SIROLIMUS
RAPAMUNE®
500 mcg and 1 mg Sugar-coated Tablet

1.0 PHARMACOLOGIC CATEGORY

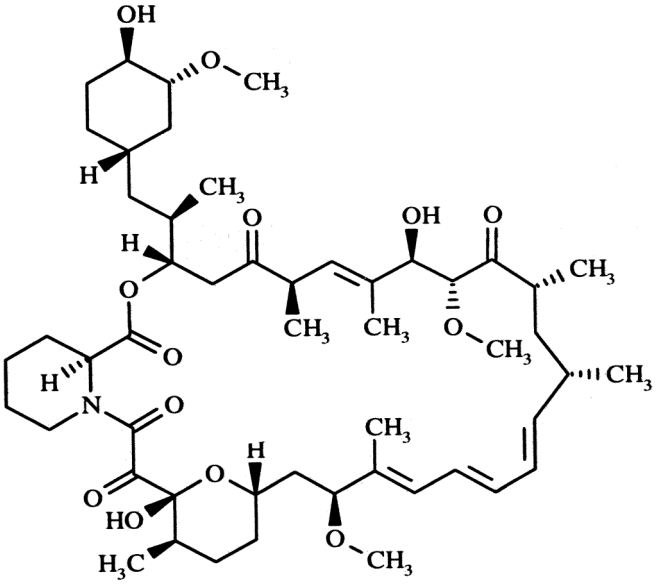
Immunosuppressant

WARNING:
Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experience in immunosuppressive therapy and management of renal transplant patients should use Sirolimus (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.

2.0 DESCRIPTION

Sirolimus (Rapamune) is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. The chemical name of Sirolimus (also known as rapamycin) is (3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[(1R)-2-[(1S,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4] oxaazacyclohentriacontine-1,5,11,28,29 (4H,6H,31H)-pentone.

The structural formula of Sirolimus is shown below.



Sirolimus is a white to off-white powder. It is insoluble in water but freely soluble in benzyl alcohol, chloroform, acetone, and acetonitrile. It has a molecular formula of $C_{51}H_{79}NO_{13}$ and molecular weight of 914.2.

Sirolimus (Rapamune) 0.5 mg Sugar-Coated Tablets is a Tan, triangular-shaped sugar-coated tablet, branded "RAPAMUNE 0.5 mg" in red ink.

Sirolimus (Rapamune) 1 mg Sugar-Coated Tablets is a White, triangular shaped sugar-coated tablet, branded "RAPAMUNE 1 mg" in red ink.

3.0 FORMULATION/COMPOSITION

Sirolimus (Rapamune) 500 mcg sugar-coated tablet: Each sugar-coated tablet contains 500 mcg of sirolimus.

Sirolimus (Rapamune) 1 mg sugar-coated tablet: Each sugar-coated tablet contains 1 mg of sirolimus.

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

In Patients at Low to Moderate Immunological Risk

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

CsA should be withdrawn 2 to 4 months after transplantation, and the Sirolimus (Rapamune) dose should be increased to reach recommended blood concentrations (see Section **4.2 Dosage and Method of Administration**). Cyclosporine withdrawal has not been studied in 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, or patients with high-panel reactive antibodies (see Section **5.1 Pharmacodynamic Properties**).

In Patients at High Immunologic Risk

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

4.2 Dosage and Method of Administration

4.2.1 Dosage

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

Two milligrams (2 mg) of Sirolimus (Rapamune) Oral Solution have been demonstrated to be clinically equivalent to 2 mg Sirolimus (Rapamune) Oral Tablets; hence, are interchangeable on a mg-to-mg basis. However, it is not known if higher doses of Sirolimus (Rapamune) Oral Solution are clinically equivalent to higher doses of Sirolimus (Rapamune) Tablets on a mg-to-mg basis.

Therapeutic drug monitoring is recommended for all patients receiving Sirolimus (Rapamune) (see details on drug monitoring in different patient populations below and Section **4.2 Dosage and Method of Administration** - Sirolimus whole blood trough level monitoring).

Prophylaxis of Organ Rejection in Renal Transplantation

Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Sirolimus (Rapamune). Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

Patients at Low to Moderate Immunologic Risk

Sirolimus (Rapamune) and CsA Combination Therapy:

For *de novo* transplant recipients, a loading dose of Sirolimus (Rapamune) corresponding to 3 times the maintenance dose should be given. A daily maintenance dose of 2 mg is recommended for use in renal transplant patients, with a loading dose of 6 mg. Although a daily maintenance dose of 5 mg, with a loading dose of 15 mg, was used in clinical trials of the oral solution and was shown to be safe and effective, no efficacy advantage over the 2 mg dose could be established for renal transplant patients. Patients receiving 2 mg of Sirolimus (Rapamune) oral solution per day demonstrated an overall better safety profile than did patients receiving 5 mg of Sirolimus (Rapamune) oral solution per day.

It is recommended that Sirolimus (Rapamune) oral solution and tablets be used initially in a regimen with CsA and corticosteroids. CsA should be withdrawn 2 to 4 months after renal transplantation in patients at low to moderate immunologic risk, and the Sirolimus (Rapamune) dose should be increased to reach recommended blood concentrations. Cyclosporine withdrawal has not been studied in patients with Banff 93 grade III acute rejection or vascular rejection prior to cyclosporine withdrawal, those who are dialysis-dependent, or with serum creatinine $>$4.5 mg/dL, Black patients, re-transplants, multi-organ transplants, or patients with high-panel reactive antibodies (see Section **4.1 Therapeutic Indications** and Section **5.1 Pharmacodynamic Properties**).

Sirolimus (Rapamune) following CsA withdrawal (Referred to as Sirolimus (Rapamune) Maintenance Regimen, RMR):

Initially, patients should be receiving Sirolimus (Rapamune) and CsA combination therapy. At 2 to 4 months following transplantation, CsA should be progressively discontinued over 4 to 8 weeks and the Sirolimus (Rapamune) dose should be adjusted to obtain whole blood trough concentrations within the range of 16 to 24 ng/mL (chromatographic method) for the first year following transplantation. Thereafter, the target sirolimus concentrations should be 12 to 20 ng/mL (chromatographic method). The actual observations at year 1 and 5 (see below) were close to these ranges (see Section **4.2 Dosage and Method of Administration** – Sirolimus whole blood trough level monitoring). Therapeutic drug monitoring should not be the sole basis for adjusting Sirolimus (Rapamune) therapy. Careful attention should be made to clinical signs/symptoms, tissue biopsy, and laboratory parameters. CsA inhibits the metabolism and transport of sirolimus, and consequently, sirolimus concentrations will decrease when CsA is discontinued unless the Sirolimus (Rapamune) dose is increased. The Sirolimus (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).

Patients at High Immunologic Risk

Sirolimus (Rapamune) Combination Therapy:

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

For patients receiving Sirolimus (Rapamune) with tacrolimus, Sirolimus (Rapamune) therapy should be initiated with a loading dose of up to 10 mg on days 1 and 2 post-transplantation. Beginning on day 3, an initial maintenance dose of 5 mg/day should be given. A trough level should be obtained between days 5 and 7, and the daily dose of Sirolimus (Rapamune) should thereafter be adjusted to achieve whole blood trough sirolimus concentrations of 10-15 ng/mL.

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

The starting dose of tacrolimus should be up to 0.2 mg/kg/day administered in divided doses, and the dose should be adjusted to achieve whole blood trough concentrations of 10-15 ng/mL for 14 days, 5-10 ng/mL from day 15 to the end of week 26, and 3-5 ng/mL from week 27 to the end of week 52. Prednisone should be administered at a minimum of 5 mg/day.

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

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

Sirolimus (Rapamune) use in all Renal Allograft Recipients:

The initial dose of Sirolimus (Rapamune) should be administered as soon as possible after transplantation. Frequent Sirolimus (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 Sirolimus (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 Sirolimus (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: Sirolimus (Rapamune) loading dose = 3 x (new maintenance dose - current maintenance dose). The maximum Sirolimus (Rapamune) dose administered on any day should not exceed 40 mg. If an estimated daily dose exceeds 40 mg due to the addition of

a loading dose, the loading dose should be administered over 2 days. Sirolimus trough concentrations should be monitored at least 3 to 4 days after a loading dose(s).

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

It is recommended that Sirolimus (Rapamune) be taken 4 hours after cyclosporine microemulsion [(cyclosporine, USP) MODIFIED]* administration (see Section **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

Use in Children

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

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

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

The safety and efficacy of Sirolimus (Rapamune) oral solution and Sirolimus (Rapamune) tablets have been studied in children aged 13 or older judged to be at low to moderate immunologic risk. Use of Sirolimus (Rapamune) oral solution and Sirolimus (Rapamune) tablets in this subpopulation of children aged 13 or older is supported by evidence from adequate and well-controlled trials of Sirolimus (Rapamune) oral solution in adults with additional pharmacokinetic data in pediatric renal transplantation recipients (see Section **5.2 Pharmacokinetic Properties**).

Use in Elderly Patients

No dose adjustment is required in elderly patients.

Clinical studies of Sirolimus (Rapamune) did not include sufficient numbers of patients aged 65 and over to determine whether safety and efficacy differ in this population from younger patients. Sirolimus trough concentration data in 35 renal transplant patients >65 years of age were similar to those in the adult population (n=822) from 18 to 65 years of age.

Patients with Hepatic Impairment

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

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

Patients with Renal Impairment

Based on clinical pharmacokinetic data, the Sirolimus (Rapamune) dosage need not be adjusted because of impaired renal function.

4.2.2 Sirolimus Whole Blood trough Level Monitoring

Blood sirolimus trough levels should be monitored: (see Section **4.2 Dosage and Method of Administration** - Assay Methodology section below)

- in patients receiving concentration-controlled Sirolimus (Rapamune)
- in pediatric patients
- in patients with hepatic impairment
- during concurrent administration of inhibitors and inducers of CYP3A4 and P-glycoprotein (P-gp)
- if the CsA dose is markedly reduced, or if CsA is discontinued

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

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

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

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

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

Assay Methodology

The recommended 24-hour trough concentration ranges for sirolimus are based on chromatographic methods. Several assay methodologies have been used to measure the whole blood concentrations of sirolimus. Currently in clinical practice, sirolimus whole blood concentrations are being measured by both chromatographic and immunoassay methodologies. The concentration values obtained by these different methodologies are not interchangeable. Adjustments to the targeted range should be made according to the assay being utilized to determine the sirolimus trough concentration. Since results are assay and laboratory dependent, and the results may change over time, adjustment to the targeted therapeutic range must be made with a detailed knowledge of the site-specific assay used. A discussion of different assay methods is contained in Clinical Therapeutics 2000; 22 Suppl B: B1-B132.

Mode of Administration

Sirolimus (Rapamune) is intended for oral administration only.

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

4.3 Contraindications

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

4.4 Special Warnings and Precautions for Use

Immunosuppression increases the susceptibility to infection and the development of lymphoma and other malignancies, particularly of the skin (see Section **4.4 Special Warnings and Precautions for Use** and Section **4.8 Undesirable Effects**). Oversuppression of the immune system can also increase susceptibility to opportunistic infections, sepsis, and fatal infections.

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

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

Liver Transplantation – Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis (HAT):
The use of Sirolimus (Rapamune) in combination with tacrolimus was associated with excess mortality and graft loss in a study in *de novo* liver transplant recipients. Many of these patients had evidence of infection at or near the time of death. In this and another study in *de novo* liver transplant recipients, the use of Sirolimus (Rapamune) 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 randomized to conversion to a sirolimus-based regimen versus continuation of a CNI-based regimen 6-144 months post-liver transplantation demonstrated an increased number of deaths in the sirolimus conversion group compared to the CNI continuation group, although the difference was not statistically significant (see Section **5.1 Pharmacodynamic Properties**).

Lung Transplantation – Bronchial Anastomotic Dehiscence:

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

Drug-Drug Interactions

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

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

Wound Healing and Fluid Accumulation

There have been reports of impaired or delayed wound healing in patients receiving Sirolimus (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 Sirolimus (Rapamune). Appropriate measures should be considered to minimize such complications. Patients with a BMI greater than 30 kg/m^2 may be at increased risk of abnormal wound healing based on data from the medical literature (see Section **4.8 Undesirable Effects**).

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

Skin Malignancies

Immunosuppression increases the susceptibility to the development of lymphoma and other malignancies, particularly of the skin. Therefore, patients taking Sirolimus (Rapamune) should limit exposure to sunlight and UV light by wearing protective clothing and using a sunscreen with a high protective factor (see Section **4.4 Special Warnings and Precautions for Use** and Section **4.8 Undesirable Effects**).

Hyperlipidemia

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

Rhabdomyolysis

In clinical trials, the concomitant administration of Sirolimus (Rapamune) and HMG-CoA reductase inhibitors and/or fibrates was well tolerated. During Sirolimus (Rapamune) therapy with or without CsA, patients should be monitored for elevated lipids, and patients administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects as described in the respective labeling for these agents.

Renal Function

Patients treated with CsA and Sirolimus (Rapamune) had higher serum creatinine levels and lower 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 Sirolimus (Rapamune) and CsA compared with control therapies (see Section **5.1 Pharmacodynamic Properties**). Therefore, renal function should be monitored during the co-administration of Sirolimus (Rapamune) with cyclosporine. Renal function should also be closely monitored during the co-administration of Sirolimus (Rapamune) with tacrolimus. Appropriate adjustments of the immunosuppressive regimen, including discontinuation of Sirolimus (Rapamune) and/or cyclosporine and/or tacrolimus, should be considered in patients with elevated serum creatinine levels.

Sirolimus (Rapamune) following Cyclosporine Withdrawal

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

In patients at low to moderate immunologic risk, continuation of combination therapy with CsA beyond 4 months following transplantation should only be considered when the benefits outweigh the risks of this combination for individual patients (see Section **4.4 Special Warnings and Precautions for Use**).

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

Proteinuria

Periodic quantitative monitoring of urinary protein excretion is recommended. In a study evaluating conversion from calcineurin inhibitors (CNI) to Sirolimus (Rapamune) in maintenance renal transplant patients 6 – 120 months post-transplant, increased urinary protein excretion was commonly observed from the 6 through 24 month after conversion to Sirolimus (Rapamune) compared with CNI continuation (23.6% versus 12.8%, respectively) (see Section **4.8 Undesirable Effects** and Section **5.1 Pharmacodynamic Properties**). Those patients in the highest quartile of urinary protein excretion prior to Sirolimus (Rapamune) conversion (urinary protein to creatinine ratio $\geq$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 Sirolimus (Rapamune). The safety and efficacy of conversion from calcineurin inhibitors to sirolimus in maintenance renal transplant patients have not been established.

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

In a study evaluating conversion from calcineurin inhibitors (CNI) to Sirolimus (Rapamune) in maintenance renal transplant patients 6-120 months post-transplant (see Section **5.1 Pharmacodynamic Properties**), in a stratum of the Sirolimus (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 Sirolimus (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 Sirolimus (Rapamune) without a calcineurin inhibitor (CNI) is not established in renal transplant patients. In two multi-center clinical studies, *de novo* renal transplant patients treated with Sirolimus (Rapamune), MMF, steroids, and an IL-2 receptor antagonist had significantly higher acute rejection rates and numerically higher death rates compared to patients treated with a calcineurin inhibitor, MMF, steroids, and IL-2 receptor antagonist. A benefit, in terms of better renal function, was not apparent in the treatment arms with *de novo* use of Sirolimus (Rapamune) without a CNI. It should be noted that an abbreviated schedule of administration of daclizumab was employed in one of the studies.

Calcineurin Inhibitor-induced Hemolytic Uremic Syndrome/Thrombotic Thrombocytopenic Purpura/Thrombotic Microangiopathy (HUS/TTP/TMA)

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

Angioedema

The concomitant administration of Sirolimus (Rapamune) and angiotensin-converting enzyme (ACE) inhibitors has resulted in angioneurotic edema-type reactions. Elevated sirolimus levels (with/without concomitant ACE inhibitors) may also potentiate angioedema (see Section **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction** - Inhibitors of Cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P gp)). In some cases, the angioedema has resolved upon discontinuation or dose reduction of Sirolimus (Rapamune).

Interstitial Lung Disease

Cases of interstitial lung disease (including pneumonitis, and infrequently bronchiolitis obliterans with organizing pneumonia [BOOP] and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving immunosuppressive regimens including Sirolimus (Rapamune). In some cases, the interstitial lung disease has resolved upon discontinuation or dose reduction of Sirolimus (Rapamune). The risk may be increased as the trough sirolimus level increases (see Section **4.8 Undesirable Effects** - Interstitial Lung Disease).

Latent Viral Infections

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

Antimicrobial Prophylaxis

Antimicrobial prophylaxis for *Pneumocystis carinii* pneumonia should be administered for 1 year following transplantation.

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

Contraception

Effective contraception must be initiated before Sirolimus (Rapamune) therapy, and maintained during Sirolimus (Rapamune) therapy and for 12 weeks after Sirolimus (Rapamune) therapy has been stopped.

Use in High Risk Patients

The safety and efficacy of 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**).

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

4.5.1 Inhibitors and Inducers of Cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp)

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

Substances that inhibit CYP3A4 include but are not limited to:

- Calcium channel blockers: diltiazem, nicardipine, verapamil
- Antifungal agents: clotrimazole, fluconazole, itraconazole, ketoconazole, voriconazole
- Antibiotics: clarithromycin, erythromycin, telithromycin, troleandomycin
- Gastrointestinal prokinetic agents: cisapride, metoclopramide
- Other drugs: bromocriptine, cimetidine, CsA, danazol, letermovir, protease inhibitors (e.g., for HIV and hepatitis C that include drugs, such as ritonavir, indinavir, boceprevir, and telaprevir)
- Grapefruit juice

Substances that induce CYP3A4 include but are not limited to:

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

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

Diltiazem

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

The simultaneous oral administration of 10 mg of Sirolimus (Rapamune) oral solution and 120 mg of diltiazem to 18 healthy volunteers significantly increased the bioavailability of sirolimus. Sirolimus C_{max}, t_{max}, and AUC were increased 1.4-, 1.3-, and 1.6-fold, respectively. Sirolimus did not affect the pharmacokinetics of either diltiazem or its metabolites desacetyldiltiazem and desmethyldiltiazem.

Verapamil

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

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

Erythromycin

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

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

Ketoconazole

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

In a study of 24 healthy volunteers, it was found that multiple-dose ketoconazole administration significantly affected the rate and extent of absorption and sirolimus exposure after administration of Sirolimus (Rapamune) oral solution, as reflected by increases in sirolimus C_{max}, t_{max}, and AUC of 4.4-fold, 1.4-fold, and 10.9-fold, respectively. However, the terminal $t_{1/2}$ of sirolimus was not changed. Single-dose Sirolimus (Rapamune) did not affect steady-state 12-hour plasma ketoconazole concentrations.

Rifampicin

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

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

4.5.2 Non-Interactions

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

4.5.3 CsA

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

Patients administered Sirolimus (Rapamune) with CsA should be monitored for the development of rhabdomyolysis (see Section **4.4 Special Warnings and Precautions for Use**).

Cyclosporine Microemulsion [(cyclosporine, USP) MODIFIED]

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

4.5.4 Cannabidiol

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

4.5.5 HMG-CoA Reductase Inhibitors, Fibrates

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

4.5.6 Calcineurin Inhibitors

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

4.5.7 Vaccinations

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

4.5.8 Food

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

Grapefruit juice reduces CYP3A4-mediated drug metabolism and potentially enhances P-gp-mediated drug counter-transport from enterocytes of the small intestine. This juice must not be taken with Sirolimus (Rapamune) tablets or oral solution or be used for oral

solution dilution (see Section **4.2 Dosage and Method of Administration** – Mode of Administration).

4.5.9 Interference with Laboratory and Other Diagnostic Tests

Not applicable

4.6 Fertility, Pregnancy and Lactation

Pregnancy

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

Sirolimus (Rapamune) should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo/fetus (see Section **4.4 Special Warnings and Precautions for Use**).

[Need for effective contraception: see statement in Section **4.4 Special Warnings and Precautions for Use**.]

Lactation

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

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Undesirable Effects

Undesirable Effects Observed with Prophylaxis of Organ Rejection in Renal Transplantation

The adverse reactions listed in the following table includes reactions reported in patients treated with Sirolimus (Rapamune) in combination with CsA and corticosteroids.

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

The adverse reactions in the table below are listed within each standard system organ class (SOC) by decreasing medical seriousness

Adverse Reactions listed within each standard system organ class (SOC) by decreasing medical seriousness - Prophylaxis of Organ Rejection in Renal Transplantation (N=1501)

System Organ Class	Adverse Drug Reactions
Infections and infestations	Sepsis; Pneumonia; Mycobacterial infection (including tuberculosis); Pyelonephritis; Fungal infection; Cytomegalovirus infection;

Adverse Reactions listed within each standard system organ class (SOC) by decreasing medical seriousness - Prophylaxis of Organ Rejection in Renal Transplantation (N=1501)

System Organ Class	Adverse Drug Reactions
	Herpes zoster; Epstein-Barr virus infection; Viral infection; Bacterial infection; Herpes simplex; Urinary tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Lymphoma; Neuroendocrine carcinoma of the skin; Malignant melanoma; Post-transplant lymphoproliferative disorder; Squamous cell carcinoma of skin; Basal cell carcinoma
Blood and lymphatic system disorders	Pancytopenia; Thrombotic thrombocytopenic purpura; Hemolytic uremic syndrome; Neutropenia; Thrombocytopenia; Anemia; Leukopenia
Immune system disorders	Hypersensitivity (including angioedema, anaphylactic reaction, and anaphylactoid reaction)
Metabolism and nutrition disorders	Hypokalemia; Hypophosphatemia; Hyperlipidemia (including hypercholesterolemia); Hyperglycemia; Hypertriglyceridemia; Fluid retention; Diabetes mellitus
Nervous system disorders	Posterior reversible encephalopathy syndrome;* Headache
Cardiac disorders	Pericardial effusion; Tachycardia
Vascular disorders	Venous thrombosis (including deep vein thrombosis); Hypertension; Lymphoedema; Lymphocele
Respiratory, thoracic and mediastinal disorders	Pulmonary hemorrhage; Pulmonary embolism; Alveolar proteinosis; Pneumonitis; Pleural effusion; Epistaxis
Gastrointestinal disorders	Pancreatitis; Stomatitis; Ascites; Abdominal pain; Constipation; Diarrhea; Nausea
Skin and subcutaneous tissue disorders	Dermatitis exfoliative; Hypersensitivity vasculitis;

Adverse Reactions listed within each standard system organ class (SOC) by decreasing medical seriousness - Prophylaxis of Organ Rejection in Renal Transplantation (N=1501)

System Organ Class	Adverse Drug Reactions
	Rash; Acne
Musculoskeletal and connective tissue disorders	Osteonecrosis; Arthralgia
Renal and urinary disorders	Nephrotic syndrome; Focal segmental glomerulosclerosis; Proteinuria
Reproductive system and breast disorders	Menstrual disorder (including amenorrhea and menorrhagia); Ovarian cyst
General disorders and administration site conditions	Impaired healing; Edema; Edema peripheral; Pyrexia; Pain
Investigations	Liver function test abnormal (including alanine aminotransferase increased and aspartate aminotransferase increased); Blood creatinine increased; Blood lactate dehydrogenase increased

*ADR identified post-marketing

Sirolimus (Rapamune) Following CsA Withdrawal:

The incidence of adverse reactions was determined through 60 months in a randomized, multicenter controlled trial in which 215 renal transplant patients received Sirolimus (Rapamune) as a maintenance regimen following CsA withdrawal, and 215 patients received Sirolimus (Rapamune) with CsA therapy. All patients were treated with corticosteroids. The safety profile prior to randomization (start of CsA withdrawal) was similar to that of the 2-mg Sirolimus (Rapamune) groups in studies of Sirolimus (Rapamune) in combination with CsA. Following randomization (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, hypokalemia, thrombocytopenia, abnormal healing, acne, ileus, and joint disorder. Conversely, the incidence of acidosis, hypertension, CsA toxicity, increased creatinine, abnormal kidney function, toxic nephropathy, edema, hyperuricemia, 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 Sirolimus (Rapamune) following CsA withdrawal, compared with patients who continued to receive Sirolimus (Rapamune) and CsA.

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

INCIDENCE (%) OF MALIGNANCIES AT 60 MONTHS POST-TRANSPLANT[a]			
Malignancy[d]	Nonrandomized[b] (n = 95)	Sirolimus (Rapamune) with CsA Therapy[b] (n = 215)	Sirolimus (Rapamune) Following CsA Withdrawal[c] (n = 215)
Lymphoma/lymphoproliferative disease	1.1	1.4	0.5
Skin Carcinoma			
Non-melanoma skin carcinoma	5.3	8.8	7.0
Melanoma	0.0	0.5	0.5
Other Malignancy	5.3	7.0	3.3

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

By 60 months, the incidence of nonskin 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.

Safety was assessed in a controlled trial (see Section **5.1 Pharmacodynamic Properties**) involving 448 patients who received at least one dose of study drug (safety population): 224 patients received at least one dose of sirolimus with tacrolimus, and 224 patients received at least one dose of sirolimus with cyclosporine. Overall, the incidence and nature of adverse events was similar to those seen in previous combination studies with Sirolimus (Rapamune). Diarrhea and herpes simplex occurred significantly more frequently in patients who received sirolimus and tacrolimus, whereas, hypertension, cardiomegaly, lymphocele, increased creatinine, acne, urinary tract disorder, ovarian cyst, and calcineurin inhibitor toxicity occurred at a significantly higher rate in patients who received sirolimus and cyclosporine. The incidence of malignancy was low (1.3% in each group).

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

The safety and efficacy of conversion from calcineurin inhibitors to Sirolimus (Rapamune) in maintenance renal transplant patients has not been established.

In a study evaluating the safety and efficacy of conversion (6 to 120 months after transplantation) from calcineurin inhibitors to Sirolimus (Rapamune) (sirolimus target levels of 12-20 ng/mL by chromatographic assay) in maintenance renal transplant patients, enrollment was stopped in the subset of patients (n = 90) with a baseline glomerular filtration rate of less than 40 mL/min. There was a higher rate of serious adverse events including pneumonia, acute rejection, graft loss and death in this Sirolimus (Rapamune) treatment arm (n = 60, median time post-transplant 36 months).

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

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

In patients with delayed graft function, Sirolimus (Rapamune) may delay recovery of renal function (see Section **4.4 Special Warnings and Precautions for Use** - Renal Function).

Interstitial Lung Disease

Cases of interstitial lung disease (including pneumonitis, and infrequently bronchiolitis obliterans organizing pneumonia [BOOP] and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving immunosuppressive regimens including Sirolimus (Rapamune). In some cases, the interstitial lung disease has resolved upon discontinuation or dose reduction of Sirolimus (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 Sirolimus (Rapamune). These infections may be associated with serious or fatal outcomes, including renal graft loss (see Section **4.4 Special Warnings and Precautions for Use** – Latent Viral Infections).

Hepatotoxicity

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

Abnormal Healing

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

Other Clinical Experience

Azoospermia has been reported with the use of Sirolimus (Rapamune) and has been reversible upon discontinuation of Sirolimus (Rapamune) in most cases (see Section **5.3 Preclinical Safety Data**).

Clostridium difficile enterocolitis has been reported in patients receiving sirolimus (Rapamune).

4.9 Overdose and Treatment

There is limited experience with overdose. In general, the adverse effects of overdose are consistent with those listed in the **Undesirable Effects** Section. General supportive measures should be followed in all cases of overdose. Based on the poor aqueous solubility and high erythrocyte and plasma protein binding of sirolimus, it is anticipated that sirolimus is not dialyzable to any significant extent. In mice and rats, the acute oral LD_{50} was greater

than 800 mg/kg.

4.10 Abuse and Dependence

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

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Immunosuppressant

ATC code: L04A A10

Mechanism of Action

Sirolimus inhibits T-lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (Interleukin [IL]-2, IL-4, and IL-15) stimulation by a mechanism that is distinct from that of other immunosuppressants. Sirolimus also inhibits antibody production. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. The sirolimus: FKBP-12 complex has no effect on calcineurin activity. This complex binds to and inhibits the activation of the mammalian Target Of Rapamycin (mTOR), a key regulatory kinase. This inhibition suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the G1 to the S phase of the cell cycle.

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

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

Clinical Trials Data on Efficacy

Prophylaxis of Organ Rejection

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

The primary efficacy analyses from these trials determined that Sirolimus (Rapamune), at doses of 2 mg/day and 5 mg/day, significantly reduced the incidence of efficacy failure at 6 months following transplantation compared to both azathioprine and placebo. The reduction in the incidence of first biopsy-confirmed acute rejection (BCAR) episodes in Sirolimus (Rapamune)-treated patients compared to the control groups included a reduction in all grades of rejection.

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

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

INCIDENCE (%) OF EFFICACY FAILURE AT 6 AND 24 MONTHS FOR STUDY 1[a,b]			
Parameter	Sirolimus (Rapamune) Oral Solution 2 mg/day (n = 284)	Sirolimus (Rapamune) Oral Solution 5 mg/day (n = 274)	Azathioprine 2-3 mg/kg/day (n = 161)
Efficacy failure at 6 months[c]	18.7	16.8	32.3
Components of efficacy failure			
Biopsy-proven acute rejection	16.5	11.3	29.2
Graft loss	1.1	2.9	2.5
Death	0.7	1.8	0
Lost to follow-up	0.4	0.7	0.6
Efficacy failure at 24 months	32.8	25.9	36.0
Components of efficacy failure			
Biopsy-proven acute rejection	23.6	17.5	32.3
Graft loss	3.9	4.7	3.1
Death	4.2	3.3	0
Lost to follow-up	1.1	0.4	0.6

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

INCIDENCE (%) OF EFFICACY FAILURE AT 6 AND 36 MONTHS FOR STUDY 2[a,b]			
Parameter	Sirolimus (Rapamune) Oral Solution 2 mg/day (n = 227)	Sirolimus (Rapamune) Oral Solution 5 mg/day (n = 219)	Placebo (n = 130)
Efficacy failure at 6 months[c]	30.0	25.6	47.7
Components of efficacy failure			
Biopsy-proven acute rejection	24.7	19.2	41.5
Graft loss	3.1	3.7	3.9
Death	2.2	2.7	2.3
Lost to follow-up	0	0	0
Efficacy failure at 36 months	44.1	41.6	54.6
Components of efficacy failure			
Biopsy-proven acute rejection	32.2	27.4	43.9
Graft loss	6.2	7.3	4.6
Death	5.7	5.9	5.4
Lost to follow-up	0	0.9	0.8

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

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

GRAFT AND PATIENT SURVIVAL (%) FOR STUDY 1 (12 AND 24 MONTHS) AND STUDY 2 (12 AND 36 MONTHS)[a,b]				
Parameter	Sirolimus (Rapamune) Oral Solution 2 mg/day	Sirolimus (Rapamune) Oral Solution 5 mg/day	Azathioprine 2-3 mg/kg/day	Placebo
Study 1	(n = 284)	(n = 274)	(n = 161)	
Graft survival				
Month 12	94.7	92.7	93.8	
Month 24	85.2	89.1	90.1	
Patient survival				
Month 12	97.2	96.0	98.1	
Month 24	92.6	94.9	96.3	
Study 2	(n = 227)	(n = 219)		(n = 130)
Graft survival				
Month 12	89.9	90.9		87.7
Month 36	81.1	79.9		80.8
Patient survival				
Month 12	96.5	95.0		94.6
Month 36	90.3	89.5		90.8

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

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

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

PERCENTAGE OF EFFICACY FAILURE BY RACE AT 6 MONTHS[a]					
		Sirolimus (Rapamune) 2 mg/day	Sirolimus (Rapamune) 5 mg/day	Azathioprine 2-3 mg/kg/day	Placebo
Sirolimus (Rapamune) (2 mg and 5 mg, once daily) versus azathioprine comparator					
Black	(n = 166)	34.9 (n = 63)	18.0 (n = 61)	33.3 (n = 42)	
Non-black	(n = 553)	14.0 (n = 221)	16.4 (n = 213)	31.9 (n = 119)	
Sirolimus (Rapamune) (2 mg and 5 mg, once daily) versus placebo comparator					
Black	(n = 66)	30.8 (n = 26)	33.7 (n = 27)		38.5 (n = 13)
Non-black	(n = 510)	29.9 (n = 201)	24.5 (n = 192)		48.7 (n = 117)
a: All patients received CsA and corticosteroids.					

Mean glomerular filtration rates (GFR) at one year post-transplant were calculated using the Nankivell equation for all subjects in each study who had serum creatinine measured at 12 months. In both studies, mean GFR at one year was lower in patients treated with CsA and Sirolimus (Rapamune) compared to those treated with CsA and the respective azathioprine or placebo control. Within each treatment group in both of these studies, mean GFR at one year post-transplant was lower in patients who experienced at least one episode of biopsy-proven acute rejection, compared to those who did not.

The safety and efficacy of Sirolimus (Rapamune) as a maintenance regimen were assessed following CsA withdrawal at 3 to 4 months post renal transplantation. In a randomized, multicenter, controlled trial conducted at 57 centers in Australia, Canada, and Europe, five hundred twenty-five (525) patients were enrolled. All patients in this study received the tablet formulation. This study compared patients who were administered Sirolimus (Rapamune), CsA, and corticosteroids continuously, with patients who received the same standardized therapy for the first 3 months after transplantation (pre-randomization period) followed by the withdrawal of CsA. During CsA withdrawal, the Sirolimus (Rapamune) dosages were adjusted to achieve targeted sirolimus whole blood trough concentration ranges (16 to 24 ng/mL until month 12, then 12 to 20 ng/mL thereafter through month 60). At 3 months, 430 patients were equally randomized to either Sirolimus (Rapamune) with CsA therapy, or Sirolimus (Rapamune) as a maintenance regimen following CsA withdrawal. Eligibility for randomization included no Banff Grade 3 acute rejection episode or vascular rejection in the 4 weeks before random assignment; serum creatinine ≤4.5 mg/dL; and adequate renal function to support CsA withdrawal (in the opinion of the investigator). The primary efficacy endpoint was graft survival at 12 months after transplantation. Secondary efficacy endpoints were the rate of biopsy-confirmed acute rejection, patient survival, incidence of efficacy failure (defined as the first occurrence of either biopsy-proven acute rejection, graft loss, or death), and treatment failure (defined as the first occurrence of either discontinuation, acute rejection, graft loss, or death).

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

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

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

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

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

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

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

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

CALCULATED GLOMERULAR FILTRATION RATES (mL/min) BY NANKIVELL EQUATION AT 12, 24, 36, 48 and 60 MONTHS
POST TRANSPLANT: AFTER CsA WITHDRAWAL[a,b,c]

Parameter	Sirolimus (Rapamune) with CsA Therapy	Sirolimus (Rapamune) Following CsA Withdrawal
Month 12		
Mean ± SEM	53.2 ± 1.5 n = 208	59.3 ± 1.5 n = 203
Month 24		
Mean ± SEM	48.4 ± 1.7 n = 203	58.4 ± 1.6 n = 201
Month 36		
Mean ± SEM	47.0 ± 1.8 (n = 196)	58.5 ± 1.9 (n = 199)
Month 48		
Mean ± SEM	43.5 ± 2.0 n = 185	58.1 ± 2.0 (n = 187)
Month 60		
Mean ± SEM	42.7 ± 2.2 n = 176	58.0 ± 2.1 n = 193

a: Includes patients who prematurely discontinued treatment.
b: Patients who had a graft loss were included in the analysis and had their GFR set to 0.0.
c: All patients received corticosteroids.

The mean GFR at 12, 24, 36, 48 and 60 months, calculated by the Nankivell equation, was significantly higher for patients receiving Sirolimus (Rapamune) as a maintenance regimen following CsA withdrawal than for those in the Sirolimus (Rapamune) with CsA therapy group. At month 60, patients with an acute rejection at any time after transplantation had a significantly higher mean calculated GFR for patients receiving Sirolimus (Rapamune) as a maintenance regimen following CsA withdrawal than for those in the Sirolimus (Rapamune) with CsA therapy group.

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

This study compared renal transplant patients (6-120 months after transplantation) who were converted from calcineurin inhibitors to Sirolimus (Rapamune), with patients who continued to receive calcineurin inhibitors. Concomitant immunosuppressive medications included mycophenolate mofetil (MMF), azathioprine (AZA), and corticosteroids. Sirolimus (Rapamune) was initiated with a single loading dose of 12-20 mg, after which dosing was adjusted to achieve a target sirolimus whole blood trough concentration of 8-20 ng/mL (chromatographic method). The primary efficacy endpoint was calculated GFR at 12 months post-randomization. Secondary endpoints included biopsy-confirmed acute rejection, graft loss, and death. Enrollment in the patient stratum with baseline calculated GFR less than 40 mL/min was discontinued due to an imbalance in safety events (see Section **4.4 Special Warnings and Precautions for Use** and Section **4.8 Undesirable Effects**). Findings in the patient stratum with baseline calculated GFR greater than 40 mL/min (Sirolimus (Rapamune) conversion, n = 497; CNI continuation, n = 246) are summarized below: There

was no clinically or statistically significant improvement in Nankivell GFR compared to baseline.

RENAL FUNCTION IN STABLE RENAL TRANSPLANT PATIENTS IN PATIENTS WITH BASELINE GFR >40 mL/min THE SIROLIMUS (RAPAMUNE) CONVERSION STUDY (STUDY 5)			
Parameter	Sirolimus (Rapamune) conversion N=496	CNI continuation N = 245	Difference (95% CI)
GFR mL/min (Nankivell) at 1 year	59.0	57.7	1.3 (-1.1, 3.7)
GFR mL/min (Nankivell) at 2 year	53.7	52.1	1.6 (-1.4, 4.6)

In the patient stratum with baseline calculated GFR greater than 40 mL/min (Sirolimus (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 Sirolimus (Rapamune) conversion. The rates of pneumonia were significantly higher for the sirolimus conversion group.

While the mean and median values for urinary protein to creatinine ratio were similar between treatment groups at baseline, significantly higher mean and median levels of urinary protein excretion were seen in the Sirolimus (Rapamune) conversion arm at 1 year and at 2 years, as shown in the table below. In addition, when compared to patients who continued to receive calcineurin inhibitors, a higher percentage of patients had urinary protein to creatinine ratios >1 at 1 and 2 years after sirolimus conversion. This difference was seen in both patients who had a urinary protein to creatinine ratio ≤1 and those who had a protein to creatinine ratio >1 at baseline. More patients in the sirolimus conversion group developed nephrotic range proteinuria, as defined by a urinary protein to creatinine ratio >3.5 (46/482 [9.5%] versus. 9/239 [3.8%]), even when the patients with baseline nephrotic range proteinuria were excluded. The rate of nephrotic range proteinuria was significantly higher in the sirolimus conversion group compared to the calcineurin inhibitor continuation group with baseline urinary protein to creatinine ratio >1 (13/29 versus. 1/14), excluding patients with baseline nephrotic range proteinuria.

MEAN AND MEDIAN VALUES FOR URINARY PROTEIN TO CREATININE RATIO (mg/mg) BETWEEN TREATMENT GROUPS AT BASELINE, 1 AND 2 YEARS IN THE STRATUM WITH BASELINE CALCULATED GFR >40 mL/min							
Study period	Sirolimus Conversion			CNI Continuation			
	N	Mean ± SD	Median	N	Mean ± SD	Median	p-value
Baseline	410	0.35 ± 0.76	0.13	207	0.28 ± 0.61	0.11	0.381
1 year	423	0.88 ± 1.61	0.31	203	0.37 ± 0.88	0.14	<0.001
2 years	373	0.86 ± 1.48	0.32	190	0.47 ± 0.98	0.13	<0.001

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

In the stratum with baseline calculated GFR greater than 40 mL/min, the mean and median

values for urinary protein to creatinine ratio were similar between treatment groups at baseline (mean: 0.35 and 0.28; median: 0.13 and 0.11 for the Sirolimus (Rapamune) conversion and CNI continuation groups, respectively). At 24 months, the mean and median urinary protein to creatinine ratios were significantly higher in the Sirolimus (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 Sirolimus (Rapamune) conversion and CNI continuation groups, respectively) (see Section **4.4 Special Warnings and Precautions for Use**). New-onset nephrosis (nephrotic syndrome) was also reported (see Section **4.8 Undesirable Effects**).

At 2 years, the rate of non-melanoma skin malignancies was significantly lower in the Sirolimus (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 Sirolimus (Rapamune) conversion and CNI continuation groups, respectively, $p<0.002$). It should be noted that Study 4 was not designed to consider malignancy risk factors or systematically screen subjects for malignancy.

In a subset of study patients with a baseline GFR greater than 40 mL/min and normal urinary protein excretion, calculated GFR was higher at 1 and 2 years in patients converted to Sirolimus (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 Sirolimus (Rapamune) treatment arm of the subset.

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

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

evaluable ITT population, were efficacy failure (defined as the first occurrence of biopsy-confirmed acute rejection, graft loss, or death), first occurrence of graft loss or death, and renal function as measured by the calculated GFR using the Nankivell formula. The table below summarizes the co-primary endpoints. The overall rates of efficacy failure and the first occurrence of graft loss or death were similar in both groups.

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

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

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

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

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

Sirolimus (Rapamune) was evaluated in a 36-month, open-label, randomized, controlled clinical trial at 14 North American centers in pediatric (aged 3 to <18 years) renal transplant recipients considered to be at high immunologic risk for developing chronic allograft nephropathy, defined as a history of one or more acute allograft rejection episodes and/or the presence of chronic allograft nephropathy on a renal biopsy. Seventy-eight (78) subjects were randomized in a 2:1 ratio to Sirolimus (Rapamune) (sirolimus target concentrations of 5 to 15 ng/mL, by chromatographic assay, n = 53) in combination with a calcineurin inhibitor and corticosteroids or to continue calcineurin-inhibitor-based immunosuppressive therapy (n = 25). The primary endpoint of the study was efficacy failure as defined by the first occurrence of biopsy confirmed acute rejection, graft loss, or death, and the trial was designed to show superiority of Sirolimus (Rapamune) added to a calcineurin-inhibitor-based immunosuppressive regimen compared to a calcineurin-inhibitor-based regimen. The cumulative incidence of efficacy failure up to 36 months was 45.3% in the Sirolimus (Rapamune) group compared to 44.0% in the control group, and did not demonstrate

superiority. There was one death in each group. The use of Sirolimus (Rapamune) in combination with calcineurin inhibitors and corticosteroids was associated with an increased risk of deterioration of renal function, serum lipid abnormalities (including but not limited to increased serum triglycerides and cholesterol), and urinary tract infections. This study does not support the addition of Sirolimus (Rapamune) to calcineurin-inhibitor-based immunosuppressive therapy in this subpopulation of pediatric renal transplant patients (see Section **4.2 Dosage and Method of Administration** and Section **5.2 Pharmacokinetic Properties**).

5.2 Pharmacokinetic Properties

Absorption

Following administration of Sirolimus (Rapamune) oral solution, sirolimus is rapidly absorbed, with a mean time-to-peak concentration (t_{max}) of approximately 1 hour after a single dose of Sirolimus (Rapamune) in healthy subjects and approximately 2 hours after multiple oral doses of Sirolimus (Rapamune) in renal transplant recipients. Following administration of Sirolimus (Rapamune) tablet, sirolimus t_{max} was approximately 3 hours after single doses in healthy volunteers and multiple doses in renal transplant patients.

The systemic availability (F) of sirolimus from Sirolimus (Rapamune) oral solution was estimated to be approximately 14%. After Sirolimus (Rapamune) tablet administration, F was estimated to be approximately 17%. Bioequivalence between 1-mg, 2-mg, and 5-mg tablets has been generally shown in healthy volunteers. The exception was that t_{max} was longer for the 5-mg tablets compared with the other tablets.

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

Distribution

The mean ($\pm$ SD) blood-to-plasma ratio of sirolimus was 36 ($\pm$ 17.9) in stable renal allograft recipients after administration of Sirolimus (Rapamune) oral solution, indicating that sirolimus is extensively partitioned into formed blood elements. The mean volume of distribution (Vss/F) of sirolimus by Sirolimus (Rapamune) oral solution is 12 $\pm$ 7.52 L/kg. Sirolimus is extensively bound (approximately 92%) to human plasma proteins.

In human whole blood, the binding of sirolimus was shown mainly to be associated with serum albumin (97%), α1-acid glycoprotein, and lipoproteins.

Metabolism

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

Elimination

After a single dose of [^{14}C] sirolimus by oral solution in healthy subjects, the majority (91%) of radioactivity was recovered from the feces, and only a minor amount (2.2%) was excreted in urine. The mean $\pm$ SD terminal elimination half life ($t_{1/2}$) of sirolimus after multiple dosing

by Sirolimus (Rapamune) oral solution in stable renal transplant patients was estimated to be about 62 $\pm$ 16 hours.

Effect of Food

In 22 healthy subjects, a high fat breakfast (860 kcal, 55% kcal from fat) altered the bioavailability characteristics of sirolimus after administration by Sirolimus (Rapamune) oral solution. Compared to fasting, a 34% decrease in the peak blood sirolimus concentration (C_{max}), a 3.5-fold increase in the time to peak concentration (t_{max}), and a 35% increase in mean total exposure (AUC) was observed. In an otherwise identical study, Sirolimus (Rapamune) was administered by tablet to 24 healthy subjects. The values for C_{max}, t_{max}, and AUC showed increases of 65%, 32%, and 23%, respectively. Thus, a high-fat meal produced differences in the two formulations with respect to rate of absorption but not in extent of absorption. Evidence from a large randomized multicenter controlled trial comparing Sirolimus (Rapamune) oral solution to tablets supports that the differences in absorption rates do not affect the efficacy of the drug.

Sirolimus (Rapamune) should be taken consistently with or without food to minimize blood level variability. Bioequivalence testing based on AUC and C_{max} showed that Sirolimus (Rapamune) administered with orange juice is equivalent to administration with water. Therefore, orange juice and water may be used interchangeably to dilute Sirolimus (Rapamune) for oral solution. Grapefruit juice reduces CYP3A4-mediated drug metabolism and potentially enhances P-gp mediated drug counter-transport from enterocytes of the small intestine and must not be used for dilution or taken with Sirolimus (Rapamune) (see Section **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

Renal Transplant Patients

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

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

High-Risk Patients

Average Sirolimus (Rapamune) doses and sirolimus whole blood trough concentrations for tablets administered daily in combination with cyclosporine or tacrolimus, and corticosteroids in high-risk renal transplant patients (see Section **5.1 Pharmacodynamic Properties**) are summarized in the table below.

AVERAGE SIROLIMUS (RAPAMUNE) DOSES AND SIROLIMUS TROUGH CONCENTRATIONS (MEAN ± SD) IN HIGH-RISK RENAL TRANSPLANT PATIENTS AFTER MULTIPLE-DOSE TABLET ADMINISTRATION		
	Sirolimus (Rapamune) with Tacrolimus Therapy	Sirolimus (Rapamune) with Cyclosporine Therapy
Sirolimus (Rapamune) Dose (mg/day)		
Months 3 to 6[a]	6.5 ± 3.0	5.1 ± 2.4
Months 9 to 12[b]	6.5 ± 3.0	5.0 ± 2.3
Sirolimus C_{min} (ng/mL)[c]		
Months 3 to 6	11.5 ± 6.2	11.8 ± 4.2
Months 9 to 12	10.7 ± 3.6	11.2 ± 3.8
a: n=110 in Sirolimus (Rapamune) /Tacrolimus group, n=109 in Sirolimus (Rapamune)/Cyclosporine Group b: n=117 in Sirolimus (Rapamune) /Tacrolimus group, n=127 in Sirolimus (Rapamune)/Cyclosporine Group c: Expressed by chromatography.		

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

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

MEAN ± SD STEADY STATE SIROLIMUS PHARMACOKINETIC PARAMETERS IN ADULT RENAL TRANSPLANT PATIENTS FOLLOWING SIROLIMUS (RAPAMUNE) 2 MG DAILY[a,b]		
	Multiple Dose (daily dose)	
	Solution	Tablets
C_{max} (ng/mL)	14.4 ± 5.3	15.0 ± 4.9
t_{max} (hr)	2.1 ± 0.8	3.5 ± 2.4
AUC (ng•h/mL)	194 ± 78	230 ± 67
C_{min} (ng/mL)[c]	5.2 ± 2.7	7.6 ± 3.1
CL/F (mL/h/kg)	173 ± 50	139 ± 63
a: In presence of cyclosporine administered 4 hours before Sirolimus (Rapamune) dosing. b: Based on data collected at months 1 and 3 post-transplantation. c: Average C_{min} over 6 months.		

Whole blood trough sirolimus concentrations, as measured by LC/MS/MS in renal transplant patients, were significantly correlated with $AUC_{\tau,ss.}$ Upon repeated, twice-daily administration without an initial loading dose in a multiple-dose study, the average trough concentration of sirolimus increases approximately 2- to 3-fold over the initial 6 days of therapy, at which time steady-state is reached. A loading dose of 3 times the maintenance dose will provide near steady-state concentrations within 1 day in most patients.

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

The following sirolimus concentrations (chromatographic equivalent) were observed in phase 3 clinical studies (see Section **5.1 Pharmacodynamic Properties**).

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

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

Patients with Renal Impairment

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

Patients with Hepatic Impairment

Sirolimus (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), B (moderate) or C (severe) primary hepatic impairment. Compared with the values in the normal hepatic function group, the patients with mild, moderate, and severe hepatic impairment had 43%, 94%, and 189% higher mean values for sirolimus AUC and 22%, 78%, and 159% higher mean values for $t_{1/2}$ and had steadily decreasing 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 Sirolimus (Rapamune) should be reduced by approximately one-third in patients with mild to moderate hepatic impairment and by approximately one-half in patients with severe hepatic impairment (see Section **4.2 Dosage and Method of Administration**). In patients with hepatic impairment, it is necessary that sirolimus whole blood trough levels be monitored. In patients with severe hepatic impairment, consideration should be given to monitoring every 5 to 7

days for a longer period of time after dose adjustment or after loading dose due to the delay in reaching steady state because of the prolonged half-life.

Children

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

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

Age (y)	n	Body weight (kg)	$C_{max,ss}$ (ng/mL)	$t_{max,ss}$ (h)	$C_{min,ss}$ (ng/mL)	$AUC_{\tau,ss}$ (ng•h/mL)	CL/F[c] (mL/h/kg)	CL/F[c] (L/h/m$_2$)
6-11	8	27 ± 10	22.1 ± 8.9	5.88 ± 4.05	10.6 ± 4.3	356 ± 127	214 ± 129	5.4 ± 2.8
12-18	14	52 ± 15	34.5 ± 12.2	2.7 ± 1.5	14.7 ± 8.6	466 ± 236	136 ± 57	4.7 ± 1.9

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

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

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN PEDIATRIC PATIENTS WITH STABLE CHRONIC RENAL FAILURE MAINTAINED ON HEMODIALYSIS OR PERITONEAL DIALYSIS (1, 3, 9, 15 MG/M^2 SINGLE DOSE)*,[139]

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

*All subjects received Sirolimus (Rapamune) oral solution.

Elderly

Clinical studies of Sirolimus (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 after Sirolimus (Rapamune) oral solution 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.

Gender

Sirolimus (Rapamune) oral dose clearance after Sirolimus (Rapamune) oral solution in males was 12% lower than that in females; male subjects had a significantly longer $t_{1/2}$ than did female subjects (72.3 hours versus 61.3 hours). Similar gender effects on oral-dose clearance and $t_{1/2}$ were obtained after administration of Sirolimus (Rapamune) by tablets. These pharmacokinetic differences do not require dose adjustment based on gender.

Race

In large phase III trials using Sirolimus (Rapamune) and cyclosporine microemulsion [(cyclosporine, USP) MODIFIED], there were no significant differences in mean trough sirolimus concentrations or AUC over time between black (n = 139) and non-black (n=724) patients during the first 6 months after transplantation at Sirolimus (Rapamune) doses of 2 mg/day and 5 mg/day by oral solution.

5.3 Preclinical Safety Data

Carcinogenicity

Carcinogenicity studies were conducted in mice and rats. In an 86-week female mouse study at 4 dosages that were approximately 16 to 135 times the clinical doses (adjusted for body surface area) there was a statistically significant increase in malignant lymphoma at all dose levels compared with controls. In a second mouse study at dosages that were approximately 3 to 16 times the clinical doses (adjusted for body surface area), hepatocellular adenoma and carcinoma (males) were considered sirolimus related. In the 104-week rat study at dosages that were approximately 0.4 to 1 times the clinical doses (adjusted for body surface area), there was a statistically significant increased incidence of testicular adenoma in the highest dose group.

Mutagenicity

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

Reproductive Toxicology

Sirolimus was embryo/fetal toxic in rats at dosages of 0.1 mg/kg and above (approximately 0.2 to 0.5 the clinical doses adjusted for body surface area). Embryo/fetal toxicity was manifested as mortality and reduced fetal weights (with associated delays in skeletal ossification). However, no teratogenesis was evident. In combination with CsA, rats had increased embryo/fetal mortality compared to sirolimus alone. There were no effects on rabbit development at the maternally toxic dosage of 0.05 mg/kg (approximately 0.3 to 0.8 times the clinical doses adjusted for body surface area).

There was no effect on fertility in female rats following the administration of sirolimus at dosages up to 0.5 mg/kg (approximately 1 to 3 times the clinical doses adjusted for body surface area). In male rats, there was a slight reduction in fertility compared to controls in one study at a dosage of 2 mg/kg (approximately 4 to 11 times the clinical doses adjusted for body surface area). A second study failed to confirm these findings. Reductions in testicular weights and/or histological lesions (eg, tubular atrophy and tubular giant cells) were observed in rats following dosages of 0.65 mg/kg (approximately 1 to 3 times the clinical doses adjusted for body surface area) and above and in a monkey study at 0.1 mg/kg (approximately 0.4 to 1 times the clinical doses adjusted for body surface area) and above. Sperm counts were reduced in male rats following the administration of sirolimus for 13 weeks at a dosage of 6 mg/kg (approximately 12 to 32 times the clinical doses adjusted for body surface area), but showed improvement by 3 months after dosing was stopped.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf-Life

See outer package for the expiry date.

6.2 Storage Conditions

Sirolimus (Rapamune) 500 mcg Sugar-Coated Tablets: Store at temperatures not exceeding 25°C

Sirolimus (Rapamune) 1 mg Sugar-Coated Tablets: Store at temperatures not exceeding 30°C

6.3 Availability

Sirolimus (Rapamune) 500 mcg Sugar-Coated Tablets:
Alu/PVC/PE/Aclar Blister Pack x 10's (Box of 100's)

Sirolimus (Rapamune) 1 mg Sugar-Coated Tablets:
Alu/PVC/PE/Aclar Blister Pack x 10's (Box of 100's)

7.0 FDA REGISTRATION NUMBER

500 mcg Sugar-Coated Tablets: DR-XY40263
1 mg Sugar-Coated Tablets: DR-XY27395

8.0 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

500 mcg Sugar-Coated Tablets: September 23, 2014
1 mg Sugar-Coated Tablets: September 23, 2014

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

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