

DATA SHEET

RAPAMUNE®

NAME OF MEDICINE

Rapamune (sirolimus)
Rapamune 0.5mg tablets
Rapamune 1 mg tablets
Rapamune 2 mg tablets
Rapamune 1 mg/mL oral solution

PRESENTATION

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

Rapamune 0.5mg Tablets: 0.5mg tan triangular-shaped sugar coated tablets in a carton of 100 tablets (10 blisters x 10 tablets each).

Rapamune 1-mg Tablets: 1-mg white triangular-shaped coated tablets in a carton of 100 tablets (10 blisters x 10 tablets each).

Rapamune 2-mg Tablets: 2-mg yellow triangular-shaped coated tablets in a carton of 100 tablets (10 blisters x 10 tablets each).

Do not halve tablet. Dose equivalence when the tablet is divided has not been established.

USES

Actions

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 cyclosporin, 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.

Pharmacokinetics

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 cyclosporin is approximately 14%.

Oral Tablets

In healthy subjects, the mean extent of bioavailability of sirolimus after single-dose administration of the 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.

SIROLIMUS PHARMACOKINETIC PARAMETERS OF RAPAMUNE 1-mg, 2-mg AND 5-mg TABLETS

Treatment 10 mg dose*	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

SIROLIMUS PHARMACOKINETIC PARAMETERS OF RAPAMUNE 0.5mg, AND 1mg TABLETS

Treatment 5 mg dose*	Statistic	C _{max} (ng/mL)	T _{max} (h)	C _{24h} (ng/mL)	AUC (ng.h/mL)
Ten 0.5mg tablets	Mean ± SD	11.95 ± 3.41	2.38 ± 1.56	N/A	352 ± 104
Five 1mg 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 0.5mg tablet is not fully bioequivalent to the 1 mg tablet when comparing C_{max}. The bioequivalence between 0.5mg tablet and the other tablet strengths has not been assessed. Therefore, multiples of the 0.5mg 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.

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%), α 1-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 too 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.

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:

In paediatric patients on dialysis (30% to 50% reduction in glomerular filtration rate) within age ranges of 5 to 11 years and 12 to 18 years, the mean weight-normalised CL/F was larger for younger paediatric patients (580 mL/h/kg) than for older paediatric patients (450 mL/h/kg) as compared with adults (287 mL/h/kg). There was a large variability for individuals within the age groups.

Hepatic impairment

Rapamune (15mg) 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 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 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 **DOSAGE AND ADMINISTRATION**). In patients with hepatic impairment, it is recommended that sirolimus whole blood trough levels be monitored.

Renal impairment

There is minimal (2.2%) renal excretion of the drug or its metabolites. The pharmacokinetics of sirolimus were similar in various populations with renal function ranging from normal to absent (dialysis patients).

Effect of food

In 22 healthy subjects, a high fat breakfast altered the bioavailability characteristics of sirolimus after administration by 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 total exposure (AUC) was observed. In an otherwise identical study, sirolimus 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 randomised multicenter controlled trial comparing Rapamune Oral Solution to Tablets, supports that the differences in absorption rates do not affect the efficacy of the drugs.

Rapamune should be taken consistently with or without food to minimise blood level variability. Bioequivalence testing based on AUC and C_{max} showed that sirolimus administered with orange juice is equivalent to administration with water. Therefore, orange juice and water may be used interchangeably to dilute sirolimus for oral solution. Grapefruit juice reduces CYP3A4-mediated drug metabolism and potentially enhances P-gp mediated drug counter-transport from enterocytes of the small intestine and must not be used for dilution or taken with sirolimus.

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 cyclosporin 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 cyclosporin, mean (10th, 90th 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 cyclosporin, mean (10th, 90th 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 cyclosporin (2-fold increase) and the augmented immunosuppressive requirement in the absence of cyclosporin (2-fold increase).

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.

DOSAGE AND ADMINISTRATION

Treatment should be initiated by and remain under the guidance of an appropriately qualified specialist in transplantation.

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. Do not halve tablet. Dose equivalence when the tablet is divided has not been established.

Adults – De Novo Use

It is recommended that Rapamune be used initially in a regimen with cyclosporin and corticosteroids (see **PRECAUTIONS**: De novo use without calcineurin inhibitor (CNI)). Elimination of cyclosporin 2 to 4 months after transplantation should be considered.

Rapamune with cyclosporin therapy (2 to 4 months post-transplantation)

The usual dosage regimen for Rapamune is a 6 mg oral loading dose, administered as soon as possible after transplantation, followed by 2 mg once daily. The Rapamune dose should then be individualised, to obtain whole blood trough levels of 4 to 12 ng/mL (chromatographic assay; see *Therapeutic Drug Monitoring*).

Two mg of Rapamune oral solution has been demonstrated to be clinically equivalent to 2 mg of 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. It is recommended that sirolimus be taken 4 hours after administration of cyclosporin oral solution and/or cyclosporin capsules (see *Interactions with Other Drugs*). Rapamune should be taken consistently either with or without food. It should not be taken with grapefruit juice.

Rapamune maintenance regimen with cyclosporin withdrawal

After 2 to 4 months, cyclosporin should be progressively discontinued over a period of 4 to 8 weeks and the Rapamune dose should be adjusted to obtain whole blood trough levels of 12 to 20 ng/mL (LC/MS/MS; see *Therapeutic Drug Monitoring*). Sirolimus has a long half-life and patients should be retained on their daily maintenance dose for at least 3 days (with a loading dose) or 7-14 days (without a loading dose) before assuming that blood samples drawn at 20-24 hours after dose administration reflect a steady-state level. Dose adjustments based on non-steady-state concentrations may lead to over-dosing. A loading dose should be added to the new maintenance dose when it is necessary to considerably increase sirolimus trough levels: sirolimus loading dose = 3 x [new maintenance dose – current maintenance dose]. Dose adjustments can be based on simple proportion: new sirolimus dose = current dose x (new concentration/current concentration). The maximum sirolimus dose administered on any day should not exceed 40 mg. If the estimated dose exceeds 40 mg, then the loading dose should be administered over 2 days. Any significant increase or decrease in sirolimus levels after reaching steady state should be verified by a check on compliance and the use of more than a single trough blood sample.

Use in Children and Adolescents

There is insufficient experience to recommend the use of sirolimus 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 sirolimus be reduced by approximately one third to one half. It is not necessary to modify the Rapamune loading dose (see **Pharmacokinetics**). 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 cyclosporin 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: (see **Assay**

Methodology below)

1. in patients receiving concentration-controlled Rapamune
2. in patients with hepatic impairment;
3. 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
4. if cyclosporin dosing is markedly reduced or discontinued,
5. as these populations are most likely to have special dosing requirements.
6. 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.

To minimise variability, Rapamune should be taken at the same time in relation to cyclosporin, 4 hours after the cyclosporin dose and consistently either with or without food (see **Pharmacokinetics**). Optimally, adjustments in Rapamune dosage should be based on more than a single trough level obtained >5 days after a previous dosing change. Patients can be switched from the oral solution to the tablet formulation on a mg per mg basis; however, it is recommended that a trough concentration be taken 1 or 2 weeks after switching formulations to confirm that the trough concentration is within the recommended target range.

Following the discontinuation of cyclosporin therapy, a target trough range of 12 to 20 ng/ml (chromatographic assay) is recommended. Cyclosporin inhibits the metabolism of sirolimus, and consequently, sirolimus levels will decrease when cyclosporin is discontinued unless the sirolimus dose is increased. On average, the sirolimus dose will need to be 4-fold higher to account for both the absence of the pharmacokinetic interaction (2-fold increase) and the augmented immunosuppressive requirement in the absence of cyclosporin (2-fold increase). The rate at which the dose of sirolimus is increased should correspond to the rate of cyclosporin elimination.

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.

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 container with at least 60 mL of water or orange juice. Do not empty the Rapamune oral solution into a plastic, paper or polystyrene cup. (see **WARNINGS and PRECAUTIONS: Interaction with PVC**) 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 glass 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 **Pharmacokinetics**). Discard the syringe after one use.

Monitoring Advice

Monitoring of triglycerides should be included as part of routine post-transplant patient management (see **PRECAUTIONS**).

Influence of Foods, Compatibility with Drugs/Fluids

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

Food increases the bioavailability of sirolimus (see **Pharmacokinetics**). To minimise variability, Rapamune oral solution and Rapamune tablets should be taken consistently with or without food.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

General

Rapamune has been administered concurrently with the following agents in clinical studies: cyclosporin, azathioprine, mycophenolate mofetil, corticosteroids and cytotoxic antibodies. The efficacy and safety of Rapamune in combination with other immunosuppressive agents has not been extensively investigated.

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 **ADVERSE REACTIONS**). 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.

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.

Infection

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

Hypersensitivity Reactions

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

Hyperlipidaemia

The use of Rapamune in renal transplant patients was associated with increased serum cholesterol and triglycerides 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.

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 clinical trials, the concomitant administration of sirolimus and HMG-CoA reductase inhibitors and/or fibrates was well tolerated. During sirolimus therapy with or without cyclosporin, patients should be monitored for elevated lipids and patients administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the development of rhabdomyolysis and other adverse effects as described in the respective prescribing information for these agents

Renal Function

Renal function should be monitored during concomitant administration of Rapamune and cyclosporin. 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 the recovery of renal function.

Patients treated with cyclosporin and Rapamune beyond 3 months had higher serum creatinine levels and lower calculated glomerular filtration rates compared to patients treated with cyclosporin and placebo or azathioprine controls. Patients who were successfully withdrawn from cyclosporin had lower serum creatinine levels and higher calculated glomerular filtration rates compared to patients remaining on cyclosporin. Therefore, the long-term combination of cyclosporin with sirolimus is not recommended.

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 **ADVERSE EFFECTS** and **CLINICAL TRIALS**). 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 **CLINICAL TRIALS**), 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-centre 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 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 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.

Concomitant use of angiotensin-converting enzyme (ACE) inhibitors

In rare cases, the concomitant administration of sirolimus and ACE inhibitors has resulted in angioneurotic oedema-type reactions.

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 **ADVERSE REACTIONS, *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 **ADVERSE REACTIONS, *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 **INTERACTIONS**).

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

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 cyclosporin 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.

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 High Risk Patients

The safety and efficacy of sirolimus in combination with cyclosporin, with subsequent cyclosporin 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 cyclosporin 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 **INDICATIONS** and **CLINICAL TRIALS**).

Carcinogenicity and Mutagenicity

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 studies were conducted in mice and rats. In an 86 week female mouse study at oral dosages of 0, 12.5, 25 and 50/6mg/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 5mg/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 6mg/kg/day (approximately 16 to 26 times the clinical exposure at the maintenance dose of 5mg/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 0.2mg/kg/day group (less than clinical exposure at the maintenance dose of 5 mg/kg/day, based on AUC).

Impairment of 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 5mg/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 (eg. 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

Pregnancy Category C. Sirolimus may cause immunosuppression in the infant. Sirolimus was embryo/foetal 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 5mg/day, based on AUC).

Embryo/foetal toxicity was manifested as mortality and reduced foetal weights (with associated delays in skeletal ossification). However, no teratogenesis was evident. In combination with cyclosporin, rats had increased embryo/foetal 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 5mg/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 foetus. 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 **INTERACTIONS**).

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

Use in Children

The safety and efficacy of Rapamune in paediatric patients below the age of 13 years have not been established. Limited pharmacokinetic information is available in children (see **Pharmacokinetics**).

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.

Interaction 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 **DOSAGE AND ADMINISTRATION** be followed closely.

Effects on Ability to Drive and Use Machines

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

ADVERSE EFFECTS

The list below contains adverse reactions seen in clinical trials and post-marketing reports. 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 cyclosporin and corticosteroids; thus the frequency of adverse reactions listed includes Rapamune administration combined with cyclosporin 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, multicenter 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 cyclosporin 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 cyclosporin. These patients were randomised to continue cyclosporin therapy or to have cyclosporin 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 according to the following categories:

Very common: $\geq 10\%$
Common: $\geq 1\%$ and $< 10\%$
Uncommon: $\geq 0.1\%$ and $< 1\%$
Rare: $< 0.1\%$

Body as a whole:

Very common Lymphocele; peripheral oedema; fever ; headache; pain
Common Abnormal wound healing; oedema; fungal; viral and bacterial infections (such as Mycobacterial infections including tuberculosis; Epstein-Barr virus; CMV and Herpes zoster); Herpes simplex; sepsis

Cardiac disorders:

Very Common Hypertension
Common: Tachycardia; venous thromboembolism (including pulmonary embolism; deep vein thrombosis)
Uncommon: Pericardial effusion (including haemodynamically significant effusions in children and adults)

Gastrointestinal disorders:

Very common: Abdominal pain; diarrhoea; constipation; nausea
Common: Stomatitis; ascites
Uncommon: Pancreatitis

Blood and the lymphatic system disorders:

Very common: Particularly at higher doses: anaemia; thrombocytopenia;
Common: Leucopenia; neutropenia; thrombotic thrombocytopenic purpura/haemolytic uraemia syndrome
Uncommon: Lymphoma / post transplant lymphoproliferative disorder; pancytopenia

Immune system

Rare: Hypersensitivity reactions; including anaphylactic/anaphylactoid reactions; angioedema and hypersensitivity vasculitis

Metabolism and nutrition disorders:

Very common: Hypertriglyceridaemia (hyperlipidaemia); hypercholesterolaemia; hypophosphataemia; hyperglycaemia; hypokalaemia; increased lactate dehydrogenase (LDH); increased creatinine
Common: Liver function tests abnormal; increased SGOT; increased SGPT; fluid accumulation

Musculoskeletal, connective tissue and bone disorders:

Very common: Arthralgia
Common: Bone necrosis

Respiratory, thoracic and mediastinal disorders:

Common: Epistaxis; pleural effusion; pneumonia; pneumonitis
Uncommon: Pulmonary haemorrhage

Rare Alveolar proteinosis

Skin and subcutaneous tissue disorders:

Very common: Acne

Common: Rash; squamous cell carcinoma; basal cell carcinoma

Uncommon: Melanoma

Rare: Exfoliative dermatitis (see Warnings and Precautions)

Renal and urinary disorders:

Very common: Urinary tract infection

Common: Pyelonephritis; proteinuria

Uncommon Nephrotic syndrome.

Adverse reactions in which frequency is unknown: Focal segmental glomerulosclerosis.

Other clinical experience

Rapamune following cyclosporin withdrawal: The incidence of adverse reactions was determined through 60 months in a randomised, multicenter controlled trial in which 215 renal transplant patients received Rapamune as a maintenance regimen following Cyclosporin withdrawal, and 215 patients received Rapamune with Cyclosporin therapy. All patients were treated with corticosteroids. The safety profile prior to randomisation (start of Cyclosporin withdrawal) was similar to that of the 2-mg Rapamune groups in studies of Rapamune in combination with Cyclosporin. Following randomisation (at 3 months), patients who had Cyclosporin 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, Cyclosporin toxicity, increased creatinine, abnormal kidney function, toxic nephropathy, oedema, hyperuricemia, gout, and gum hyperplasia was significantly higher in patients who remained on Cyclosporin than those who had Cyclosporin withdrawn from therapy. Mean systolic and diastolic blood pressure improved significantly following Cyclosporin withdrawal.

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

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

INCIDENCE (%) OF MALIGNANCIES AT 60 MONTHS POST-TRANSPLANT^A

	Nonrandomised ^b (n = 95)	Rapamune with Cyclosporin Therapy ^c (n = 215)	Rapamune Following Cyclosporin Withdrawal ^c (n = 215)
Malignancy			
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, Cyclosporin 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 Cyclosporin as compared with the cohort who had Cyclosporin withdrawn (8.4% vs. 3.8%, respectively). For skin cancer, the median time to first occurrence was significantly delayed (491 vs 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 Cyclosporin withdrawal group as compared with the group that continued Cyclosporin.

The concomitant use of sirolimus with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced HUS/TTP/TMA (see **PRECAUTIONS**).

Immunosuppression increases the susceptibility to the development of lymphoma and other malignancies, particularly of the skin.

In patients with delayed graft function, Rapamune may delay recovery of renal function (see **PRECAUTIONS: Renal Function**).

Azoospermia has been reported with the use of Rapamune and has been reversible upon discontinuation of Rapamune in most cases.

Clostridium difficile enterocolitis has been reported in patients receiving Rapamune.

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.

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 **WARNINGS AND PRECAUTIONS, 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).

INTERACTIONS

Interactions with Other Drugs

Inhibitors and Inducers of Cytochrome P450 3A4 (CYP3A4)

Co-administration of sirolimus 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 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 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, cyclosporin, danazol, HIV-protease inhibitors (eg, ritonavir, indinavir)
- 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 **DOSAGE AND ADMINISTRATION**).

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

Cyclosporin (CYP3A4 substrate): Cyclosporin is a substrate and inhibitor of CYP3A4 and P-gp. Patients administered Rapamune with cyclosporin should be monitored for the development of rhabdomyolysis (see **PRECAUTIONS**). The rate and extent of sirolimus absorption is significantly affected by cyclosporin. In healthy volunteers, simultaneous administration of sirolimus oral solution and cyclosporin microemulsion resulted in increases in sirolimus C_{max} and AUC of 116% and 230%, respectively compared to sirolimus alone. When sirolimus was given 4 hours after cyclosporin, sirolimus C_{max} and AUC were increased by 40% and 80%, respectively. It is therefore recommended that sirolimus be administered 4 hours after cyclosporin 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 cyclosporin administration, sirolimus C_{max} and AUC were both increased by only 33% compared with administration of sirolimus alone.

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

Rifampicin (CYP3A4 inducer): Rifampicin is a strong inducer of CYP3A4. Co-administration of sirolimus 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 sirolimus and ketoconazole is not recommended. 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. 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. If diltiazem is co-administered, sirolimus blood levels should be monitored and a dose adjustment may be necessary.

Verapamil (CYP3A4 inhibitor): Sirolimus levels should be monitored and appropriate dose reductions of both medications should be considered. Multiple-dose administration of verapamil and sirolimus oral solution significantly affected the rate and extent of absorption of both drugs. 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 sirolimus oral solution significantly increased the rate and extent of absorption of both drugs. 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 sirolimus 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.

Other

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

Other possible interactions: Inhibitors of CYP3A4 may decrease the metabolism of sirolimus and increase sirolimus blood levels. 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. Inhibitors of P-gp may decrease the efflux of sirolimus from intestinal cells and increase sirolimus levels.

Laboratory Tests

Whole blood sirolimus levels should be monitored in all patients.

OVERDOSAGE

At present, there is limited experience with overdose. In general, the adverse effects of overdose are consistent with those listed in the Adverse Reactions section. One patient experienced an episode of atrial fibrillation after ingestion of 150 mg of Rapamune. 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.

PHARMACEUTICAL PRECAUTIONS

Store Rapamune oral solution at 2°C to 8°C (Refrigerate. Do not freeze). Store Rapamune tablets below 25°C. 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 (see **WARNINGS and PRECAUTIONS: Interaction with PVC**). 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 occur, wash thoroughly with soap and water; rinse eyes with plain water.

MEDICINE CLASSIFICATION

Prescription Only Medicine

PACKAGE QUANTITIES

Rapamune Oral Solution comes in a 60 mL amber glass bottle with syringe adapter and 30 amber, plastic dosing syringes and a carrying case.

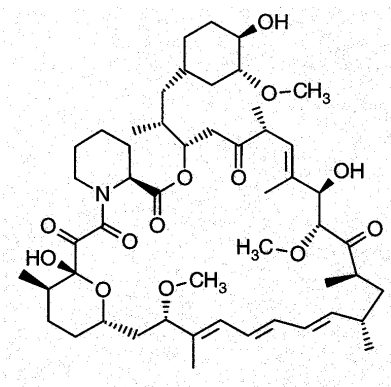
Rapamune 0.5mg tablets come in a blister pack of 10 tablets x 10 blisters per carton.

Rapamune 1mg tablets come in a blister pack of 10 tablets x 10 blisters per carton.

Rapamune 2mg tablets come in a blister pack of 10 tablets x 10 blisters per carton.

FURTHER INFORMATION

Sirolimus (also known as rapamycin) is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. Its molecular formula is C₅₁H₇₉NO₁₃ and its molecular weight is 914.2. The structural formula of sirolimus is:



C.A.S. 53123-88-9

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

Rapamune tablets contain the active ingredient sirolimus as well as the following excipients: lactose, macrogol 8000, magnesium stearate, talc, macrogol 20000, glyceryl mono-oleate, Shellac, calcium sulfate anhydrous, cellulose-microcrystalline, sucrose, titanium dioxide, poloxamer 188, povidone, carnauba wax, DL alpha tocopheryl acetate and Opacode Red S-1-15095 ink.

Rapamune 0.5 mg and Rapamune 2 mg tablets also contain the colouring agents iron oxide yellow CI 77492, iron oxide black CI77499 and iron oxide red CI 77491.

Rapamune oral solution contains the active ingredient, sirolimus, as well as the following excipients; Polysorbate 80, Phosal 50 PG (phosphatidylcholine, propylene glycol, mono- and di-glycerides, ethanol, ascorbyl palmitate and soya fatty acids).

Clinical Trials

Rapamune maintenance regimen with cyclosporin withdrawal

The safety and efficacy of Rapamune in a regimen in which cyclosporin was withdrawn after 3 to 4 months following renal transplantation were assessed in a randomised multicenter controlled trial. This study compared patients who were administered Rapamune, cyclosporin 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 cyclosporin. During cyclosporin 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 cyclosporin 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 cyclosporin or Rapamune maintenance regimen with cyclosporin 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 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 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 Cyclosporin withdrawal group.

Graft and Patient Survival (%): After Cyclosporin Withdrawal^a

Parameter	Rapamune with cyclosporin therapy (n = 215)	Rapamune maintenance regimen with cyclosporin 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 ^b	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 Cyclosporin continuation group from randomisation to 12 months; however by month 60, the difference between groups was not significant.

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

Period	Rapamune with Cyclosporin Therapy (n = 215)	Rapamune Following Cyclosporin 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)
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 cyclosporin withdrawal group than for those in the Rapamune with cyclosporin 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 cyclosporine withdrawal than for those in the Rapamune with cyclosporine therapy group.

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

CALCULATED GLOMERULAR FILTRATION RATES (mL/min +/-SEM) BY NANKIVELL EQUATION: ON THERAPY^{a,b,c}

	Rapamune with cyclosporin therapy	Rapamune maintenance regimen with cyclosporin 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 Cyclosporin withdrawal group compared with the cyclosporin 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 cyclosporine withdrawal group as compared with the cyclosporine continuation 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 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 vs. greater than 40 mL/min). 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 postrandomisation. Secondary endpoints included biopsy-confirmed acute rejection, graft loss, and death. Enrolment in the patient stratum with baseline calculated GFR less than 40 mL/min was discontinued due to an imbalance in safety events (see sections 6 and 15). 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. 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 6]. New-onset nephrosis (nephrotic syndrome) was also reported (see **ADVERSE EVENTS**).

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 the study 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.

Rapamune regimens without cyclosporin

The safety and efficacy of Rapamune in regimens that did not contain cyclosporin 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 cyclosporin ($n=42$). 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. Cyclosporin 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 cyclosporin 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 cyclosporin treated patients and 41.5% (17/41) in the sirolimus treated patients.

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

In the second study cadaveric renal allograft recipients were randomised to receive Rapamune ($n=40$) or cyclosporin ($n=38$). All patients received corticosteroids and mycophenolate mofetil, initially 2g/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. Cyclosporin 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 cyclosporin 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 cyclosporin group and 26.3% in the sirolimus group.

Compared to cyclosporin, sirolimus was associated with a higher incidence of diarrhoea (37.5% vs. 10.5%), vomiting (20.0% vs. 2.6%), thrombocytopenia (47.5% vs. 7.9%), hypercholesterolaemia (65.0% vs. 47.4%) and hyperlipidaemia (72.5% vs. 50%). Cyclosporin was associated with increased incidence of asthenia (15.8% vs. 0%), hyperuricaemia (21.1% vs. 2.5%), tremor (21.1% vs. 5%) and sinusitis (13.2% vs. 0%). Renal function, as measured by serum creatinine and GFR, was better in sirolimus-treated patients (GFR: 69.64 ± 3.80 vs. 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 cyclosporin in combination regimens in *de novo* renal transplant patients.

Rapamune oral solution with cyclosporin

The safety and efficacy of Rapamune oral solution for the prevention of organ rejection following renal transplantation were assessed in two randomised, double-blind, multicenter, controlled trials. These studies compared two dose levels of Rapamune oral solution (2 mg and 5 mg, once daily) with azathioprine (Study 1) or placebo (Study 2) when administered in combination with cyclosporin 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; 2mg/day 18.7% (n=284); 5mg/day 16.8% n=274); Aza 32.3% n=161 Study 2: 2mg/day 30.0% (n=227); 5mg/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 and survival was 94.7%, 92.7% and 93.8% for patients receiving Rapamune 2mg/day, Rapamune 5mg/day and Azathioprine, respectively. In Study 2 the graft survival was 89.9%, 90.9% and 87.7% for patients receiving Rapamune 2mg/day, Rapamune 5mg/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 2mg/day, Rapamune 5mg/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 2mg/day, Rapamune 5mg/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 cyclosporin and Rapamune oral solution compared with those treated with cyclosporin and the respective azathioprine or placebo control.

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

Rapamune tablets with cyclosporin

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 (Study 3). This study compared a single dose level (2 mg, once daily) of Rapamune oral solution and Rapamune tablets when administered in combination with cyclosporin 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.

NAME AND ADDRESS

Pfizer New Zealand Ltd
P O Box 3998
Auckland, New Zealand, 1140.

Toll Free Number: 0800 736 363

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