplantation – Bronchial Anastomotic Dehiscence

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

Use in Hepatic Impairment

The clearance of sirolimus was 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 Dose and method of administration).

Use in High Risk Patients

The safety and efficacy of sirolimus in combination with ciclosporin (CsA), with subsequent CsA 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 CsA withdrawal, those who are dialysis-dependent or with serum creatinine >4.5 mg/dL, black patients, renal re-transplants, multi-organ transplants, and patients with a high panel of reactive antibodies (see Section 4.1 Therapeutic indications and Section 5.1 Pharmacodynamic properties, Clinical Trials, Rapamune Maintenance Regimen with Ciclosporin Withdrawal).

Interaction of Oral Solution with PVC

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

Use in the Elderly

No data available.

Paediatric Use

The safety and efficacy of Rapamune in paediatric patients below the age of 18 years have not been established. Limited pharmacokinetic information is available in children (see Section 5.2 Pharmacokinetic properties).

Safety was assessed in a controlled clinical trial in paediatric (<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. 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.

Effects on Laboratory Tests

Whole blood sirolimus levels should be monitored in all patients.

4.5 Interactions with other medicines and other forms of interactions

Inhibitors and Inducers of Cytochrome P450 3A4 (CYP3A4)

Co-administration of Rapamune with strong inhibitors of CYP3A4 and/or P-glycoprotein (P-gp) (such as ketoconazole, voriconazole, itraconazole, telithromycin, or clarithromycin) or strong inducers of CYP3A4 and/or P-gp (such as rifampicin or rifabutin) is not recommended. Sirolimus is extensively metabolised 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 medicines 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, verapamil
- Antifungal agents: clotrimazole, fluconazole, itraconazole, ketoconazole, voriconazole
- Antibiotics: clarithromycin, erythromycin
- Gastrointestinal prokinetic agents: cisapride, metoclopramide
- Other drugs: bromocriptine, cimetidine, ciclosporin, danazol, protease inhibitors (e.g., for HIV and hepatitis C that include drugs such as ritonavir, indinavir, boceprevir and telaprevir)
- Grapefruit juice.

Substances that induce CYP3A4 include, but are not limited to:

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

Grapefruit juice potentially reduces CYP3A4-mediated metabolism of sirolimus and must not be taken with sirolimus or be used for dilution (see Section 4.2 Dose and method of administration).

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

Ciclosporin (CYP3A4 substrate)

Ciclosporin (CsA) is a substrate and inhibitor of CYP3A4 and P-gp. Patients administered Rapamune with CsA should be monitored for the development of rhabdomyolysis (see Section 4.4 Special warnings and precautions for use, Rhabdomyolysis). The rate and extent of sirolimus absorption is significantly affected by CsA. In healthy volunteers, simultaneous administration of Rapamune oral solution and CsA microemulsion resulted in increases in sirolimus C_{max} and AUC of 116% and 230%, respectively compared to sirolimus alone. When Rapamune was given 4 hours after CsA, sirolimus C_{max} and AUC were increased by 40% and 80%, respectively. It is therefore recommended that Rapamune be administered 4 hours after CsA microemulsion, as was the case in the large Phase III clinical trials.

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

After multiple-dose administration of Rapamune given 4 hours after CsA microemulsion in renal transplant patients over 6 months, CsA oral dose clearance was reduced and lower doses of CsA microemulsion were needed to maintain target CsA concentration.

Rifampicin (CYP3A4 inducer)

Rifampicin is a strong inducer of CYP3A4. Co-administration of Rapamune and rifampicin is

not recommended. Administration of multiple doses of rifampicin decreased sirolimus whole blood concentrations following a single 10 mg dose of Rapamune oral solution. Rifampicin increased the clearance of sirolimus by approximately 5.5-fold and decreased AUC and C_{max} by approximately 82% and 71%, respectively.

Ketoconazole (CYP3A4 inhibitor)

Ketoconazole is a strong inhibitor of CYP3A4 and P-gp. Co-administration of Rapamune and ketoconazole is not recommended. In a study of 24 healthy volunteers, it was found that multiple-dose ketoconazole administration significantly affected the rate and extent of absorption and sirolimus exposure from Rapamune oral solution as reflected by increases in sirolimus C_{max} , t_{max} and AUC of 4.3-fold, 1.4-fold and 10.9-fold, respectively.

Diltiazem (CYP3A4 inhibitor)

Diltiazem is a substrate and inhibitor of CYP3A4 and P-gp. Sirolimus levels should be monitored and a dose reduction may be necessary if diltiazem is co-administered. The simultaneous oral administration of 10 mg of Rapamune oral solution and 120 mg of diltiazem significantly affected the bioavailability of sirolimus. Sirolimus C_{max} , t_{max} , and AUC were increased 1.4-fold, 1.3-fold, and 1.6-fold, respectively. Sirolimus did not affect the pharmacokinetics of either diltiazem or its metabolites desacetyldiltiazem and desmethyl diltiazem.

Verapamil (CYP3A4 inhibitor)

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

Erythromycin (CYP3A4 inhibitor)

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

Oral Contraceptives

No clinically significant pharmacokinetic interaction was observed between Rapamune and 0.3 mg norgestrel / 0.03 mg ethinyl oestradiol. Although the results of a single dose drug interaction study with an oral contraceptive suggest the lack of a pharmacokinetic interaction, the results cannot exclude the possibility of changes in the pharmacokinetics that might affect the efficacy of the oral contraceptive during long term treatment with Rapamune.

Vaccination

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

Medicines Showing No Clinically Significant Interaction with Rapamune

In healthy volunteer studies no clinically significant pharmacokinetic interaction was observed between Rapamune and any of the following medicines: acyclovir, atorvastatin, digoxin, glibenclamide, norgestrel/ethinyloestradiol, methylprednisolone, nifedipine, prednisolone, trimethoprim/sulphamethoxazole and tacrolimus.

Possible Interactions of Rapamune with Other Cytochrome P450 Isozymes

Although sirolimus inhibits human liver microsomal cytochrome P450 CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 *in vitro*, the drug is not expected to inhibit the activity of these isozymes *in vivo* since the sirolimus concentrations necessary to produce inhibition are much higher (about 100-fold) than those observed in patients receiving therapeutic doses of Rapamune.

4.6 Fertility, pregnancy and lactation

Effects on Fertility

There was no effect on fertility in female rats following the administration of sirolimus at dosages up to 0.5 mg/kg/day (less than 0.1 times the clinical exposure at the maintenance dose of 5 mg/day, based on AUC). In male rats, there was no significant difference in fertility rate compared to controls at a dosage of 2 mg/kg. 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 (less than 0.1 times the clinical exposure) and above and in a monkey study at 0.1 mg/kg/day (less than clinical exposure) and above. Sperm counts were reduced in male rats following the administration of sirolimus for 13 weeks at a dosage of 6 mg/kg/day (approximately 0.7 times the clinical exposure) but showed improvement within 3 months after dosing was stopped.

Use in Pregnancy - Category C

Sirolimus may cause immunosuppression in the infant. Sirolimus was embryo/fetal toxic in rats at dosages of 0.1 mg/kg/day and above (less than 0.1 times the clinical exposure at the maintenance dose of 5 mg/day, based on AUC).

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 CsA, rats had increased embryo/fetal toxicity compared with sirolimus alone. There were no effects on rabbit development at the maternally toxic dosage of 0.05 mg/kg (approximately 0.2 times the clinical exposure at the maintenance dose of 5 mg/day, based on AUC).

There are no adequate and well-controlled studies with Rapamune in pregnant women. Rapamune should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Effective contraception must be initiated before and maintained during Rapamune therapy and for 12 weeks after Rapamune has been stopped. Although the results of a single dose drug interaction study with an oral contraceptive suggest the lack of a pharmacokinetic interaction, the results cannot exclude the possibility of changes in the pharmacokinetics that might affect the efficacy of the oral contraceptive under long term dosing conditions with Rapamune (see Section 4.5 Interactions with other medicines and other forms of interactions, Oral Contraceptives).

Use in Lactation

Sirolimus metabolites, and to a lesser extent, parent drug were excreted in lactating rat milk. It is not known whether sirolimus is excreted in human milk. The pharmacokinetic and safety profiles of sirolimus in infants are not known. Because many medicines are excreted in human

milk and because of the potential for adverse reactions in nursing infants from sirolimus, a decision should be made whether to discontinue nursing or to discontinue sirolimus, taking into account the importance of sirolimus to the mother.

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (undesirable effects)

The list below contains adverse reactions seen in patients treated with Rapamune-based regimens in clinical trials. Only events for which there is at least reasonable suspicion of a causal relationship to Rapamune treatment are listed. In general, adverse events related to administration of sirolimus were dependent on dose/concentration.

The majority of patients in clinical trials were treated with CsA and corticosteroids; thus the frequency of adverse reactions listed includes Rapamune administration combined with CsA and corticosteroids.

The frequency of the adverse reactions taken from clinical trial data listed below was determined in five clinical trials in renal transplantation. These included two randomised, double-blind, multi-centre controlled trials in which 499 renal transplant patients received Rapamune oral solution 2 mg/day and 477 received Rapamune oral solution 5 mg/day together with CsA and corticosteroids. One randomised open-label study enrolling 477 patients compared the tablet (238 patients) and the solution (239 patients). Additionally, two open-label studies enrolled 771 patients who initially received Rapamune and CsA. These patients were randomised to continue CsA therapy or to have CsA withdrawn after 2-3 months post-transplant. Overall the safety profile of Rapamune tablets did not differ from that of the oral solution formulation in clinical trials.

Adverse reactions are listed within each standard system organ class (SOC) by decreasing medical seriousness according to the following categories:

Very common:	≥10%
Common:	≥1% and <10%
Uncommon:	≥0.1% and <1%
Rare:	≥0.01% and <0.1%

System Organ Class

Blood and lymphatic system disorders

Very common:	Thrombocytopenia [†] ; anaemia [†] ; leukopenia.
Common:	Haemolytic uraemic syndrome; neutropenia.
Uncommon:	Pancytopenia; thrombotic thrombocytopenic purpura.

Cardiac disorders

Very common:	Tachycardia.
Common:	Pericardial effusion [‡] .

Gastrointestinal disorders

Very common: Abdominal pain; constipation; diarrhoea; nausea.

Common: Pancreatitis; stomatitis; ascites.

General disorders and administration site conditions

Very common: Impaired healing; oedema, oedema peripheral; pyrexia; pain.

Immune system disorders

Common: Hypersensitivity (including angioedema, anaphylactic reaction, and anaphylactoid reaction).

Infections and infestations

Very common: Pneumonia; fungal infection; viral infection; bacterial infection; herpes simplex; urinary tract infection.

Common: Sepsis; pyelonephritis; cytomegalovirus infection; herpes zoster.

Uncommon: Mycobacterial infection (including tuberculosis); Epstein-Barr virus infection.

Investigations

Very common: Liver function test abnormal (including alanine aminotransferase increased and aspartate aminotransferase increased); blood creatinine increased; blood lactate dehydrogenase increased.

Metabolism and nutrition disorders

Very common: Hypokalaemia; hypophosphataemia; hyperlipidaemia (including hypercholesterolaemia); hyperglycaemia; hypertriglyceridaemia; fluid retention; diabetes mellitus.

Musculoskeletal, connective tissue and bone disorders

Very common: Arthralgia.

Common: Osteonecrosis.

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Common: Squamous cell carcinoma of skin; basal cell carcinoma.

Uncommon: Lymphoma; malignant melanoma; post-transplant lymphoproliferative disorder.

Nervous system disorders

Very common: Headache.

Renal and urinary disorders

Very common: Proteinuria.

Uncommon: Nephrotic syndrome; focal segmental glomerulosclerosis.

Reproductive system and breast disorders

Very common: Menstrual disorder (including amenorrhoea and menorrhagia).

Common: Ovarian cyst.

Respiratory, thoracic and mediastinal disorders

Common: Pulmonary embolism; pneumonitis; pleural effusion; epistaxis.

Uncommon: Pulmonary haemorrhage.

Rare: Alveolar proteinosis.

Skin and subcutaneous tissue disorders

Very common: Rash; acne.

Uncommon: Dermatitis exfoliative (see Section 4.4 Special warnings and precautions for use, Hypersensitivity Reactions).

Rare: Hypersensitivity vasculitis.

Vascular disorders

Very common: Hypertension; lymphocele.

Common: Venous thrombosis (including deep vein thrombosis).

Uncommon: Lymphoedema.

† Particularly at higher doses.

‡ Including haemodynamically significant effusions in children and adults.

Post-marketing Experience

In addition, the following adverse reactions have been identified during post-approval use of Rapamune. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders

Clostridium difficile enterocolitis.

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Neuroendocrine carcinoma of the skin.

Nervous system disorders

Posterior reversible encephalopathy syndrome (PRES).

Reproductive system and breast disorders

Azoospermia (reversible upon discontinuation in most cases).

Other Clinical Experience

Rapamune Following CsA Withdrawal

The incidence of adverse reactions was determined through 60 months in a randomised, multicentre controlled trial in which 215 renal transplant patients received Rapamune as a

maintenance regimen following CsA withdrawal, and 215 patients received Rapamune with CsA therapy. All patients were treated with corticosteroids. The safety profile prior to randomisation (start of CsA withdrawal) was similar to that of the 2 mg Rapamune groups in studies of Rapamune in combination with CsA. Following randomisation (at 3 months), patients who had CsA eliminated from their therapy experienced significantly higher incidences of increased AST/SGOT and increased ALT/SGPT, liver damage, hypokalaemia, thrombocytopenia, abnormal healing, acne, ileus, and joint disorder. Conversely, the incidence of acidosis, hypertension, CsA toxicity, increased creatinine, abnormal kidney function, toxic nephropathy, oedema, hyperuricaemia, gout, and gum hyperplasia was significantly higher in patients who remained on CsA than those who had CsA withdrawn from therapy. Mean systolic and diastolic blood pressure improved significantly following CsA withdrawal.

Following CsA withdrawal, (at 60 months), the incidence of Herpes zoster infection was significantly lower in patients receiving Rapamune following CsA withdrawal, compared with patients who continued to receive Rapamune and CsA.

The incidence of malignancies in the CsA withdrawal study is presented in Table 1. There are no significant differences between the two groups overall (15.8% in the Rapamune with CsA group versus 10.7% in the Rapamune with CsA withdrawal group; $p=0.155$).

Table 1: Incidence (%) of Malignancies at 60 Months Post-Transplant^a

Malignancy	Non-randomised ^b (n = 95)	Rapamune with CsA Therapy ^c (n = 215)	Rapamune Following CsA Withdrawal ^c (n = 215)
Lymphoma/lymphoproliferative disease	1.1	1.4	0.5
Skin Carcinoma ^d			
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, CsA 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 CsA as compared with the cohort who had CsA 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 CsA withdrawal group as compared with the group that continued CsA.

In an open-label Phase IV study, conversion to Rapamune was compared to continuation of CNI-based treatment in 86 renal transplant patients who had a history of non-melanoma skin cancer (NMSC) within 3 years of enrolment and were at least 1 year post-transplant, calculated GFR \geq 40 mL/min and proteinuria \leq 500 mg/day. Patients were randomised to continue baseline CNI treatment (n=47) or convert to Rapamune treatment (n=39). Randomisation was stratified by the

number of new NMSC lesions in the 12 months prior to enrolment. Sirolimus dose was adjusted to maintain a sirolimus whole blood trough concentration of 5 to 15 ng/mL, as measured by high performance liquid chromatography (6 to 18 ng/mL as measured by immunoassay).

Mean duration of follow-up for the Rapamune and CNI treatment groups was 1.68 years (range 0.06 to 2.13) and 1.75 years (range 0.06 to 2.23) ($p=0.127$) for the intent-to-treat (ITT) population, respectively. The mean duration of treatment in the Rapamune and CNI treatment groups was 0.95 years (range 0.03 to 2.02) and 1.62 years (range 0.05 to 2.10) ($p<0.001$), respectively.

Treatment-emergent adverse events were reported by 38 subjects (97.4%) from the Rapamune treatment group and 40 subjects (85.1%) from the CNI treatment group. Treatment-emergent adverse events were reported in a significantly greater number of subjects in the Rapamune treatment group for diarrhoea, peripheral oedema, mouth ulceration, rash, pneumonitis, albuminuria, acne and epistaxis. No treatment-emergent adverse events were reported in a significantly greater number of subjects in the CNI treatment group than the Rapamune treatment group. Treatment-emergent adverse events reported in the study were consistent with the known safety profile of Rapamune.

The rate of new NMSC lesions in the Rapamune treatment group compared to the CNI treatment group was 1.31 versus 2.48 NMSC lesions per subject year (ITT analysis). The rate of new squamous cell carcinoma (SCC) in the Rapamune treatment group compared to the CNI treatment group was 0.88 versus 1.71. The rate of new basal cell carcinoma (BCC) in the Rapamune treatment group compared to the CNI treatment group was 0.43 versus 0.77. The rate of new lesions in the Rapamune treatment group compared to the CNI treatment group was 1.35 versus 2.50 NMSC lesions per subject year (on-therapy OT analysis).

In the Rapamune treatment group, 18 subjects (46.2%) discontinued study treatment due to adverse events. Pneumonitis (10.3%), diarrhoea (5.1%) and decreased tolerance (5.1%) most frequently caused discontinuation of Rapamune treatment. There were no discontinuations due to adverse events in the CNI treatment group.

Calcineurin Inhibitor-Induced HUS/TTP/TMA

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, Calcineurin Inhibitor-Induced Haemolytic Uraemic Syndrome / Thrombotic Thrombocytopenic Purpura / Thrombotic Microangiopathy (HUS/TTP/TMA)).

Patients with Delayed Graft Function

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).

Hepatotoxicity

Hepatotoxicity has been reported, including fatal hepatic necrosis, with elevated trough sirolimus levels.

Interstitial Lung Disease

Cases of interstitial lung disease (including pneumonitis and infrequently bronchiolitis obliterans organising pneumonia (BOOP) and pulmonary fibrosis), some fatal, with no identified infectious aetiology have occurred in patients receiving immunosuppressive regimens including Rapamune. In some cases, the pneumonitis 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).

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).

High Risk Patients

Rapamune was studied in a one-year, randomised, 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 randomised 1:1 to concentration-controlled sirolimus and tacrolimus or concentration-controlled sirolimus and ciclosporin and both groups received corticosteroids per local practice. Antibody induction was allowed per protocol as prospectively defined at each transplant centre, and was used in 85.3% of patients.

Safety was assessed in 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 ciclosporin. Overall, the incidence and nature of adverse events was similar to those seen in previous combination studies with Rapamune. Diarrhoea 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 ciclosporin.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

At present, there is limited experience with overdose.

Signs and Symptoms

In general, the adverse effects of overdose are consistent with those listed in the Section 4.8 – Adverse effects (undesirable effects). One patient experienced an episode of atrial fibrillation after ingestion of 150 mg of Rapamune.

Recommended Treatment

General supportive measures should be initiated in all cases of overdose. Based on the poor

aqueous solubility and high erythrocyte and plasma protein binding of Rapamune, it is anticipated that Rapamune is not dialysable to any significant extent.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

Sirolimus is a selective immunosuppressant agent. Sirolimus inhibits T cell activation induced by most stimuli by blocking calcium dependent and calcium-independent intracellular signal transduction. Studies demonstrated that its effects are mediated by a mechanism that is different from that of ciclosporin, tacrolimus and other immunosuppressive agents. Experimental evidence suggests that sirolimus binds to the specific cytosolic protein FKBP-12 and that the FKBP-12-sirolimus complex inhibits the activation of the mammalian Target Of Rapamycin (mTOR), a critical kinase for cell cycle progression. The inhibition of mTOR results in blockage of several specific signal transduction pathways. The net result is the inhibition of lymphocyte activation, which results in immunosuppression.

In animals, sirolimus has a direct effect on T and B cell activation suppressing immune-mediated reactions such as allograft rejection.

Clinical Trials

Rapamune Maintenance Regimen with Ciclosporin Withdrawal

The safety and efficacy of Rapamune in a regimen in which ciclosporin was withdrawn after 3 to 4 months following renal transplantation were assessed in a randomised multicentre controlled trial. This study compared patients who were administered Rapamune, ciclosporin and corticosteroids continuously with patients who received the same standardised therapy for the first three months after transplantation (pre-randomisation period) followed by the elimination of ciclosporin. During ciclosporin elimination, the Rapamune doses were adjusted to achieve targeted serum trough concentration ranges (20 to 30 ng/mL, immunoassay equivalent to 16 to 24 ng/mL by chromatographic assay).

A total of 525 patients were enrolled. Patients were excluded from entry if they were to receive antibody induction therapy at the time of transplantation. Patients entered in the clinical trial were excluded from randomisation if they experienced a Banff Grade 3 acute rejection or vascular rejection in the preceding 4 weeks, if they had a serum creatinine level >400 µmol/L or were dialysis-dependent, or if, in the opinion of the investigator, they had inadequate renal function to support ciclosporin withdrawal. The patient population enrolled included only small numbers of black patients, who are known to be at a higher risk of rejection.

At 3 months, 430 patients were equally randomised to either Rapamune with ciclosporin or Rapamune maintenance regimen with ciclosporin withdrawal. 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 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 ciclosporin withdrawal group, it was decided by the sponsor to discontinue subjects from the Rapamune with ciclosporin group. When the protocol was amended, all subjects had reached 48 months and some completed the 60 months of the study. The following table summarises the resulting graft and patient survival at 12, 24, 36, 48 and 60 months.

From 48 months, graft and patient survival were significantly better in the Rapamune with CsA withdrawal group.

Table 2: Graft and Patient Survival (%): After CsA Withdrawal^a

Parameter	Rapamune with ciclosporin therapy (n = 215)	Rapamune maintenance regimen with ciclosporin withdrawal (n = 215)	Difference between groups (95% CI)
Graft survival			
Month 12 ^b	95.3 ^c	97.2	-1.9 (-5.4, 1.7)
Month 24	91.6	94.0	-2.3 (-7.2, 2.6)
Month 36 ^d	87.0	91.6	-4.7 (-10.5, 1.2)
Month 48	75.3	86.0	-10.7 (-18.1, -3.3)
Month 60	67.9	80.0	-12.1 (-20.3, -3.9)
Patient survival			
Month 12	97.2	98.1	-0.9 (-3.8, 1.9)
Month 24	94.4	95.8	-1.4 (-5.5, 2.7)
Month 36 ^d	91.6	94.0	-2.3 (-7.2, 2.6)
Month 48	78.6	86.5	-7.9 (-15.0, -0.8)
Month 60	68.8	80.9	-12.1 (-20.2, -4.0)

a: Includes patients who prematurely discontinued treatment

b: Primary efficacy endpoint

c: Survival including loss to follow-up as an event.

d: Initial planned duration of the study.

The incidence of first biopsy-proven acute rejection was significantly lower in the Rapamune with CsA continuation group from randomisation to 12 months; however by month 60, the difference between groups was not significant.

Table 3: Incidence of Biopsy Proven Acute Rejection (%) by Treatment Group at 60 Months^{a,b}

Period	Rapamune with Ciclosporin Therapy (n = 215)	Rapamune Following Ciclosporin withdrawal (n = 215)	Difference between groups (95% CI)
Pre-randomisation ^c	9.3	10.2	-0.9 (-6.5, 4.7)
Post-randomisation through 12 months ^b	4.2	9.8	-5.6 (-10.4, -0.8)

Period	Rapamune with Ciclosporin Therapy (n = 215)	Rapamune Following Ciclosporin withdrawal (n = 215)	Difference between groups (95% CI)
Post-randomisation through 60 months	6.5	10.2	-3.7 (-8.9, 1.5)
Total at 60 months	15.8	20.5	-4.7 (-11.9, 2.6)

a: Includes patients who prematurely discontinued treatment

b: All patients received corticosteroids

c: Randomisation occurred at 3 month +/- 2 weeks

The mean GFR at 12, 24, 36, 48 and 60 months, calculated by the Nankivell equation, was significantly higher for patients in the Rapamune maintenance regimen with ciclosporin withdrawal group than for those in the Rapamune with ciclosporin therapy group ($p < 0.001$). 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 ciclosporin withdrawal than for those in the Rapamune with ciclosporin therapy group.

Table 4 summarises the mean calculated GFR for all patients who had serum creatinine measured at 12, 24, 36, 48 and 60 months.

Table 4: Calculated Glomerular Filtration Rates (mL/min +/-SEM) by Nankivell Equation: On Therapy^{a,b,c}

	Rapamune with ciclosporin therapy	Rapamune maintenance regimen with ciclosporin withdrawal	Difference between groups (ANCOVA p-value)
12 months	53.2 ± 1.5 n = 208	59.3 ± 1.5 n = 203	<0.001
24 months	48.4 ± 1.7 n = 203	58.4 ± 1.6 n = 201	<0.001
36 months	47.0 ± 1.8 n = 196	58.5 ± 1.9 n = 199	<0.001
48 months	43.5 ± 2.0 n = 185	58.1 ± 2.0 n = 187	<0.001
60 months	42.7 ± 2.2 n = 176	58.0 ± 2.1 n = 193	<0.001

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.

There was a trend to lower systolic and diastolic blood pressure in the CsA withdrawal group compared with the CsA continuation group. The difference between groups was greatest at 36 months (mean difference 8.7 mmHg systolic / 4.7 mmHg diastolic) and least at 60 months (mean difference 5.1 mmHg systolic / 0.8 mmHg diastolic).

From randomisation through month 60, the use of antihypertensive medications and the incidence of new-onset hypertension was significantly lower in the ciclosporin withdrawal group as compared with the ciclosporin continuation group.

Conversion from Calcineurin Inhibitors to Rapamune

The safety and efficacy of conversion from calcineurin inhibitors (CNI) to Rapamune were assessed in maintenance renal transplant patients. This study was a randomised, multicentre, controlled trial conducted at 111 centres 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).

This study compared renal transplant patients (6-120 months after transplantation) who were converted from calcineurin inhibitors to Rapamune over a 24-hour period, 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-randomisation. The stratum with baseline calculated GFR less than 40 mL/min was discontinued due to higher rates of safety events including acute rejection, graft loss, and death and pneumonia in the sirolimus treatment group (see Section 4.4 Special warnings and precautions for use, Conversion to Rapamune).

In the patient stratum with baseline calculated GFR greater than 40 mL/min (Rapamune conversion, n = 497; CNI continuation, n = 246), renal function, as defined by calculated GFR, was not significantly different between treatment groups. At 12 months there was no significant treatment difference in the rate of the composite primary safety endpoint (first occurrence of biopsy confirmed acute rejection, graft loss, or death); this prospectively defined primary outcome analysis was conducted on the intention to treat population of all randomised subjects in both sirolimus (n=497) and CNI (n=246) treatment groups. Likewise, there were no significant treatment differences in the rates of any of the secondary endpoints (individual components of the primary endpoint), at either 1 or 2 years.

Treatment-emergent adverse events occurred more frequently during the first 6 months after Rapamune 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, Proteinuria). New-onset nephrosis (nephrotic syndrome) was also reported.

In an open-label, randomised, comparative, multicentre 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 (BCAR) 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 randomisation, a fasting glucose ≥ 126 mg/dL or a non-fasting glucose ≥ 200 mg/dL after randomisation (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 Regimens without Ciclosporin

The safety and efficacy of Rapamune in regimens that did not contain ciclosporin have been tested in two randomised, open, parallel-group Phase II pilot studies.

In the first study cadaveric renal allograft recipients were randomised to receive Rapamune ($n=41$) or ciclosporin ($n=42$). All patients received corticosteroids and azathioprine, initially 2 mg/kg/day. Sirolimus was monitored to achieve whole blood concentrations of 30 ng/mL up to week 8 and 15 ng/mL thereafter. Ciclosporin was monitored to achieve whole blood trough levels of 200-400 ng/mL for 2 months and 100-200 ng/mL thereafter.

After 1 month the primary acute rejection rate was 28.6% (12/42) for patients receiving ciclosporin compared with 39.0% (16/41) of those receiving sirolimus. The treatment failure rate (defined as acute rejection or discontinuation of treatment for any reason) at 1 month was 38.1% (16/42) in the ciclosporin treated patients and 41.5% (17/41) in the sirolimus treated patients.

Compared to ciclosporin, sirolimus was associated with a higher incidence of arthralgia (20% versus 0%), leucopenia (39% versus 17%), thrombocytopaenia (39% versus 0%), hypercholesterolaemia (44% versus 17%), hypertriglyceridaemia (51% versus 14%), hypokalaemia (34% versus 0%), hypophosphataemia (15% versus 0%), increased lactate dehydrogenase (20% versus 2%) and increased aspartate aminotransferase (17% versus 2%). The incidence of clinically significant infections was also higher in the sirolimus group. Hypertension occurred less frequently with sirolimus (41% versus 17%) and renal function, as measured by serum creatinine and GFR, was improved (GFR: 68.56 ± 5.48 versus 56.27 ± 4.61 after 24 months).

In the second study cadaveric renal allograft recipients were randomised to receive Rapamune ($n=40$) or ciclosporin ($n=38$). All patients received corticosteroids and mycophenolate mofetil, initially 2 g/day. Mycophenolate mofetil was continued for up to 6 months and could be replaced with azathioprine. Sirolimus was monitored to achieve whole blood concentrations of 30 ng/mL up to week 8 or week 12 and 15 ng/mL thereafter. Ciclosporin was monitored to achieve whole blood trough levels of 200-400 ng/mL for 8 weeks and 100-200 ng/mL thereafter.

At 1 month, the incidence of biopsy-proven primary acute rejection was 7.9% (3/38) in the ciclosporin group and 15% (6/40) in the sirolimus group, (90% CI; -4.6% to 18.9%). Treatment failure at 1 month was 8% in the ciclosporin group and 26.3% in the sirolimus group.

Compared to ciclosporin, sirolimus was associated with a higher incidence of diarrhoea (37.5% versus 10.5%), vomiting (20.0% versus 2.6%), thrombocytopaenia (47.5% versus 7.9%), hypercholesterolaemia (65.0% versus 47.4%) and hyperlipidaemia (72.5% versus 50%). Ciclosporin was associated with increased incidence of asthenia (15.8% versus 0%), hyperuricaemia (21.1% versus 2.5%), tremor (21.1% versus 5%) and sinusitis (13.2% versus 0%). Renal function, as measured by serum creatinine and GFR, was better in sirolimus-treated patients (GFR: 69.64 ± 3.80 versus 57.25 ± 3.54 after 24 months).

The results of these two Phase II pilot studies do not support the use of sirolimus in place of ciclosporin in combination regimens in *de novo* renal transplant patients.

Rapamune Oral Solution with Ciclosporin

The safety and efficacy of Rapamune oral solution for the prevention of organ rejection following renal transplantation were assessed in two randomised, double-blind, multicentre, controlled trials. These studies compared two dose levels of Rapamune oral solution (2 mg and 5 mg, once daily) with azathioprine (2-3 mg/day) (Study 1) or placebo (Study 2) when administered in combination with ciclosporin and corticosteroids. Study 1 enrolled 719 patients who were randomised following transplantation while Study 2 consisted of 576 patients. In both studies, the primary efficacy endpoint was the rate of efficacy failure in the first 6 months after transplantation. Efficacy failure was defined as the occurrence of an acute rejection episode (confirmed by biopsy), graft loss or death.

Rapamune oral solution, at doses of 2 mg/day and 5 mg/day, significantly reduced the incidence of efficacy failure (statistically significant at the <0.025 level; nominal significance level adjusted for multiple [2] dose comparisons) at 6 months following transplantation compared to both azathioprine and placebo (Study 1: 2 mg/day 18.7% (n=284); 5 mg/day 16.8% n=274); Aza 32.3% n=161 Study 2: 2 mg/day 30.0% (n=227); 5 mg/day 25.6% n=219); Placebo 47.7% n=130).

Patient and graft survival at 1 year were co-primary endpoints. In Study 1 the graft survival was 94.7%, 92.7% and 93.8% for patients receiving Rapamune 2 mg/day, Rapamune 5 mg/day and azathioprine, respectively. In Study 2 the graft survival was 89.9%, 90.9% and 87.7% for patients receiving Rapamune 2 mg/day, Rapamune 5 mg/day and placebo, respectively.

The patient survival at 12 months in Study 1 was 97.2%, 96.0% and 98.1% for patients receiving Rapamune 2 mg/day, Rapamune 5 mg/day and Azathioprine, respectively. In Study 2 the patient survival at 12 months in Study 1 was 96.5%, 95.0% and 94.6% for patients receiving Rapamune 2 mg/day, Rapamune 5 mg/day and placebo, respectively.

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

These findings suggest that sirolimus potentiates the renal toxicity of ciclosporin. Therefore the use of sirolimus in combination with ciclosporin for periods longer than 2-4 months is not recommended.

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

Rapamune Tablets with Ciclosporin

The safety and efficacy of Rapamune oral solution and Rapamune tablets for the prevention of organ rejection following renal transplantation were compared in a randomised, controlled trial of 477 patients. This study compared a single dose level (2 mg, once daily) of Rapamune oral solution and Rapamune tablets when administered in combination with ciclosporin and corticosteroids. 238 patients received Rapamune oral solution 2 mg/day and 239 patients

received Rapamune tablets 2 mg/day. Efficacy failure was defined as the first occurrence of an acute rejection episode (confirmed by biopsy), graft loss or death. The overall rate of efficacy failure in the tablet treatment group was equivalent to the rate in the oral solution treatment group at both 3 and 6 months (3 months: solution 23.5%; tablets 24.7%; 6 months: solution 26.1%; tablets 27.2%).

Graft and patient survival at 12 months were co-primary efficacy endpoints. There was no significant difference between the oral solution and tablet formulations for both graft and patient survival. Graft survival was 92.0% and 88.7% for the oral solution and tablet treatment groups, respectively. The patient survival rates in the oral solution and tablet treatment groups were 95.8% and 96.2%, respectively.

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

5.2 Pharmacokinetic properties

Absorption

Oral Solution

Following oral administration, sirolimus is rapidly absorbed displaying linear kinetics, with a time to peak concentration of 1 hour in healthy subjects receiving single doses and 2 hours in patients with stable renal allografts receiving multiple doses. The systemic availability of sirolimus in combination with simultaneously administered ciclosporin is approximately 14%.

Oral Tablets

In healthy subjects, the mean extent of bioavailability of sirolimus after single-dose administration of the 1 mg tablet formulation is about 27% higher relative to the oral solution. The difference in bioavailability was less marked upon steady-state administration to renal transplant recipients and therapeutic equivalence has been demonstrated in a randomised study of 477 patients at the 2 mg dose level. When switching patients between oral solution and tablet formulations, it is recommended to give the same dose and to verify the sirolimus trough concentration 1 to 2 weeks later to assure that it remains within recommended target ranges.

Sirolimus concentrations, following the administration of Rapamune tablets to healthy subjects as single doses are dose proportional between 5 and 40 mg.

A single-dose, open-label, randomised, 3-period crossover study in twenty-two (22) healthy subjects was conducted to test the bioequivalence of Rapamune 1 mg, 2 mg and 5 mg tablets.

Subjects were randomly assigned to receive equimolar doses of sirolimus during each period as either ten 1 mg tablets, five 2 mg tablets, or two 5 mg triangular tablets. Each dose was administered with 120 mL of room-temperature water after an overnight fast of at least 10 hours. The intake of any food or beverage (including water) was prohibited during the first 4 hours after dose administration.

Table 5: Pharmacokinetic Parameters of Rapamune 1 mg, 2 mg and 5 mg Tablets

Treatment	Statistic	C _{max} (ng/mL)	t _{max} (h)	C _{24h} (ng/mL)	AUC (ng·h/mL)
Ten 1 mg tablets	Mean ± SD	23.6 ± 6.62	2.55 ± 1.77	6.62 ± 1.73	765 ± 191

Five 2 mg tablets	Mean ± SD	22.4 ± 7.4	2.82 ± 2.65	7.23 ± 1.96	792 ± 212
Two 5 mg tablets	Mean ± SD	20.8 ± 6.0	4.14 ± 2.82	8.19 ± 2.40	866 ± 241

Table 6: Pharmacokinetic Parameters of Rapamune 0.5 mg and 1 mg Tablets

Treatment	Statistic	C _{max} (ng/mL)	t _{max} (h)	C _{24h} (ng/mL)	AUC (ng.h/mL)
5 mg dose*					
Ten 0.5 mg tablets	Mean ± SD	11.95 ± 3.41	2.38 ± 1.56	N/A	352 ± 104
Five 1 mg tablets	Mean ± SD	10.29 ± 3.17	2.65 ± 1.83	N/A	340 ± 102

* Data presented in the above two tables are derived from separate studies and the total doses used for the pharmacokinetic assessments are different.

The data for the bioequivalence pairwise comparisons showed that the 1 mg, 2 mg and 5 mg tablets were equivalent with respect to C_{max}, AUC_t, and AUC because the 90% log-transformed confidence intervals for each parameter fell within the 80% to 125% equivalence window. The 5 mg tablet t_{max} was significantly longer than that of the 1 mg and 2 mg tablets.

The 0.5 mg tablet is not fully bioequivalent to the 1 mg tablet when comparing C_{max}. The bioequivalence between 0.5 mg tablet and the other tablet strengths has not been assessed. Therefore, multiples of the 0.5 mg tablet should not be assumed to be bioequivalent to the other tablet strengths.

When switching between tablet strengths, it is recommended to give the same dose and to verify the sirolimus trough concentration 1 to 2 weeks later to ensure that it remains within recommended target ranges.

Effect of Food

In healthy volunteers, a high fat meal altered the bioavailability characteristics of oral liquid sirolimus. There was a 34% decrease in the peak blood sirolimus concentration (C_{max}), a 3.5-fold increase in the time to peak concentration (t_{max}) and a 35% increase in total exposure (AUC).

In 24 healthy volunteers receiving Rapamune tablets with a high-fat meal, C_{max}, t_{max} and AUC showed increases of 65%, 32% and 23%, respectively. To minimise variability, Rapamune tablets should be taken consistently with or without food.

Grapefruit juice affects CYP3A4-mediated metabolism and potentially enhances P-glycoprotein (P-gp) mediated drug counter transport from enterocytes of the small intestine and must not be used for dilution or taken with Rapamune.

Distribution

Upon repeated administration, the average blood concentration of sirolimus is increased approximately 3-fold. The blood to plasma ratio (B/P) of 36 indicates that sirolimus is extensively partitioned into formed blood elements. The mean volume distribution (V_{ss}/F) of sirolimus is 12 ± 7.52 L/kg. Sirolimus is extensively bound (approximately 92%) to human plasma proteins. In man, the binding of sirolimus was shown mainly to be associated with serum albumin (97%), α1-acid glycoprotein and lipoproteins.

Metabolism

Sirolimus is a substrate for both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein. Sirolimus is extensively metabolised by o-demethylation and/or hydroxylation. Seven major metabolites, including hydroxyl, demethyl and hydroxydemethyl are identifiable in whole blood.

Sirolimus is the major component in human whole blood and contributes to greater than 90% of the immunosuppressive activity. The terminal half-life in stable renal transplant patients after multiple oral doses was 62 ± 16 hours. The effective half-life, however, is shorter and mean steady-state concentrations were achieved after 5 to 7 days.

Excretion

After a single dose of [^{14}C]-sirolimus in healthy volunteers, the majority (91.1%) of radioactivity was recovered from the faeces and only a minor amount (2.2%) was excreted in urine.

Special Populations

Elderly Patients (>65 years)

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. 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.

Children and Adolescents

Limited pharmacokinetic data are available in paediatric patients. Table 7 below summarises pharmacokinetic data obtained in paediatric dialysis patients with chronically impaired renal function.

Table 7: Sirolimus Pharmacokinetic Parameters (Mean \pm SD) in Pediatric Patients with Stable Chronic Renal Failure Maintained on Hemodialysis or Peritoneal Dialysis (1, 3, 9, 15 mg/m² Single Dose)

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

Hepatic Impairment

Rapamune (15 mg) was administered as a single oral dose by oral solution to subjects with normal hepatic function and to patients with Child-Pugh classification A (mild), or B (moderate) or C (severe) primary hepatic impairment. Compared with the values in the normal hepatic group, the hepatic impairment group had higher mean values for sirolimus AUC and t_{1/2} and had lower mean values for sirolimus CL/F. 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 clearance of sirolimus was 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 Dose and method of administration). In patients with hepatic impairment, it is recommended that sirolimus whole blood trough levels be monitored.

Renal Impairment

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

Initial Therapy (2 to 4 Months Post-Transplant)

In most patients receiving Rapamune tablets with a loading dose of 6 mg followed by an initial maintenance dose of 2 mg, whole blood sirolimus trough concentrations rapidly achieved steady-state concentrations within the recommended target range (4 to 12 ng/mL, chromatographic

assay). Sirolimus pharmacokinetic parameters following daily doses of 2 mg Rapamune tablets administered in combination with ciclosporin (CsA) microemulsion (4 hours prior to Rapamune tablets) and corticosteroids in 13 renal transplant patients, based on data collected at months 1 and 3 after transplantation, were: $C_{\min,ss}$, 7.39 ± 2.18 ng/mL; $C_{\max,ss}$, 15.0 ± 4.9 ng/mL; $t_{\max,ss}$, 3.46 ± 2.40 hours; $AUC_{\tau,ss}$, 230 ± 67 ng.h/mL; $CL/F/WT$, 139 ± 63 ml/h/kg (parameters calculated from LC-MS/MS assay results). Whole blood trough sirolimus concentrations, as measured by LC/MS/MS, were significantly correlated ($r^2 = 0.85$) with $AUC_{\tau,ss}$. Based on monitoring in all patients during the period of concomitant therapy with CsA, mean (10^{th} , 90^{th} percentiles) troughs (by immunoassay) and daily doses were 10.8 ± 3.8 ng/mL (6.3 to 15.8 ng/mL) and 2.1 ± 0.70 mg (1.5 to 2.7 mg), respectively.

Rapamune Maintenance Therapy

From month 3 to month 12, following discontinuation of CsA, mean (10^{th} , 90^{th} percentiles) troughs (by immunoassay) and daily doses were 23.3 ± 5.1 ng/mL (16.9 to 29.6 ng/mL) and 8.2 ± 4.2 mg (3.6 to 13.6 mg), respectively. Therefore, the sirolimus dose was approximately 4-fold higher to account for both the absence of the pharmacokinetic interaction with CsA (2-fold increase) and the augmented immunosuppressive requirement in the absence of CsA (2-fold increase).

5.3 Preclinical safety data

Genotoxicity

Sirolimus was not genotoxic in a series of assays for gene mutation (*in vitro* bacterial reverse mutation assay and mouse lymphoma forward mutation assay) and chromosomal damage (Chinese hamster ovary cell chromosomal aberration assay and the *in vivo* mouse micronucleus assay).

Carcinogenicity

Carcinogenicity studies were conducted in mice and rats. In an 86 week female mouse study at oral dosages of 0, 12.5, 25 and 50/6 mg/kg/day (dosage lowered from 50 to 6 mg/kg/day at week 31 due to infection secondary to immunosuppression) there was a statistically significant increase in malignant lymphomas at all dosages (approximately 16 to 26 times the clinical exposure at the maintenance dose of 5 mg/day, based on AUC) compared to controls. In a second study in male and female mice at oral dosages of up to 6 mg/kg/day there was a statistically significant increase in malignant lymphomas at 6 mg/kg/day (approximately 16 to 26 times the clinical exposure at the maintenance dose of 5 mg/day, based on AUC) compared to controls. In the 104 week rat study at dosages up to 0.2 mg/kg/day, there was a statistically significant increased incidence of testicular adenoma in the 0.1 and 0.2 mg/kg/day group (less than clinical exposure at the maintenance dose of 5 mg/kg/day, based on AUC).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Rapamune tablets:

Lactose monohydrate

Macrogol 8000

Magnesium stearate

Purified talc
Macrogol 20000
Glyceryl monooleate
Shellac
Calcium sulfate
Microcrystalline cellulose
Sucrose
Titanium dioxide
Poloxamer
Povidone
Carnauba wax
dl-alpha-tocopherol
OPACODE monogramming ink S-1-15095 RED.

Rapamune 0.5 mg, 2 mg and 5 mg tablets also contain the colouring agents iron oxide yellow, iron oxide black and iron oxide red.

Rapamune oral solution:

Polysorbate 80
Phosal 50 PG (soy phosphatidylcholine - hydrogenated, propylene glycol, mono- and di-glycerides, ethanol, and ascorbyl palmitate).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Rapamune tablets:

Store Rapamune tablets below 25°C. Protect from light.

Rapamune oral solution:

Store Rapamune oral solution at 2°C to 8°C. Refrigerate. Do not freeze. Protect from light.

Once the oral solution bottle is opened, the contents should be kept refrigerated at 2°C to 8°C and used within one month.

Rapamune oral solution may be kept at room temperature (up to 25°C) or refrigerated at 2°C to

8°C in the dosing syringe for up to 24 hours. After dilution, the preparation should be used immediately.

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

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

6.5 Nature and contents of container

Rapamune oral solution: 60 mL amber glass bottles with syringe adapter, 30 amber, plastic dosing syringes and a carrying case.

Rapamune 0.5 mg tablets: Carton of 100 tablets (10 blisters x 10 tablets each).

Rapamune 1 mg tablets: Cartons of 30 tablets (3 blisters x 10 tablets each) or of 100 tablets (10 blisters x 10 tablets each).

Rapamune 2 mg tablets: Carton of 100 tablets (10 blisters x 10 tablets each).

Rapamune 5 mg tablets: Carton of 30 tablets (3 x 10 tablets).

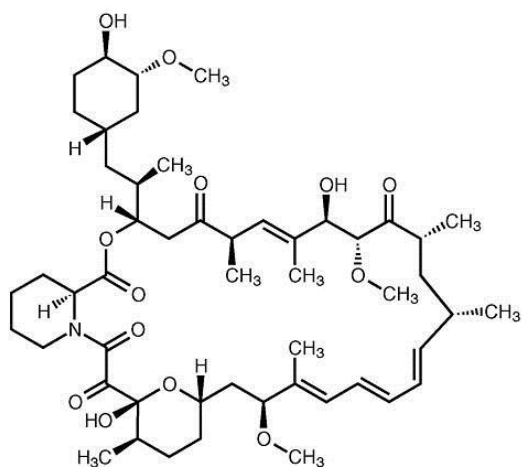
Not all presentations may be marketed.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical Structure



Molecular formula: $C_{51}H_{79}NO_{13}$

Molecular weight: 914.2

Sirolimus (also known as rapamycin) is a macrocyclic lactone produced by *Streptomyces hygroscopicus*.

CAS Number

53123-88-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
SYDNEY NSW 2000
Toll Free Number: 1800 675 229
www.pfizer.com.au

9. DATE OF FIRST APPROVAL

Rapamune oral solution: 21 May 2002

Rapamune 0.5 mg tablets: 03 February 2011

Rapamune 1 mg, 2 mg tablets: 04 July 2006

Rapamune 5 mg tablets: 24 October 2005

10. DATE OF REVISION

19 July 2019

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Summary Table of Changes

Section changed	Summary of new information
All	Reformatting according to new Australian PI template
3	Update Rapamune oral solution product description per ARTG data
4.2	Update Instructions for Dilution and Administration for Rapamune oral solution
4.2, 4.4, 4.8, 5.1	Align to AAN for Ciclosporin and some excipients

& 6.1	
6.4	Align the storage condition per ARTG data
8	Sponsor address change