ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rapamune 1 mg/mL oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 1 mg sirolimus.
Each 60 mL bottle contains 60 mg sirolimus.

Excipients with known effect
Each mL contains up to 25 mg of ethanol, approximately 350 mg of propylene glycol (E1520), and 20 mg of soya oil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.
Pale yellow to yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rapamune is indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant. It is recommended that Rapamune be used initially in combination with ciclosporin microemulsion and corticosteroids for 2 to 3 months. Rapamune may be continued as maintenance therapy with corticosteroids only if ciclosporin microemulsion can be progressively discontinued (see sections 4.2 and 5.1).

Rapamune is indicated for the treatment of patients with sporadic lymphangioleiomyomatosis with moderate lung disease or declining lung function (see sections 4.2 and 5.1).

4.2 Posology and method of administration

Posology

Prophylaxis of organ rejection

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

Initial therapy (2 to 3 months post-transplantation)
The usual dose regimen for Rapamune is a 6 mg single oral loading dose, administered as soon as possible after transplantation, followed by 2 mg once daily until results of therapeutic monitoring of the medicinal product are available (see *Therapeutic monitoring of the medicinal product and dose adjustment*). The Rapamune dose should then be individualised to obtain whole blood trough levels of 4 to 12 ng/mL (chromatographic assay). Rapamune therapy should be optimised with a tapering regimen of steroids and ciclosporin microemulsion. Suggested ciclosporin trough concentration ranges for the first 2-3 months after transplantation are 150-400 ng/mL (monoclonal assay or equivalent technique) (see section 4.5*)*.

To minimise variability, Rapamune should be taken at the same time in relation to ciclosporin, 4 hours after the ciclosporin dose, and consistently either with or without food (see section 5.2).

Maintenance therapy
Ciclosporin should be progressively discontinued over 4 to 8 weeks, and the Rapamune dose should be adjusted to obtain whole blood trough levels of 12 to 20 ng/mL (chromatographic assay; see *Therapeutic monitoring of the medicinal product and dose adjustment*). Rapamune should be given with corticosteroids. In patients for whom ciclosporin withdrawal is either unsuccessful or cannot be attempted, the combination of ciclosporin and Rapamune should not be maintained for more than 3 months post-transplantation. In such patients, when clinically appropriate, Rapamune should be discontinued and an alternative immunosuppressive regimen instituted.

Therapeutic monitoring of the medicinal product and dose adjustment
Whole blood sirolimus levels should be closely monitored in the following populations*:*

(1) in patients with hepatic impairment
(2) when inducers or inhibitors of CYP3A4 and/or P-glycoprotein (P-gp) are concurrently administered and after their discontinuation (see section 4.5) and/or
(3) if ciclosporin dosing is markedly reduced or discontinued, as these populations are most likely to have special dosing requirements.

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

Most patients who received 2 mg of Rapamune 4 hours after ciclosporin had whole blood trough concentrations of sirolimus within the 4 to 12 ng/mL target range (expressed as chromatographic assay values). Optimal therapy requires therapeutic concentration monitoring of the medicinal product in all patients.

Optimally, adjustments in Rapamune dose should be based on more than a single trough level obtained more than 5 days after a previous dosing change.

Patients can be switched from Rapamune oral solution to the tablet formulation on a mg per mg basis. It is recommended that a trough concentration be taken 1 or 2 weeks after switching formulations or tablet strength to confirm that the trough concentration is within the recommended target range.

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

If further dose adjustment(s) are required during maintenance therapy (after discontinuation of ciclosporin), in most patients these adjustments can be based on simple proportion: new Rapamune dose=current dose x (target concentration/current concentration). A loading dose should be considered in addition to a new maintenance dose when it is necessary to considerably increase sirolimus trough concentrations: Rapamune loading dose=3 x (new maintenance dose – current maintenance dose). The maximum Rapamune dose administered on any day should not exceed 40 mg. If an estimated daily dose exceeds 40 mg due to the addition of a loading dose, the loading dose should be administered over 2 days. Sirolimus trough concentrations should be monitored at least 3 to 4 days after a loading dose(s).

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. All sirolimus concentrations reported in this Summary of Product Characteristics were either measured using chromatographic methods or have been converted to chromatographic method equivalents. Adjustments to the targeted range should be made according to the assay being utilised to determine the sirolimus trough concentrations. Since results are assay and laboratory dependent, and the results may change over time, adjustment to the targeted therapeutic range must be made with a detailed knowledge of the site-specific assay used. Physicians should therefore remain continuously informed by responsible representatives for their local laboratory on the performance of the locally used method for concentration determination of sirolimus.

Patients with sporadic lymphangioleiomyomatosis (S-LAM)

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

For patients with S-LAM, the initial Rapamune dose should be 2 mg/day. Sirolimus whole blood trough concentrations should be measured in 10 to 20 days, with dosage adjustment to maintain concentrations between 5 to 15 ng/mL.

In most patients, dose adjustments can be based on simple proportion: new Rapamune dose=current dose x (target concentration/current concentration). Frequent Rapamune dose adjustments based on non-steady-state sirolimus concentrations can lead to overdosing or underdosing because sirolimus has a long half-life. Once Rapamune maintenance dose is adjusted, patients should continue on the new maintenance dose for at least 7 to 14 days before further dosage adjustment with concentration monitoring. Once a stable dose is achieved, therapeutic drug monitoring should be performed at least every 3 months.

Data from controlled studies for treatment of S-LAM longer than one year are currently not available, therefore the benefit of treatment should be reassessed when used long-term.

Special populations

Black population
There is limited information indicating that Black renal transplant recipients (predominantly African-American) require higher doses and trough levels of sirolimus to achieve the same efficacy as observed in non-Black patients. The efficacy and safety data are too limited to allow specific recommendations for use of sirolimus in Black recipients.

Elderly
Clinical studies with Rapamune oral solution did not include a sufficient number of patients above 65 years of age to determine whether they will respond differently than younger patients (see section 5.2).

Renal impairment
No dose adjustment is required (see section 5.2).

Hepatic impairment
The clearance of sirolimus may be reduced in patients with impaired hepatic function (see section 5.2). In patients with severe hepatic impairment, it is recommended that the maintenance dose of Rapamune be reduced by approximately one-half.

It is recommended that sirolimus whole blood trough levels be closely monitored in patients with impaired hepatic function (see *Therapeutic monitoring of the medicinal product and dose adjustment*). It is not necessary to modify the Rapamune loading dose.

In patients with severe hepatic impairment, monitoring should be performed every 5 to 7 days until 3 consecutive trough levels have shown stable concentrations of sirolimus after dose adjustment or after loading dose due to the delay in reaching steady-state because of the prolonged half-life.

Paediatric population
The safety and efficacy of Rapamune in children and adolescents less than 18 years of age have not been established.

Currently available data are described in sections 4.8, 5.1 and 5.2, but no recommendation on a posology can be made.

Method of administration

Rapamune is for oral use only.

To minimise variability, Rapamune should consistently be taken either with or without food.

Grapefruit juice should be avoided (see section 4.5).

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Rapamune oral solution contains soya oil. Patients allergic to peanut or soya must not take this medicine.

4.4 Special warnings and precautions for use

Rapamune has not been adequately studied in renal transplant patients at high immunological risk, therefore use is not recommended in this group of patients (see section 5.1).

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

Hypersensitivity reactions

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

Concomitant therapy

Immunosuppressive agents (Renal transplant patients only)
Sirolimus has been administered concurrently with the following agents in clinical studies: tacrolimus, ciclosporin, azathioprine, mycophenolate mofetil, corticosteroids and cytotoxic antibodies. Sirolimus in combination with other immunosuppressive agents has not been extensively investigated.

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

Patients treated with ciclosporin and Rapamune beyond 3 months had higher serum creatinine levels and lower calculated glomerular filtration rates compared to patients treated with ciclosporin and placebo or azathioprine controls. Patients who were successfully withdrawn from ciclosporin had

lower serum creatinine levels and higher calculated glomerular filtration rates, as well as lower incidence of malignancy, compared to patients remaining on ciclosporin. The continued co-administration of ciclosporin and Rapamune as maintenance therapy cannot be recommended.

Based on information from subsequent clinical studies, the use of Rapamune, mycophenolate mofetil, and corticosteroids, in combination with IL-2 receptor antibody (IL2R Ab) induction, is not recommended in the *de novo* renal transplant setting (see section 5.1).

Periodic quantitative monitoring of urinary protein excretion is recommended. In a study evaluating conversion from calcineurin inhibitors to Rapamune in maintenance renal transplant patients, increased urinary protein excretion was commonly observed at 6 to 24 months after conversion to Rapamune (see section 5.1). New onset nephrosis (nephrotic syndrome) was also reported in 2% of the patients in the study (see section 4.8). Based on information from an open-label randomised study, conversion from the calcineurin inhibitor tacrolimus to Rapamune in maintenance renal transplant patients was associated with an unfavourable safety profile without efficacy benefit and can therefore not be recommended (see section 5.1).

The concomitant use of Rapamune with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA).

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

Cytochrome P450 isozymes and P-glycoprotein
Co-administration of sirolimus with strong inhibitors of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (P-gp) (such as ketoconazole, voriconazole, itraconazole, telithromycin or clarithromycin) may increase sirolimus blood levels and is not recommended.

Co-administration with strong inducers of CYP3A4 and/or P-gp (such as rifampin, rifabutin) is not recommended.

If co-administration of inducers or inhibitors of CYP3A4 and/or P-gp cannot be avoided, it is recommended that sirolimus whole blood trough concentrations and the clinical condition of the patient be monitored while they are concurrently administered with sirolimus and after their discontinuation. Dose adjustments of sirolimus may be required (see sections 4.2 and 4.5).

Angioedema
The concomitant administration of Rapamune and angiotensin-converting enzyme (ACE) inhibitors has resulted in angioneurotic oedema-type reactions. Elevated sirolimus levels, for example due to interaction with strong CYP3A4 inhibitors, (with/without concomitant ACE inhibitors) may also potentiate angioedema (see section 4.5). In some cases, the angioedema has resolved upon discontinuation or dose reduction of Rapamune.

Increased rates of biopsy confirmed acute rejection (BCAR) in renal transplant patients have been observed with concomitant use of sirolimus with ACE inhibitors (see section 5.1). Patients receiving sirolimus should be monitored closely if taking ACE inhibitors concomitantly.

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

Malignancy

Increased susceptibility to infection and the possible development of lymphoma and other malignancies, particularly of the skin, may result from immunosuppression (see section 4.8). As usual for patients with increased risk for skin cancer, exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Infections

Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections, and sepsis.

Among these conditions in renal transplant patients 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 conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms.

Cases of *Pneumocystis carinii* pneumonia have been reported in renal transplant patients not receiving antimicrobial prophylaxis. Therefore, antimicrobial prophylaxis for *Pneumocystis carinii* pneumonia should be administered for the first 12 months following transplantation.

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

Hepatic impairment

In hepatically impaired patients, it is recommended that sirolimus whole blood trough levels be closely monitored. In patients with severe hepatic impairment, reduction in maintenance dose by one half is recommended based on decreased clearance (see sections 4.2 and 5.2). Since half-life is prolonged in these patients, therapeutic monitoring of the medicinal product after a loading dose or a change of dose should be performed for a prolonged period of time until stable concentrations are reached (see sections 4.2 and 5.2).

Lung and liver transplant populations

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

In two clinical studies in *de novo* liver transplant patients, the use of sirolimus plus ciclosporin or tacrolimus was associated with an increase in hepatic artery thrombosis, mostly leading to graft loss or death.

A clinical study in liver transplant patients randomised to conversion from a calcineurin inhibitor (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 rate of death in the sirolimus conversion group was higher than the CNI continuation group, although the rates were not significantly different. 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.

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

Systemic effects

There have been reports of impaired or delayed wound healing in patients receiving Rapamune, including lymphocele in renal transplant patients and wound dehiscence. Patients with a body mass index (BMI) greater than 30 kg/m^2 may be at increased risk of abnormal wound healing based on data from the medical literature.

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

The use of Rapamune was associated with increased serum cholesterol and triglycerides that may require treatment. Patients administered Rapamune should be monitored for hyperlipidaemia using laboratory tests and if hyperlipidaemia is detected, subsequent interventions such as diet, exercise, and lipid-lowering agents should be initiated. The risk/benefit should be considered in patients with established hyperlipidaemia before initiating an immunosuppressive regimen, including Rapamune. Similarly the risk/benefit of continued Rapamune therapy should be re-evaluated in patients with severe refractory hyperlipidaemia.

Ethanol

Rapamune oral solution contains up to 3.17 vol % ethanol (alcohol). A 6 mg loading dose contains up to 150 mg of alcohol which is equivalent to 3.80 mL beer or 1.58 mL wine. This dose could potentially be harmful for those suffering from alcoholism and should be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy.

Maintenance doses of 4 mg or less contain small amounts of ethanol (100 mg or less) that are likely to be too low to be harmful.

4.5 Interaction with other medicinal products and other forms of interaction

Sirolimus is extensively metabolised by the CYP3A4 isozyme in the intestinal wall and liver. Sirolimus is also a substrate for the multidrug efflux pump, P-glycoprotein (P-gp) located in the small intestine. Therefore, absorption and the subsequent elimination of sirolimus may be influenced by substances that affect these proteins. Inhibitors of CYP3A4 (such as ketoconazole, voriconazole, itraconazole, telithromycin, or clarithromycin) decrease the metabolism of sirolimus and increase sirolimus levels. Inducers of CYP3A4 (such as rifampin or rifabutin) increase the metabolism of sirolimus and decrease sirolimus levels. Co-administration of sirolimus with strong inhibitors of CYP3A4 or inducers of CYP3A4 is not recommended (see section 4.4).

Rifampicin (CYP3A4 inducer)

Administration of multiple doses of rifampicin decreased sirolimus whole blood concentrations following a single 10 mg dose of Rapamune oral solution. Rifampicin increased the clearance of sirolimus by approximately 5.5-fold and decreased AUC and C_{max} by approximately 82% and 71%, respectively. Co-administration of sirolimus and rifampicin is not recommended (see section 4.4).

Ketoconazole (CYP3A4 inhibitor)

Multiple-dose ketoconazole administration significantly affected the rate and extent of absorption and sirolimus exposure from Rapamune oral solution as reflected by increases in sirolimus C_{max}, t_{max}, and AUC of 4.4-fold, 1.4-fold, and 10.9-fold, respectively. Co-administration of sirolimus and ketoconazole is not recommended (see section 4.4).

Voriconazole (CYP3A4 inhibitor)

Co-administration of sirolimus (2 mg single dose) with multiple-dose administration of oral voriconazole (400 mg every 12 hours for 1 day, then 100 mg every 12 hours for 8 days) in healthy subjects has been reported to increase sirolimus C_{max} and AUC by an average of 7-fold and 11-fold respectively. Co-administration of sirolimus and voriconazole is not recommended (see section 4.4).

Diltiazem (CYP3A4 inhibitor)

The simultaneous oral administration of 10 mg of Rapamune oral solution and 120 mg of diltiazem significantly affected the bioavailability of sirolimus. Sirolimus C_{max}, t_{max}, and AUC were increased 1.4-fold, 1.3-fold, and 1.6-fold, respectively. Sirolimus did not affect the pharmacokinetics of either diltiazem or its metabolites desacetyldiltiazem and desmethyldiltiazem. If diltiazem is administered, sirolimus blood levels should be monitored and a dose adjustment may be necessary.

Verapamil (CYP3A4 inhibitor)

Multiple-dose administration of verapamil and sirolimus oral solution significantly affected the rate and extent of absorption of both medicinal products. 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%. Sirolimus levels should be monitored, and appropriate dose reductions of both medicinal products should be considered.

Erythromycin (CYP3A4 inhibitor)

Multiple-dose administration of erythromycin and sirolimus oral solution significantly increased the rate and extent of absorption of both medicinal products. 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. Sirolimus levels should be monitored and appropriate dose reductions of both medicinal products should be considered.

Ciclosporin (CYP3A4 substrate)

The rate and extent of sirolimus absorption was significantly increased by ciclosporin A (CsA). Sirolimus administered concomitantly (5 mg), and at 2 hours (5 mg) and 4 hours (10 mg) after CsA (300 mg), resulted in increased sirolimus AUC by approximately 183%, 141% and 80%, respectively. The effect of CsA was also reflected by increases in sirolimus C_{max} and t_{max}. When given 2 hours before CsA administration, sirolimus C_{max} and AUC were not affected. Single-dose sirolimus did not affect the pharmacokinetics of ciclosporin (microemulsion) in healthy volunteers when administered simultaneously or 4 hours apart. It is recommended that Rapamune be administered 4 hours after ciclosporin (microemulsion).

Cannabidiol (P-gp inhibitor)

There have been reports of increased blood levels of sirolimus during concomitant use with cannabidiol. Co-administration of cannabidiol with another orally administered mTOR inhibitor in a healthy volunteer study led to an increase in exposure to the mTOR inhibitor of approximately 2.5-fold for both C_{max} and AUC, due to inhibition of intestinal P-gp efflux by cannabidiol. Caution should be used when cannabidiol and Rapamune are co-administered, closely monitoring for side effects. Monitor sirolimus blood levels and adjust the dose as needed (see sections 4.2 and 4.4).

Oral contraceptives

No clinically significant pharmacokinetic interaction was observed between Rapamune oral solution and 0.3 mg norgestrel/0.03 mg ethinyl estradiol. Although the results of a single-dose interaction study with an oral contraceptive suggest the lack of a pharmacokinetic interaction, the results cannot exclude

the possibility of changes in the pharmacokinetics that might affect the efficacy of the oral contraceptive during long-term treatment with Rapamune.

Other possible interactions

Inhibitors of CYP3A4 may decrease the metabolism of sirolimus and increase sirolimus blood levels. Such inhibitors include certain antifungals (e.g. clotrimazole, fluconazole, itraconazole, voriconazole), certain antibiotics (e.g. troleandomycin, telithromycin, clarithromycin), certain protease inhibitors (e.g. ritonavir, indinavir, boceprevir, telaprevir), nicardipine, bromocriptine, cimetidine, danazol and letermovir.

Inducers of CYP3A4 may increase the metabolism of sirolimus and decrease sirolimus blood levels (e.g. St. John's Wort (*Hypericum perforatum*), anticonvulsants: carbamazepine, phenobarbital, phenytoin).

Although sirolimus inhibits human liver microsomal cytochrome P_{450} CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 *in vitro*, the active substance is not expected to inhibit the activity of these isozymes *in vivo* since the sirolimus concentrations necessary to produce inhibition are much higher than those observed in patients receiving therapeutic doses of Rapamune. Inhibitors of P-gp may decrease the efflux of sirolimus from intestinal cells and increase sirolimus levels.

Grapefruit juice affects CYP3A4-mediated metabolism, and should therefore be avoided.

Pharmacokinetic interactions may be observed with gastrointestinal prokinetic agents, such as cisapride and metoclopramide.

No clinically significant pharmacokinetic interaction was observed between sirolimus and any of the following substances: acyclovir, atorvastatin, digoxin, glibenclamide, methylprednisolone, nifedipine, prednisolone, and trimethoprim/sulfamethoxazole.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Effective contraception must be used during Rapamune therapy and for 12 weeks after Rapamune has been stopped (see section 4.5).

Pregnancy

There are no or limited amount of data from the use of sirolimus in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Rapamune should not be used during pregnancy unless clearly necessary. Effective contraception must be used during Rapamune therapy and for 12 weeks after Rapamune has been stopped.

Breast-feeding

Following administration of radiolabelled sirolimus, radioactivity is excreted in the milk of lactating rats. It is unknown whether sirolimus is excreted in human milk. Because of the potential for adverse reactions in breast-fed infants from sirolimus, breast-feeding should be discontinued during treatment with Rapamune.

Fertility

Impairments of sperm parameters have been observed among some patients treated with Rapamune. These effects have been reversible upon discontinuation of Rapamune in most cases (see section 5.3).

4.7 Effects on ability to drive and use machines

Rapamune has no known influence on the 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 most commonly reported adverse reactions (occurring in >10% of patients) are thrombocytopaenia, anaemia, pyrexia, hypertension, hypokalaemia, hypophosphataemia, urinary tract infection, hypercholesterolaemia, hyperglycaemia, hypertriglyceridaemia, abdominal pain, lymphocoele, peripheral oedema, arthralgia, acne, diarrhoea, pain, constipation, nausea, headache, increased blood creatinine, and increased blood lactate dehydrogenase (LDH).

The incidence of any adverse reaction(s) may increase as the trough sirolimus level increases.

The following list of adverse reactions is based on experience from clinical studies and on postmarketing experience.

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Most patients were on immunosuppressive regimens, which included Rapamune in combination with other immunosuppressive agents.

System organ class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Frequency not known (cannot be estimated from available data)**
Infections and infestations	Pneumonia; Fungal infection; Viral infection; Bacterial infection; Herpes simplex infection; Urinary tract infection	Sepsis; Pyelonephritis; Cytomegalo-virus infection; Herpes zoster caused by the varicella zoster virus	*Clostridium difficile* colitis; Mycobacterial infection (including tuberculosis); Epstein-Barr virus infection		

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Frequency not known (cannot be estimated from available data)
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Non-melanoma skin cancer*	Lymphoma*; Malignant melanoma*; Post transplant lympho-proliferative disorder		Neuroendo crine carcinoma of the skin*
Blood and lymphatic system disorders	Thrombo-cytopaenia; Anaemia; Leucopenia	Haemolytic uraemic syndrome; Neutropaenia	Pancytopaenia; Thrombotic thrombo-cytopaenic purpura		
Immune system disorders		Hyper-sensitivity (including angioedema, anaphylactic reaction, and anaphylactoid reaction)			
Metabolism and nutrition disorders	Hypokalaemia; Hypophos-phataemia; Hyperlipidaemia (including hypercholesterol-aemia); Hyperglycaemia; Hyper-triglyceridaemia; Diabetes mellitus				
Nervous system disorders	Headache				Posterior reversible encephalo-pathy syndrome
Cardiac disorders	Tachycardia	Pericardial effusion			
Vascular disorders	Hypertension; Lymphocele	Venous thrombosis (including deep vein thrombosis)	Lymphoedema		
Respiratory, thoracic and mediastinal disorders		Pulmonary embolism; Pneumonitis*; Pleural effusion; Epistaxis	Pulmonary haemorrhage	Alveolar proteinosis	

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Frequency not known (cannot be estimated from available data)
Gastrointestinal disorders	Abdominal pain; Constipation; Diarrhoea; Nausea	Pancreatitis; Stomatitis; Ascites			
Hepatobiliary disorders	Liver function test abnormal (including alanine aminotransferase increased and aspartate amino-transferase increased)		Hepatic failure*		
Skin and subcutaneous tissue disorders	Rash; Acne		Dermatitis exfoliative	Hypersen-sitivity vasculitis	
Musculoskeletal and connective tissue disorders	Arthralgia	Osteonecrosis			
Renal and urinary disorders	Proteinuria		Nephrotic syndrome (see section 4.4); Focal segmental glomerulo-sclerosis*		
Reproductive system and breast disorders	Menstrual disorder (including amenorrhoea and menorrhagia)	Ovarian cyst			
General disorders and administration site conditions	Oedema; Oedema peripheral; Pyrexia; Pain; Impaired healing*				
Investigations	Blood lactate dehydrogenase increased; Blood creatinine increased				

*See section below.

Description of selected adverse reactions

Immunosuppression increases the susceptibility to the development of lymphoma and other malignancies, particularly of the skin (see section 4.4).

Cases of BK virus-associated nephropathy, as well as cases of JC virus-associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including Rapamune.

Hepatoxicity has been reported. The risk may increase as the trough sirolimus level increases. Rare reports of fatal hepatic necrosis have been reported with elevated trough sirolimus levels.

Cases of interstitial lung disease (including pneumonitis and infrequently bronchiolitis obliterans organising pneumonia (BOOP) and pulmonary fibrosis), some fatal, with no identified infectious aetiology have occurred in patients receiving immunosuppressive regimens including Rapamune. In some cases, the interstitial lung disease has resolved upon discontinuation or dose reduction of Rapamune. The risk may be increased as the trough sirolimus level increases.

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

Impairments of sperm parameters have been observed among some patients treated with Rapamune. These effects have been reversible upon discontinuation of Rapamune in most cases (see section 5.3).

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

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

Focal segmental glomerulosclerosis has been reported.

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

In a study evaluating the safety and efficacy of conversion from calcineurin inhibitors to sirolimus (target levels of 12 - 20 ng/mL 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 (see section 5.1). There was a higher rate of serious adverse events, including pneumonia, acute rejection, graft loss and death, in this sirolimus treatment arm (n=60, median time post-transplant 36 months).

Ovarian cysts and menstrual disorders (including amenorrhoea and menorrhagia) have been reported. Patients with symptomatic ovarian cysts should be referred for further evaluation. The incidence of ovarian cysts may be higher in premenopausal females compared to postmenopausal females. In some cases, ovarian cysts and these menstrual disorders have resolved upon discontinuation of Rapamune.

Paediatric population

Controlled clinical studies with posology comparable to that currently indicated for the use of Rapamune in adults have not been conducted in children or adolescents below 18 years of age.

Safety was assessed in a controlled clinical study enrolling renal transplant patients below 18 years of age considered of 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). The use of Rapamune in combination with calcineurin inhibitors and corticosteroids was associated with an increased risk of deterioration of renal function, serum lipid abnormalities (including, but not limited to, increased serum triglycerides and cholesterol), and urinary tract infections. The treatment

regimen studied (continuous use of Rapamune in combination with calcineurin inhibitor) is not indicated for adult or paediatric patients (see section 4.1).

In another study enrolling renal transplant patients 20 years of age and below that was intended to assess the safety of progressive corticosteroid withdrawal (beginning at six months post-transplantation) from an immunosuppressive regimen initiated at transplantation that included full-dose immunosuppression with both Rapamune and a calcineurin inhibitor in combination with basiliximab induction, of the 274 patients enrolled, 19 (6.9%) were reported to have developed post-transplant lymphoproliferative disorder (PTLD). Among 89 patients known to be Epstein-Barr virus (EBV) seronegative prior to transplantation, 13 (15.6%) were reported to have developed PTLD. All patients who developed PTLD were aged below 18 years.

There is insufficient experience to recommend the use of Rapamune in children and adolescents (see section 4.2).

Undesirable effects observed with patients with S-LAM

Safety was assessed in a controlled study involving 89 patients with LAM, of which 81 patients had S-LAM and 42 of whom were treated with Rapamune (see section 5.1). The adverse drug reactions observed in patients with S-LAM were consistent with the known safety profile of the product for the indication prophylaxis of organ rejection in renal transplantation with the addition of weight decreased, which was reported in the study at a greater incidence with Rapamune when compared to that observed with placebo (common, 9.5% vs. common, 2.6%).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

At present, there is minimal experience with overdose. One patient experienced an episode of atrial fibrillation after ingestion of 150 mg of Rapamune. In general, the adverse effects of overdose are consistent with those listed in section 4.8. General supportive measures should be initiated in all cases of overdose. Based on the poor aqueous solubility and high erythrocyte and plasma protein binding of Rapamune, it is anticipated that Rapamune will not be dialysable to any significant extent.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, ATC code: L04AH01.

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

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

LAM involves lung tissue infiltration with smooth muscle-like cells that harbour inactivating mutations of the tuberous sclerosis complex (TSC) gene (LAM cells). Loss of TSC gene function activates the mTOR signaling pathway, resulting in cellular proliferation and release of lymphangiogenic growth factors. Sirolimus inhibits the activated mTOR pathway and thus the proliferation of LAM cells.

Clinical studies

Prophylaxis of Organ Rejection

Patients at low to moderate immunological risk were studied in the phase 3 ciclosporin elimination-Rapamune maintenance study, which included patients receiving a renal allograft from a cadaveric or living donor. In addition, re-transplant recipients whose previous grafts survived for at least 6 months after transplantation were included. Ciclosporin was not withdrawn in patients experiencing Banff Grade 3 acute rejection episodes, who were dialysis-dependent, who had a serum creatinine higher than 400 µmol/L, or who had inadequate renal function to support ciclosporin withdrawal. Patients at high immunological risk of graft loss were not studied in sufficient number in the ciclosporin elimination-Rapamune maintenance studies and are not recommended for this treatment regimen.

At 12, 24 and 36 months, graft and patient survival were similar for both groups. At 48 months, there was a statistically significant difference in graft survival in favour of the Rapamune following ciclosporin elimination group compared to the Rapamune with ciclosporin therapy group (including and excluding loss to follow-up). There was a significantly higher rate of first biopsy-proven rejection in the ciclosporin elimination group compared to the ciclosporin maintenance group during the period post-randomisation to 12 months (9.8% vs. 4.2%, respectively). Thereafter, the difference between the two groups was not significant.

The mean calculated glomerular filtration rate (GFR) at 12, 24, 36, 48 and 60 months was significantly higher for patients receiving Rapamune following ciclosporin elimination than for those in the Rapamune with ciclosporin therapy group. Based upon the analysis of data from 36 months and beyond, which showed a growing difference in graft survival and renal function, as well as significantly lower blood pressure in the ciclosporin elimination group, it was decided to discontinue subjects from the Rapamune with ciclosporin group. By 60 months, the incidence of non-skin malignancies was significantly higher in the cohort who continued ciclosporin as compared with the cohort who had ciclosporin withdrawn (8.4% vs. 3.8%, respectively). For skin carcinoma, the median time to first occurrence was significantly delayed.

The safety and efficacy of conversion from calcineurin inhibitors to Rapamune in maintenance renal transplant patients (6-120 months after transplantation) was assessed in a randomised, multicentre, controlled trial, stratified by calculated GFR at baseline (20-40 mL/min vs. above 40 mL/min). Concomitant immunosuppressive agents included mycophenolate mofetil, azathioprine, and corticosteroids. Enrollment in the patient stratum with baseline calculated GFR below 40 mL/min was discontinued due to an imbalance in safety events (see section 4.8).

In the patient stratum with baseline calculated GFR above 40 mL/min, renal function was not improved overall. The rates of acute rejection, graft loss, and death were similar at 1 and 2 years. Treatment emergent adverse events occurred more frequently during the first 6 months after Rapamune conversion. In the stratum with baseline calculated GFR above 40 mL/min, the mean and median urinary protein to creatinine ratios were significantly higher in the Rapamune conversion group as compared to those of the calcineurin inhibitors continuation group at 24 months (see section 4.4). New onset nephrosis (nephrotic syndrome) was also reported (see section 4.8).

At 2 years, the rate of non-melanoma skin malignancies was significantly lower in the Rapamune conversion group as compared to the calcineurin inhibitors continuation group (1.8% and 6.9%). In a subset of the study patients with a baseline GFR above 40 mL/min and normal urinary protein excretion, calculated GFR was higher at 1 and 2 years in patients converted to Rapamune than for the

corresponding subset of calcineurin inhibitor continuation patients. The rates of acute rejection, graft loss, and death were similar, but urinary protein excretion was increased in the Rapamune treatment arm of this subset.

In an open-label, randomised, comparative, multi-centre 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% vs. 91.1%, p=0.002*) and more discontinuations from the treatment due to adverse events (26.7% vs. 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 randomisation, a fasting glucose ≥126 mg/dL or a non-fasting glucose ≥200 mg/dL after randomisation (18.3% vs. 5.6%, p=0.025*). A lower incidence of squamous cell carcinoma of the skin was observed in the sirolimus group (0% vs. 4.9%). *Note: p-values not controlled for multiple testing.

In two multi-centre clinical studies, *de novo* renal transplant patients treated with sirolimus, mycophenolate mofetil (MMF), corticosteroids, 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, corticosteroids, and an IL-2 receptor antagonist (see section 4.4). Renal function was not better in the treatment arms with *de novo* sirolimus without a calcineurin inhibitor. An abbreviated dosing schedule of daclizumab was used in one of the studies.

In a randomised, comparative evaluation of ramipril versus placebo for the prevention of proteinuria in kidney transplant patients converted from calcineurin inhibitors to sirolimus, a difference in the number of patients with BCAR through 52 weeks was observed [13 (9.5%) vs. 5 (3.2%), respectively; p=0.073]. Patients initiated on ramipril 10 mg had a higher rate of BCAR (15%) compared to patients initiated on ramipril 5 mg (5%). Most rejections occurred within the first six months following conversion and were mild in severity; no graft losses were reported during the study (see section 4.4).

Sporadic Lymphangioleiomyomatosis (S-LAM) Patients

The safety and efficacy of Rapamune for treatment of S-LAM were assessed in a randomised, double-blind, multicentre, controlled trial. This study compared Rapamune (dose adjusted to 5-15 ng/mL) with placebo for a 12-month treatment period, followed by a 12-month observation period in patients with TSC-LAM or S-LAM. Eighty-nine (89) patients were enrolled at 13 study sites in the United States, Canada, and Japan of which 81 patients had S-LAM; of these patients with S-LAM, 39 were randomised to receive placebo and 42 to receive Rapamune. The key inclusion criteria was post-bronchodilator forced expiratory volume in 1 second (FEV1) ≤70% of predicted during the baseline visit. In patients with S-LAM, enrolled patients had moderately advanced lung disease, with baseline FEV1 of 49.2±13.6% (mean ±SD) of the predicted value. The primary endpoint was the difference between the groups in the rate of change (slope) in FEV1. During the treatment period in patients with S-LAM, the mean ±SE FEV1 slope was -12±2 mL per month in the placebo group and 0.3±2 mL per month in the Rapamune group (p<0.001). The absolute between-group difference in the mean change in FEV1 during the treatment period was 152 mL, or approximately 11% of the mean FEV1 at enrollment.

As compared with the placebo group, the sirolimus group had improvement from baseline to 12 months in measures of forced vital capacity (-12±3 vs. 7±3 mL per month, respectively, p<0.001), serum vascular endothelial growth factor D (VEGF-D; -8.6±15.2 vs. -85.3±14.2 pg/mL per month, respectively, p<0.001), and quality of life (Visual Analogue Scale – Quality of Life [VAS-QOL] score: -0.3±0.2 vs. 0.4±0.2 per month, respectively, p=0.022) and functional performance (-0.009±0.005 vs. 0.004±0.004 per month, respectively, p=0.044) in patients with S-LAM. There was

no significant between-group difference in this interval in the change in functional residual capacity, 6-minute walk distance, diffusing capacity of the lung for carbon monoxide, or general well-being score in patients with S-LAM.

Paediatric population

Rapamune was assessed in a 36-month controlled clinical study enrolling renal transplant patients below 18 years of age considered at high-immunologic risk, defined as having a history of one or more acute allograft rejection episodes and/or the presence of chronic allograft nephropathy on a renal biopsy. Subjects were to receive Rapamune (sirolimus target concentrations of 5 to 15 ng/mL) in combination with a calcineurin inhibitor and corticosteroids or to receive calcineurin-inhibitor-based immunosuppression without Rapamune. The Rapamune group failed to demonstrate superiority to the control group in terms of the first occurrence of biopsy confirmed acute rejection, graft loss, or death. One death occurred in each group. The use of Rapamune in combination with calcineurin inhibitors and corticosteroids was associated with an increased risk of deterioration of renal function, serum lipid abnormalities (including, but not limited to, increased serum triglycerides and total cholesterol), and urinary tract infections (see section 4.8).

An unacceptably high frequency of PTLD was seen in a paediatric clinical transplant study when full-dose Rapamune was administered to children and adolescents in addition to full-dose calcineurin inhibitors with basiliximab and corticosteroids (see section 4.8).

In a retrospective review of hepatic veno-occlusive disease (VOD) in patients who underwent myeloablative stem cell transplantation using cyclosphophamide and total body irradiation, an increased incidence of hepatic VOD was observed in patients treated with Rapamune, especially with concomitant use of methotrexate.

5.2 Pharmacokinetic properties

Oral solution

Following administration of the Rapamune oral solution, sirolimus is rapidly absorbed, with a time to peak concentration of 1 hour in healthy subjects receiving single doses and 2 hours in patients with stable renal allografts receiving multiple doses. The systemic availability of sirolimus in combination with simultaneously administered ciclosporin (Sandimune) is approximately 14%. Upon repeated administration, the average blood concentration of sirolimus is increased approximately 3-fold. The terminal half-life in stable renal transplant patients after multiple oral doses was 62±16h. The effective half-life, however, is shorter and mean steady-state concentrations were achieved after 5 to 7 days. The blood to plasma ratio (B/P) of 36 indicates that sirolimus is extensively partitioned into formed blood elements.

Sirolimus is a substrate for both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein. Sirolimus is extensively metabolised by O-demethylation and/or hydroxylation. Seven major metabolites, including hydroxyl, demethyl, and hydroxydemethyl, are identifiable in whole blood. Sirolimus is the major component in human whole blood and contributes to greater than 90% of the immunosuppressive activity. After a single dose of [^{14}C] sirolimus in healthy volunteers, the majority (91.1%) of radioactivity was recovered from the faeces, and only a minor amount (2.2%) was excreted in urine.

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

In paediatric patients on dialysis (30% to 50% reduction in glomerular filtration rate) within age ranges of 5 to 11 years and 12 to 18 years, the mean weight-normalised CL/F was larger for younger

paediatric patients (580 mL/h/kg) than for older paediatric patients (450 mL/h/kg) as compared with adults (287 mL/h/kg). There was a large variability for individuals within the age groups.

Sirolimus concentrations were measured in concentration-controlled studies of paediatric renal-transplant patients who were also receiving ciclosporin and corticosteroids. The target for trough concentrations was 10-20 ng/mL. At steady-state, 8 children aged 6-11 years received mean ± SD doses of 1.75 ± 0.71 mg/day (0.064 ± 0.018 mg/kg, 1.65 ± 0.43 mg/m^2) while 14 adolescents aged 12-18 years received mean ± SD doses of 2.79 ± 1.25 mg/day (0.053 ± 0.0150 mg/kg, 1.86 ± 0.61 mg/m^2). The younger children had a higher weight-normalized Cl/F (214 mL/h/kg) compared with the adolescents (136 mL/h/kg). These data indicate that younger children might require higher bodyweight-adjusted doses than adolescents and adults to achieve similar target concentrations. However, the development of such special dosing recommendations for children requires more data to be definitely confirmed.

In mild and moderate hepatically impaired patients (Child-Pugh classification A or B), mean values for sirolimus AUC and $t_{1/2}$ were increased 61% and 43%, respectively, and CL/F was decreased 33% compared to normal healthy subjects. In severe hepatically impaired patients (Child-Pugh classification C), mean values for sirolimus AUC and $t_{1/2}$ were increased 210% and 170% respectively, and CL/F was decreased by 67% compared to normal healthy subjects. The longer half-lives observed in hepatically impaired patients delay reaching steady state.

Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetics of sirolimus were similar in various populations with renal function ranging from normal to absent (dialysis patients).

Lymphangioleiomyomatosis (LAM)

In a clinical trial of patients with LAM, the median whole blood sirolimus trough concentration after 3 weeks of receiving sirolimus tablets at a dose of 2 mg/day was 6.8 ng/mL (interquartile range 4.6 to 9.0 ng/mL; n=37). With concentration-control (target concentrations 5 to 15 ng/mL), the median sirolimus concentration at the end of 12 months of treatment was 6.8 ng/mL (interquartile range 5.9 to 8.9 ng/mL; n=37).

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows: pancreatic islet cell vacuolation, testicular tubular degeneration, gastrointestinal ulceration, bone fractures and calluses, hepatic haematopoiesis, and pulmonary phospholipidosis.

Sirolimus was not mutagenic in the *in vitro* bacterial reverse mutation assays, the Chinese Hamster Ovary cell chromosomal aberration assay, the mouse lymphoma cell forward mutation assay, or the *in vivo* mouse micronucleus assay.

Carcinogenicity studies conducted in mouse and rat showed increased incidences of lymphomas (male and female mouse), hepatocellular adenoma and carcinoma (male mouse) and granulocytic leukaemia (female mouse). It is known that malignancies (lymphoma) secondary to the chronic use of immunosuppressive agents can occur and have been reported in patients in rare instances. In mouse, chronic ulcerative skin lesions were increased. The changes may be related to chronic immunosuppression. In rat, testicular interstitial cell adenomas were likely indicative of a species-dependent response to lutenising hormone levels and are usually considered of limited clinical relevance.

In reproduction toxicity studies decreased fertility in male rats was observed. Partly reversible reductions in sperm counts were reported in a 13-week rat study. Reductions in testicular weights and/or histological lesions (e.g. tubular atrophy and tubular giant cells) were observed in rats and in a

monkey study. In rats, sirolimus caused embryo/foetotoxicity that was manifested as mortality and reduced foetal weights (with associated delays in skeletal ossification) (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 80 (E433)

Phosal 50 PG (phosphatidylcholine, propylene glycol [E1520], mono-and diglycerides, ethanol, soya fatty acids and ascorbyl palmitate).

6.2 Incompatibilities

Rapamune must not be diluted in grapefruit juice or any other liquid other than water or orange juice (see section 6.6).

Rapamune oral solution contains polysorbate-80, which is known to increase the rate of di-(2-ethylhexyl)phthalate (DEHP) extraction from polyvinyl chloride (PVC). It is important to follow the instructions to drink Rapamune oral solution at once when a plastic container is used for the dilution and/or administration (see section 6.6).

6.3 Shelf life

2 years.

30 days for opened bottle.

24 hours in the dosing syringe (at room temperature, but not to exceed 25°C).

After dilution (see section 6.6), the preparation should be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Store in the original bottle in order to protect from light.

If necessary, the patient may store the bottles at room temperatures up to 25°C for a short period of time (24 hours).

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Each pack contains: one bottle (amber glass) containing 60 mL of Rapamune solution, one syringe adapter, 30 dosing syringes (amber polypropylene) and one syringe carry case.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Instructions for use and handling:

The dosing syringe should be used to withdraw the prescribed amount of Rapamune from the bottle. Empty the correct amount of Rapamune from the syringe into only a glass or plastic container with at least 60 mL of water or orange juice. No other liquids, including grapefruit juice, should be used for dilution. Stir vigorously and drink at once. Refill the container with an additional volume (minimum of 120 mL) of water or orange juice, stir vigorously, and drink at once.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/171/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 March 2001
Date of latest renewal: 13 March 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Rapamune 0.5 mg coated tablets
Rapamune 1 mg coated tablets
Rapamune 2 mg coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rapamune 0.5 mg coated tablets
Each coated tablet contains 0.5 mg sirolimus.

Rapamune 1 mg coated tablets
Each coated tablet contains 1 mg sirolimus.

Rapamune 2 mg coated tablets
Each coated tablet contains 2 mg sirolimus.

Excipients with known effect

Rapamune 0.5 mg coated tablets
Each tablet contains 86.4 mg of lactose monohydrate and 215.7 mg of sucrose.

Rapamune 1 mg coated tablets
Each tablet contains 86.4 mg of lactose monohydrate and 215.8 mg of sucrose.

Rapamune 2 mg coated tablets
Each tablet contains 86.4 mg of lactose monohydrate and 214.4 mg of sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablet (tablet).

Rapamune 0.5 mg coated tablets
Tan-coloured, triangular-shaped, coated tablet marked “RAPAMUNE 0.5 mg” on one side.

Rapamune 1 mg coated tablets
White-coloured, triangular-shaped, coated tablet marked “RAPAMUNE 1 mg” on one side.

Rapamune 2 mg coated tablets
Yellow to beige-coloured, triangular-shaped, coated tablet marked “RAPAMUNE 2 mg” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rapamune is indicated for the prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant. It is recommended that Rapamune be used initially in combination with ciclosporin microemulsion and corticosteroids for 2 to 3 months. Rapamune may be continued as maintenance therapy with corticosteroids only if ciclosporin microemulsion can be progressively discontinued (see sections 4.2 and 5.1).

Rapamune is indicated for the treatment of patients with sporadic lymphangioleiomyomatosis with moderate lung disease or declining lung function (see sections 4.2 and 5.1).

4.2 Posology and method of administration

Posology

Prophylaxis of organ rejection

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

Initial therapy (2 to 3 months post-transplantation)
The usual dose regimen for Rapamune is a 6 mg single oral loading dose, administered as soon as possible after transplantation, followed by 2 mg once daily until results of therapeutic monitoring of the medicinal product are available (see *Therapeutic monitoring of the medicinal product and dose adjustment*). The Rapamune dose should then be individualised to obtain whole blood trough levels of 4 to 12 ng/mL (chromatographic assay). Rapamune therapy should be optimised with a tapering regimen of steroids and ciclosporin microemulsion. Suggested ciclosporin trough concentration ranges for the first 2-3 months after transplantation are 150-400 ng/mL (monoclonal assay or equivalent technique) (see section 4.5*)*.

To minimise variability, Rapamune should be taken at the same time in relation to ciclosporin, 4 hours after the ciclosporin dose, and consistently either with or without food (see section 5.2).

Maintenance therapy
Ciclosporin should be progressively discontinued over 4 to 8 weeks, and the Rapamune dose should be adjusted to obtain whole blood trough levels of 12 to 20 ng/mL (chromatographic assay; see *Therapeutic monitoring of the medicinal product and dose adjustment*). Rapamune should be given with corticosteroids. In patients for whom ciclosporin withdrawal is either unsuccessful or cannot be attempted, the combination of ciclosporin and Rapamune should not be maintained for more than 3 months post-transplantation. In such patients, when clinically appropriate, Rapamune should be discontinued and an alternative immunosuppressive regimen instituted.

Therapeutic monitoring of the medicinal product and dose adjustment
Whole blood sirolimus levels should be closely monitored in the following populations*:*

(1) in patients with hepatic impairment
(2) when inducers or inhibitors of CYP3A4 and/or P-glycoprotein (P-gp) are concurrently administered and after their discontinuation (see section 4.5) and/or
(3) if ciclosporin dosing is markedly reduced or discontinued, as these populations are most likely to have special dosing requirements.

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

Most patients who received 2 mg of Rapamune 4 hours after ciclosporin had whole blood trough concentrations of sirolimus within the 4 to 12 ng/mL target range (expressed as chromatographic assay values). Optimal therapy requires therapeutic concentration monitoring of the medicinal product in all patients.

Optimally, adjustments in Rapamune dose should be based on more than a single trough level obtained more than 5 days after a previous dosing change.

Patients can be switched from Rapamune oral solution to the tablet formulation on a mg per mg basis. It is recommended that a trough concentration be taken 1 or 2 weeks after switching formulations or tablet strength to confirm that the trough concentration is within the recommended target range.

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

If further dose adjustment(s) are required during maintenance therapy (after discontinuation of ciclosporin), in most patients these adjustments can be based on simple proportion: new Rapamune dose=current dose x (target concentration/current concentration). A loading dose should be considered in addition to a new maintenance dose when it is necessary to considerably increase sirolimus trough concentrations: Rapamune loading dose=3 x (new maintenance dose – current maintenance dose). The maximum Rapamune dose administered on any day should not exceed 40 mg. If an estimated daily dose exceeds 40 mg due to the addition of a loading dose, the loading dose should be administered over 2 days. Sirolimus trough concentrations should be monitored at least 3 to 4 days after a loading dose(s).

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. All sirolimus concentrations reported in this Summary of Product Characteristics were either measured using chromatographic methods or have been converted to chromatographic method equivalents. Adjustments to the targeted range should be made according to the assay being utilised to determine the sirolimus trough concentrations. Since results are assay and laboratory dependent, and the results may change over time, adjustment to the targeted therapeutic range must be made with a detailed knowledge of the site-specific assay used. Physicians should therefore remain continuously informed by responsible representatives for their local laboratory on the performance of the locally used method for concentration determination of sirolimus.

Patients with sporadic lymphangioleiomyomatosis (S-LAM)

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

For patients with S-LAM, the initial Rapamune dose should be 2 mg/day. Sirolimus whole blood trough concentrations should be measured in 10 to 20 days, with dosage adjustment to maintain concentrations between 5 to 15 ng/mL.

In most patients, dose adjustments can be based on simple proportion: new Rapamune dose=current dose x (target concentration/current concentration). Frequent Rapamune dose adjustments based on non-steady-state sirolimus concentrations can lead to overdosing or underdosing because sirolimus has a long half-life. Once Rapamune maintenance dose is adjusted, patients should continue on the new maintenance dose for at least 7 to 14 days before further dosage adjustment with concentration monitoring. Once a stable dose is achieved, therapeutic drug monitoring should be performed at least every 3 months.

Data from controlled studies for treatment of S-LAM longer than one year are currently not available, therefore the benefit of treatment should be reassessed when used long-term.

Special populations

Black population
There is limited information indicating that Black renal transplant recipients (predominantly African-American) require higher doses and trough levels of sirolimus to achieve the same efficacy as observed in non-Black patients. The efficacy and safety data are too limited to allow specific recommendations for use of sirolimus in Black recipients.

Elderly
Clinical studies with Rapamune oral solution did not include a sufficient number of patients above 65 years of age to determine whether they will respond differently than younger patients (see section 5.2).

Renal impairment
No dose adjustment is required (see section 5.2).

Hepatic impairment
The clearance of sirolimus may be reduced in patients with impaired hepatic function (see section 5.2). In patients with severe hepatic impairment, it is recommended that the maintenance dose of Rapamune be reduced by approximately one-half.

It is recommended that sirolimus whole blood trough levels be closely monitored in patients with impaired hepatic function (see *Therapeutic monitoring of the medicinal product and dose adjustment*). It is not necessary to modify the Rapamune loading dose.

In patients with severe hepatic impairment, monitoring should be performed every 5 to 7 days until 3 consecutive trough levels have shown stable concentrations of sirolimus after dose adjustment or after loading dose due to the delay in reaching steady-state because of the prolonged half-life.

Paediatric population
The safety and efficacy of Rapamune in children and adolescents less than 18 years of age have not been established.

Currently available data are described in sections 4.8, 5.1 and 5.2, but no recommendation on a posology can be made.

Method of administration

Rapamune is for oral use only.

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

To minimise variability, Rapamune should consistently be taken either with or without food.

Grapefruit juice should be avoided (see section 4.5).

Multiples of 0.5 mg tablets should not be used as a substitute for the 1 mg tablet or for other strengths (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Rapamune has not been adequately studied in renal transplant patients at high immunological risk, therefore use is not recommended in this group of patients (see section 5.1).

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

Hypersensitivity reactions

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

Concomitant therapy

Immunosuppressive agents (Renal transplant patients only)
Sirolimus has been administered concurrently with the following agents in clinical studies: tacrolimus, ciclosporin, azathioprine, mycophenolate mofetil, corticosteroids and cytotoxic antibodies. Sirolimus in combination with other immunosuppressive agents has not been extensively investigated.

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

Patients treated with ciclosporin and Rapamune beyond 3 months had higher serum creatinine levels and lower calculated glomerular filtration rates compared to patients treated with ciclosporin and placebo or azathioprine controls. Patients who were successfully withdrawn from ciclosporin had lower serum creatinine levels and higher calculated glomerular filtration rates, as well as lower incidence of malignancy, compared to patients remaining on ciclosporin. The continued co-administration of ciclosporin and Rapamune as maintenance therapy cannot be recommended.

Based on information from subsequent clinical studies, the use of Rapamune, mycophenolate mofetil, and corticosteroids, in combination with IL-2 receptor antibody (IL2R Ab) induction, is not recommended in the *de novo* renal transplant setting (see section 5.1).

Periodic quantitative monitoring of urinary protein excretion is recommended. In a study evaluating conversion from calcineurin inhibitors to Rapamune in maintenance renal transplant patients, increased urinary protein excretion was commonly observed at 6 to 24 months after conversion to Rapamune (see section 5.1). New onset nephrosis (nephrotic syndrome) was also reported in 2% of the patients in the study (see section 4.8). Based on information from an open-label randomised study, conversion from the calcineurin inhibitor tacrolimus to Rapamune in maintenance renal transplant patients was associated with an unfavourable safety profile without efficacy benefit and can therefore not be recommended (see section 5.1).

The concomitant use of Rapamune with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced haemolytic uraemic syndrome/thrombotic thrombocytopaenic purpura/thrombotic microangiopathy (HUS/TTP/TMA).

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

Cytochrome P450 isozymes and P-glycoprotein
Co-administration of sirolimus with strong inhibitors of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (P-gp) (such as ketoconazole, voriconazole, itraconazole, telithromycin or clarithromycin) may increase sirolimus blood levels and is not recommended.

Co-administration with strong inducers of CYP3A4 and/or P-gp (such as rifampin, rifabutin) is not recommended.

If co-administration of inducers or inhibitors of CYP3A4 and/or P-gp cannot be avoided, it is recommended that sirolimus whole blood trough concentrations and the clinical condition of the patient be monitored while they are concurrently administered with sirolimus and after their discontinuation. Dose adjustments of sirolimus may be required (see sections 4.2 and 4.5).

Angioedema
The concomitant administration of Rapamune and angiotensin-converting enzyme (ACE) inhibitors has resulted in angioneurotic oedema-type reactions. Elevated sirolimus levels, for example due to interaction with strong CYP3A4 inhibitors, (with/without concomitant ACE inhibitors) may also potentiate angioedema (see section 4.5). In some cases, the angioedema has resolved upon discontinuation or dose reduction of Rapamune.

Increased rates of biopsy confirmed acute rejection (BCAR) in renal transplant patients have been observed with concomitant use of sirolimus with ACE inhibitors (see section 5.1). Patients receiving sirolimus should be monitored closely if taking ACE inhibitors concomitantly.

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

Malignancy

Increased susceptibility to infection and the possible development of lymphoma and other malignancies, particularly of the skin, may result from immunosuppression (see section 4.8). As usual for patients with increased risk for skin cancer, exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Infections

Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections (bacterial, fungal, viral and protozoal), fatal infections, and sepsis.

Among these conditions in renal transplant patients 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 conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms.

Cases of *Pneumocystis carinii* pneumonia have been reported in renal transplant patients not receiving antimicrobial prophylaxis. Therefore, antimicrobial prophylaxis for *Pneumocystis carinii* pneumonia should be administered for the first 12 months following transplantation.

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

Hepatic impairment

In hepatically impaired patients, it is recommended that sirolimus whole blood trough levels be closely monitored. In patients with severe hepatic impairment, reduction in maintenance dose by one-half is recommended based on decreased clearance (see sections 4.2 and 5.2). Since half-life is prolonged in these patients, therapeutic monitoring of the medicinal product after a loading dose or a change of dose should be performed for a prolonged period of time until stable concentrations are reached (see sections 4.2 and 5.2).

Lung and liver transplant populations

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

In two clinical studies in *de novo* liver transplant patients, the use of sirolimus plus ciclosporin or tacrolimus was associated with an increase in hepatic artery thrombosis, mostly leading to graft loss or death.

A clinical study in liver transplant patients randomised to conversion from a calcineurin inhibitor (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 rate of death in the sirolimus conversion group was higher than the CNI continuation group, although the rates were not significantly different. 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.

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

Systemic effects

There have been reports of impaired or delayed wound healing in patients receiving Rapamune, including lymphocele in renal transplant patients and wound dehiscence. Patients with a body mass index (BMI) greater than 30 kg/m^2 may be at increased risk of abnormal wound healing based on data from the medical literature.

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

The use of Rapamune was associated with increased serum cholesterol and triglycerides that may require treatment. Patients administered Rapamune should be monitored for hyperlipidaemia using laboratory tests and if hyperlipidaemia is detected, subsequent interventions such as diet, exercise, and lipid-lowering agents should be initiated. The risk/benefit should be considered in patients with established hyperlipidaemia before initiating an immunosuppressive regimen, including Rapamune. Similarly the risk/benefit of continued Rapamune therapy should be re-evaluated in patients with severe refractory hyperlipidaemia.

Sucrose and lactose

Sucrose
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Sirolimus is extensively metabolised by the CYP3A4 isozyme in the intestinal wall and liver. Sirolimus is also a substrate for the multidrug efflux pump, P-glycoprotein (P-gp) located in the small intestine. Therefore, absorption and the subsequent elimination of sirolimus may be influenced by substances that affect these proteins. Inhibitors of CYP3A4 (such as ketoconazole, voriconazole, itraconazole, telithromycin, or clarithromycin) decrease the metabolism of sirolimus and increase sirolimus levels. Inducers of CYP3A4 (such as rifampin or rifabutin) increase the metabolism of sirolimus and decrease sirolimus levels. Co-administration of sirolimus with strong inhibitors of CYP3A4 or inducers of CYP3A4 is not recommended (see section 4.4).

Rifampicin (CYP3A4 inducer)

Administration of multiple doses of rifampicin decreased sirolimus whole blood concentrations following a single 10 mg dose of Rapamune oral solution. Rifampicin increased the clearance of sirolimus by approximately 5.5-fold and decreased AUC and C_{max} by approximately 82% and 71%, respectively. Co-administration of sirolimus and rifampicin is not recommended (see section 4.4).

Ketoconazole (CYP3A4 inhibitor)

Multiple-dose ketoconazole administration significantly affected the rate and extent of absorption and sirolimus exposure from Rapamune oral solution as reflected by increases in sirolimus C_{max}, t_{max}, and AUC of 4.4-fold, 1.4-fold, and 10.9-fold, respectively. Co-administration of sirolimus and ketoconazole is not recommended (see section 4.4).

Voriconazole (CYP3A4 inhibitor)

Co-administration of sirolimus (2 mg single dose) with multiple-dose administration of oral voriconazole (400 mg every 12 hours for 1 day, then 100 mg every 12 hours for 8 days) in healthy subjects has been reported to increase sirolimus C_{max} and AUC by an average of 7-fold and 11-fold, respectively. Co-administration of sirolimus and voriconazole is not recommended (see section 4.4).

Diltiazem (CYP3A4 inhibitor)

The simultaneous oral administration of 10 mg of Rapamune oral solution and 120 mg of diltiazem significantly affected the bioavailability of sirolimus. Sirolimus C_{max}, t_{max}, and AUC were increased 1.4-fold, 1.3-fold, and 1.6-fold, respectively. Sirolimus did not affect the pharmacokinetics of either diltiazem or its metabolites desacetyldiltiazem and desmethyldiltiazem. If diltiazem is administered, sirolimus blood levels should be monitored and a dose adjustment may be necessary.

Verapamil (CYP3A4 inhibitor)

Multiple-dose administration of verapamil and sirolimus oral solution significantly affected the rate and extent of absorption of both medicinal products. 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%. Sirolimus levels should be monitored, and appropriate dose reductions of both medicinal products should be considered.

Erythromycin (CYP3A4 inhibitor)

Multiple-dose administration of erythromycin and sirolimus oral solution significantly increased the rate and extent of absorption of both medicinal products. 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. Sirolimus levels should be monitored and appropriate dose reductions of both medicinal products should be considered.

Ciclosporin (CYP3A4 substrate)

The rate and extent of sirolimus absorption was significantly increased by ciclosporin A (CsA). Sirolimus administered concomitantly (5 mg), and at 2 hours (5 mg) and 4 hours (10 mg) after CsA (300 mg), resulted in increased sirolimus AUC by approximately 183%, 141% and 80%, respectively. The effect of CsA was also reflected by increases in sirolimus C_{max} and t_{max}. When given 2 hours before CsA administration, sirolimus C_{max} and AUC were not affected. Single-dose sirolimus did not affect the pharmacokinetics of ciclosporin (microemulsion) in healthy volunteers when administered simultaneously or 4 hours apart. It is recommended that Rapamune be administered 4 hours after ciclosporin (microemulsion).

Cannabidiol (P-gp inhibitor)

There have been reports of increased blood levels of sirolimus during concomitant use with cannabidiol. Co-administration of cannabidiol with another orally administered mTOR inhibitor in a healthy volunteer study led to an increase in exposure to the mTOR inhibitor of approximately 2.5-fold for both C_{max} and AUC, due to inhibition of intestinal P-gp efflux by cannabidiol. Caution should be used when cannabidiol and Rapamune are co-administered, closely monitoring for side effects. Monitor sirolimus blood levels and adjust the dose as needed (see sections 4.2 and 4.4).

Oral contraceptives

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

Other possible interactions

Inhibitors of CYP3A4 may decrease the metabolism of sirolimus and increase sirolimus blood levels. Such inhibitors include certain antifungals (e.g. clotrimazole, fluconazole, itraconazole, voriconazole), certain antibiotics (e.g. troleandomycin, telithromycin, clarithromycin), certain protease inhibitors (e.g. ritonavir, indinavir, boceprevir, and telaprevir), nicardipine, bromocriptine, cimetidine, danazol and letermovir.

Inducers of CYP3A4 may increase the metabolism of sirolimus and decrease sirolimus blood levels (e.g., St. John's Wort (*Hypericum perforatum*), anticonvulsants: carbamazepine, phenobarbital, phenytoin).

Although sirolimus inhibits human liver microsomal cytochrome P_{450} CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 *in vitro*, the active substance is not expected to inhibit the activity of these isozymes *in vivo* since the sirolimus concentrations necessary to produce inhibition are much higher than those observed in patients receiving therapeutic doses of Rapamune. Inhibitors of P-gp may decrease the efflux of sirolimus from intestinal cells and increase sirolimus levels.

Grapefruit juice affects CYP3A4-mediated metabolism, and should therefore be avoided.

Pharmacokinetic interactions may be observed with gastrointestinal prokinetic agents, such as cisapride and metoclopramide.

No clinically significant pharmacokinetic interaction was observed between sirolimus and any of the following substances: acyclovir, atorvastatin, digoxin, glibenclamide, methylprednisolone, nifedipine, prednisolone, and trimethoprim/sulfamethoxazole.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Effective contraception must be used during Rapamune therapy and for 12 weeks after Rapamune has been stopped (see section 4.5).

Pregnancy

There are no or limited amount of data from the use of sirolimus in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Rapamune should not be used during pregnancy unless clearly necessary. Effective contraception must be used during Rapamune therapy and for 12 weeks after Rapamune has been stopped.

Breast-feeding

Following administration of radiolabelled sirolimus, radioactivity is excreted in the milk of lactating rats. It is unknown whether sirolimus is excreted in human milk. Because of the potential for adverse reactions in breast-fed infants from sirolimus, breast-feeding should be discontinued during treatment with Rapamune.

Fertility

Impairments of sperm parameters have been observed among some patients treated with Rapamune. These effects have been reversible upon discontinuation of Rapamune in most cases (see section 5.3).

4.7 Effects on ability to drive and use machines

Rapamune has no known influence on the 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 most commonly reported adverse reactions (occurring in >10% of patients) are thrombocytopaenia, anaemia, pyrexia, hypertension, hypokalaemia, hypophosphataemia, urinary tract infection, hypercholesterolaemia, hyperglycaemia, hypertriglyceridaemia, abdominal pain, lymphocoele, peripheral oedema, arthralgia, acne, diarrhoea, pain, constipation, nausea, headache, increased blood creatinine, and increased blood lactate dehydrogenase (LDH).

The incidence of any adverse reaction(s) may increase as the trough sirolimus level increases.

The following list of adverse reactions is based on experience from clinical studies and on postmarketing experience.

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Most patients were on immunosuppressive regimens, which included Rapamune in combination with other immunosuppressive agents.

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Frequency not known (cannot be estimated from available data)
Infections and infestations	Pneumonia; Fungal infection; Viral infection; Bacterial infection; Herpes simplex infection; Urinary tract infection	Sepsis; Pyelonephritis; Cytomegalo-virus infection; Herpes zoster caused by the varicella zoster virus	*Clostridium difficile* colitis; Mycobacterial infection (including tuberculosis); Epstein-Barr virus infection		
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Non-melanoma skin cancer*	Lymphoma*; Malignant melanoma*; Post transplant lympho-proliferative disorder		Neuroendo crine carcinoma of the skin*
Blood and lymphatic system disorders	Thrombo-cytopaenia; Anaemia; Leucopenia	Haemolytic uraemic syndrome; Neutropaenia	Pancytopaenia; Thrombotic thrombo-cytopaenic purpura		
Immune system disorders		Hyper-sensitivity (including angioedema, anaphylactic reaction, and anaphylactoid reaction)			
Metabolism and nutrition disorders	Hypokalaemia; Hypophos-phataemia; Hyperlipidaemia (including hypercholesterol-aemia); Hyperglycaemia; Hyper-triglyceridaemia; Diabetes mellitus				
Nervous system disorders	Headache				Posterior reversible encephalo-pathy syndrome

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Frequency not known (cannot be estimated from available data)
Cardiac disorders	Tachycardia	Pericardial effusion			
Vascular disorders	Hypertension; Lymphocele	Venous thrombosis (including deep vein thrombosis)	Lymphoedema		
Respiratory, thoracic and mediastinal disorders		Pulmonary embolism; Pneumonitis*; Pleural effusion; Epistaxis	Pulmonary haemorrhage	Alveolar proteinosis	
Gastrointestinal disorders	Abdominal pain; Constipation; Diarrhoea; Nausea	Pancreatitis; Stomatitis; Ascites			
Hepatobiliary disorders	Liver function test abnormal (including alanine aminotransferase increased and aspartate amino-transferase increased)		Hepatic failure*		
Skin and subcutaneous tissue disorders	Rash; Acne		Dermatitis exfoliative	Hypersen-sitivity vasculitis	
Musculoskeletal and connective tissue disorders	Arthralgia	Osteonecrosis			
Renal and urinary disorders	Proteinuria		Nephrotic syndrome (see section 4.4); Focal segmental glomerulo-sclerosis*		
Reproductive system and breast disorders	Menstrual disorder (including amenorrhoea and menorrhagia)	Ovarian cyst			

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Frequency not known (cannot be estimated from available data)
General disorders and administration site conditions	Oedema; Oedema peripheral; Pyrexia; Pain; Impaired healing*				
Investigations	Blood lactate dehydrogenase increased; Blood creatinine increased				

*See section below.

Description of selected adverse reactions

Immunosuppression increases the susceptibility to the development of lymphoma and other malignancies, particularly of the skin (see section 4.4).

Cases of BK virus-associated nephropathy, as well as cases of JC virus-associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including Rapamune.

Hepatoxicity has been reported. The risk may increase as the trough sirolimus level increases. Rare reports of fatal hepatic necrosis have been reported with elevated trough sirolimus levels.

Cases of interstitial lung disease (including pneumonitis and infrequently bronchiolitis obliterans organising pneumonia (BOOP) and pulmonary fibrosis), some fatal, with no identified infectious aetiology have occurred in patients receiving immunosuppressive regimens including Rapamune. In some cases, the interstitial lung disease has resolved upon discontinuation or dose reduction of Rapamune. The risk may be increased as the trough sirolimus level increases.

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

Impairments of sperm parameters have been observed among some patients treated with Rapamune. These effects have been reversible upon discontinuation of Rapamune in most cases (see section 5.3).

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

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

Focal segmental glomerulosclerosis has been reported.

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

In a study evaluating the safety and efficacy of conversion from calcineurin inhibitors to sirolimus (target levels of 12-20 ng/mL 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 (see section 5.1). There was a higher rate of serious adverse events, including pneumonia, acute rejection, graft loss and death, in this sirolimus treatment arm (n=60, median time post-transplant 36 months).

Ovarian cysts and menstrual disorders (including amenorrhoea and menorrhagia) have been reported. Patients with symptomatic ovarian cysts should be referred for further evaluation. The incidence of ovarian cysts may be higher in premenopausal females compared to postmenopausal females. In some cases, ovarian cysts and these menstrual disorders have resolved upon discontinuation of Rapamune.

Paediatric population

Controlled clinical studies with posology comparable to that currently indicated for the use of Rapamune in adults have not been conducted in children or adolescents below 18 years of age).

Safety was assessed in a controlled clinical study enrolling renal transplant patients below 18 years of age considered of 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). The use of Rapamune in combination with calcineurin inhibitors and corticosteroids was associated with an increased risk of deterioration of renal function, serum lipid abnormalities (including, but not limited to, increased serum triglycerides and cholesterol), and urinary tract infections. The treatment regimen studied (continuous use of Rapamune in combination with calcineurin inhibitor) is not indicated for adult or paediatric patients (see section 4.1).

In another study enrolling renal transplant patients 20 years of age and below that was intended to assess the safety of progressive corticosteroid withdrawal (beginning at six months post-transplantation) from an immunosuppressive regimen initiated at transplantation that included full-dose immunosuppression with both Rapamune and a calcineurin inhibitor in combination with basiliximab induction, of the 274 patients enrolled, 19 (6.9%) were reported to have developed post-transplant lymphoproliferative disorder (PTLD). Among 89 patients known to be Epstein-Barr virus (EBV) seronegative prior to transplantation, 13 (15.6%) were reported to have developed PTLD. All patients who developed PTLD were aged below 18 years.

There is insufficient experience to recommend the use of Rapamune in children and adolescents (see section 4.2).

Undesirable effects observed with patients with S-LAM

Safety was assessed in a controlled study involving 89 patients with LAM, of which 81 patients had S-LAM and 42 of whom were treated with Rapamune (see section 5.1). The adverse drug reactions observed in patients with S-LAM were consistent with the known safety profile of the product for the indication prophylaxis of organ rejection in renal transplantation with the addition of weight decreased, which was reported in the study at a greater incidence with Rapamune when compared to that observed with placebo (common, 9.5% vs. common, 2.6%).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

At present, there is minimal experience with overdose. One patient experienced an episode of atrial fibrillation after ingestion of 150 mg of Rapamune. In general, the adverse effects of overdose are consistent with those listed in section 4.8. General supportive measures should be initiated in all cases

of overdose. Based on the poor aqueous solubility and high erythrocyte and plasma protein binding of Rapamune, it is anticipated that Rapamune will not be dialysable to any significant extent.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, ATC code: L04AH01.

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

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

LAM involves lung tissue infiltration with smooth muscle-like cells that harbour inactivating mutations of the tuberous sclerosis complex (TSC) gene (LAM cells). Loss of TSC gene function activates the mTOR signaling pathway, resulting in cellular proliferation and release of lymphangiogenic growth factors. Sirolimus inhibits the activated mTOR pathway and thus the proliferation of LAM cells.

Clinical studies

Prophylaxis of Organ Rejection

Patients at low to moderate immunological risk were studied in the phase 3 ciclosporin elimination-Rapamune maintenance study, which included patients receiving a renal allograft from a cadaveric or living donor. In addition, re-transplant recipients whose previous grafts survived for at least 6 months after transplantation were included. Ciclosporin was not withdrawn in patients experiencing Banff Grade 3 acute rejection episodes, who were dialysis-dependent, who had a serum creatinine higher than 400 μmol/L, or who had inadequate renal function to support ciclosporin withdrawal. Patients at high immunological risk of graft loss were not studied in sufficient number in the ciclosporin elimination-Rapamune maintenance studies and are not recommended for this treatment regimen.

At 12, 24 and 36 months, graft and patient survival were similar for both groups. At 48 months, there was a statistically significant difference in graft survival in favour of the Rapamune following ciclosporin elimination group compared to the Rapamune with ciclosporin therapy group (including and excluding loss to follow-up). There was a significantly higher rate of first biopsy-proven rejection in the ciclosporin elimination group compared to the ciclosporin maintenance group during the period post-randomisation to 12 months (9.8% vs. 4.2%, respectively). Thereafter, the difference between the two groups was not significant.

The mean calculated glomerular filtration rate (GFR) at 12, 24, 36, 48 and 60 months was significantly higher for patients receiving Rapamune following ciclosporin elimination than for those in the Rapamune with ciclosporin therapy group. Based upon the analysis of data from 36 months and beyond, which showed a growing difference in graft survival and renal function, as well as significantly lower blood pressure in the ciclosporin elimination group, it was decided to discontinue subjects from the Rapamune with ciclosporin group. By 60 months, the incidence of non-skin malignancies was significantly higher in the cohort who continued ciclosporin as compared with the

cohort who had ciclosporin withdrawn (8.4% vs. 3.8%, respectively). For skin carcinoma, the median time to first occurrence was significantly delayed.

The safety and efficacy of conversion from calcineurin inhibitors to Rapamune in maintenance renal transplant patients (6-120 months after transplantation) was assessed in a randomised, multicentre, controlled trial, stratified by calculated GFR at baseline (20-40 mL/min vs. above 40 mL/min). Concomitant immunosuppressive agents included mycophenolate mofetil, azathioprine, and corticosteroids. Enrollment in the patient stratum with baseline calculated GFR below40 mL/min was discontinued due to an imbalance in safety events (see section 4.8).

In the patient stratum with baseline calculated GFR above 40 mL/min, renal function was not improved overall. The rates of acute rejection, graft loss, and death were similar at 1 and 2 years. Treatment emergent adverse events occurred more frequently during the first 6 months after Rapamune conversion. In the stratum with baseline calculated GFR above 40 mL/min, the mean and median urinary protein to creatinine ratios were significantly higher in the Rapamune conversion group as compared to those of the calcineurin inhibitors continuation group at 24 months (see section 4.4). New onset nephrosis (nephrotic syndrome) was also reported (see section 4.8).

At 2 years, the rate of non-melanoma skin malignancies was significantly lower in the Rapamune conversion group as compared to the calcineurin inhibitors continuation group (1.8% and 6.9%). In a subset of the study patients with a baseline GFR above 40 mL/min and normal urinary protein excretion, calculated GFR was higher at 1 and 2 years in patients converted to Rapamune than for the corresponding subset of calcineurin inhibitor continuation patients. The rates of acute rejection, graft loss, and death were similar, but urinary protein excretion was increased in the Rapamune treatment arm of this subset.

In an open-label, randomised, comparative, multi-centre 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% vs. 91.1%, p=0.002*) and more discontinuations from the treatment due to adverse events (26.7% vs. 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 randomisation, a fasting glucose ≥126 mg/dL or a non-fasting glucose ≥200 mg/dL after randomisation (18.3% vs. 5.6%, p=0.025*). A lower incidence of squamous cell carcinoma of the skin was observed in the sirolimus group (0% vs. 4.9%). *Note: p-values not controlled for multiple testing.

In two multi-centre clinical studies, *de novo* renal transplant patients treated with sirolimus, mycophenolate mofetil (MMF), corticosteroids, 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, corticosteroids, and an IL-2 receptor antagonist (see section 4.4). Renal function was not better in the treatment arms with *de novo* sirolimus without a calcineurin inhibitor. An abbreviated dosing schedule of daclizumab was used in one of the studies.

In a randomised, comparative evaluation of ramipril versus placebo for the prevention of proteinuria in kidney transplant patients converted from calcineurin inhibitors to sirolimus, a difference in the number of patients with BCAR through 52 weeks was observed [13 (9.5%) vs. 5 (3.2%), respectively; p=0.073]. Patients initiated on ramipril 10 mg had a higher rate of BCAR (15%) compared to patients initiated on ramipril 5 mg (5%). Most rejections occurred within the first six months following conversion and were mild in severity; no graft losses were reported during the study (see section 4.4).

Sporadic Lymphangioleiomyomatosis (S-LAM) Patients

The safety and efficacy of Rapamune for treatment of S-LAM were assessed in a randomised, double-blind, multicentre, controlled trial. This study compared Rapamune (dose adjusted to 5-15 ng/mL) with placebo for a 12-month treatment period, followed by a 12-month observation period in patients with TSC-LAM or S-LAM. Eighty-nine (89) patients were enrolled at 13 study sites in the United States, Canada, and Japan of which 81 patients had S-LAM; of these patients with S-LAM, 39 were randomised to receive placebo and 42 to receive Rapamune. The key inclusion criteria was post-bronchodilator forced expiratory volume in 1 second (FEV1) ≤70% of predicted during the baseline visit. In patients with S-LAM, enrolled patients had moderately advanced lung disease, with baseline FEV1 of 49.2±13.6% (mean ±SD) of the predicted value. The primary endpoint was the difference between the groups in the rate of change (slope) in FEV1. During the treatment period in patients with S-LAM, the mean ±SE FEV1 slope was -12±2 mL per month in the placebo group and 0.3±2 mL per month in the Rapamune group ($p<0.001$). The absolute between-group difference in the mean change in FEV1 during the treatment period was 152 mL, or approximately 11% of the mean FEV1 at enrollment.

As compared with the placebo group, the sirolimus group had improvement from baseline to 12 months in measures of forced vital capacity (-12±3 vs. 7±3 mL per month, respectively, $p<0.001$), serum vascular endothelial growth factor D (VEGF-D; -8.6±15.2 vs. -85.3±14.2 pg/mL per month, respectively, $p<0.001$), and quality of life (Visual Analogue Scale – Quality of Life [VAS-QOL] score: -0.3±0.2 vs. 0.4±0.2 per month, respectively, $p=0.022$) and functional performance (-0.009±0.005 vs. 0.004±0.004 per month, respectively, $p=0.044$) in patients with S-LAM. There was no significant between-group difference in this interval in the change in functional residual capacity, 6-minute walk distance, diffusing capacity of the lung for carbon monoxide, or general well-being score in patients with S-LAM.

Paediatric population

Rapamune was assessed in a 36-month controlled clinical study enrolling renal transplant patients below 18 years of age considered at high-immunologic risk, defined as having a history of one or more acute allograft rejection episodes and/or the presence of chronic allograft nephropathy on a renal biopsy. Subjects were to receive Rapamune (sirolimus target concentrations of 5 to 15 ng/mL) in combination with a calcineurin inhibitor and corticosteroids or to receive calcineurin-inhibitor-based immunosuppression without Rapamune. The Rapamune group failed to demonstrate superiority to the control group in terms of the first occurrence of biopsy confirmed acute rejection, graft loss, or death. One death occurred in each group. The use of Rapamune in combination with calcineurin inhibitors and corticosteroids was associated with an increased risk of deterioration of renal function, serum lipid abnormalities (including, but not limited to, increased serum triglycerides and total cholesterol), and urinary tract infections (see section 4.8).

An unacceptably high frequency of PTLD was seen in a paediatric clinical transplant study when full-dose Rapamune was administered to children and adolescents in addition to full-dose calcineurin inhibitors with basiliximab and corticosteroids (see section 4.8).

In a retrospective review of hepatic veno-occlusive disease (VOD) in patients who underwent myeloablative stem cell transplantation using cyclosphophamide and total body irradiation, an increased incidence of hepatic VOD was observed in patients treated with Rapamune, especially with concomitant use of methotrexate.

5.2 Pharmacokinetic properties

Much of the general pharmacokinetic information was obtained using the Rapamune oral solution, which is summarised first. Information directly related to the tablet formulation is summarised specifically in the Oral tablet section.

Oral solution

Following administration of the Rapamune oral solution, sirolimus is rapidly absorbed, with a time to peak concentration of 1 hour in healthy subjects receiving single doses and 2 hours in patients with stable renal allografts receiving multiple doses. The systemic availability of sirolimus in combination with simultaneously administered ciclosporin (Sandimune) is approximately 14%. Upon repeated administration, the average blood concentration of sirolimus is increased approximately 3-fold. The terminal half-life in stable renal transplant patients after multiple oral doses was 62 ± 16 hours. The effective half-life, however, is shorter and mean steady-state concentrations were achieved after 5 to 7 days. The blood to plasma ratio (B/P) of 36 indicates that sirolimus is extensively partitioned into formed blood elements.

Sirolimus is a substrate for both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein. Sirolimus is extensively metabolised by O-demethylation and/or hydroxylation. Seven major metabolites, including hydroxyl, demethyl, and hydroxydemethyl, are identifiable in whole blood. Sirolimus is the major component in human whole blood and contributes to greater than 90% of the immunosuppressive activity. After a single dose of [^{14}C] sirolimus in healthy volunteers, the majority (91.1%) of radioactivity was recovered from the faeces, and only a minor amount (2.2%) was excreted in urine.

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

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

Sirolimus concentrations were measured in concentration-controlled studies of paediatric renal-transplant patients who were also receiving ciclosporin and corticosteroids. The target for trough concentrations was 10-20 ng/mL. At steady-state, 8 children aged 6-11 years received mean ± SD doses of 1.75 ± 0.71 mg/day (0.064 ± 0.018 mg/kg, 1.65 ± 0.43 mg/m^2) while 14 adolescents aged 12-18 years received mean ± SD doses of 2.79 ± 1.25 mg/day (0.053 ± 0.0150 mg/kg, 1.86 ± 0.61 mg/m^2). The younger children had a higher weight-normalised CL/F (214 mL/h/kg) compared with the adolescents (136 mL/h/kg). These data indicate that younger children might require higher bodyweight-adjusted doses than adolescents and adults to achieve similar target concentrations. However, the development of such special dosing recommendations for children requires more data to be definitely confirmed.

In mild and moderate hepatically impaired patients (Child-Pugh classification A or B), mean values for sirolimus AUC and $t_{1/2}$ were increased 61% and 43%, respectively, and CL/F was decreased 33% compared to normal healthy subjects. In severe hepatically impaired patients (Child-Pugh classification C), mean values for sirolimus AUC and $t_{1/2}$ were increased 210% and 170%, respectively, and CL/F was decreased by 67% compared to normal healthy subjects. The longer half-lives observed in hepatically impaired patients delay reaching steady-state.

Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetics of sirolimus were similar in various populations, with renal function ranging from normal to absent (dialysis patients).

Oral tablet

The 0.5 mg tablet is not fully bioequivalent to the 1 mg, 2 mg and 5 mg tablets when comparing C_{max}. Multiples of the 0.5 mg tablets should therefore not be used as a substitute for other tablet strengths.

In healthy subjects, the mean extent of bioavailability of sirolimus after single-dose administration of the tablet formulation is about 27% higher relative to the oral solution. The mean C_{max} was decreased by 35%, and mean t_{max} increased by 82%. The difference in bioavailability was less marked upon steady-state administration to renal transplant recipients, and therapeutic equivalence has been demonstrated in a randomised study of 477 patients. When switching patients between oral solution and tablet formulations, it is recommended to give the same dose and to verify the sirolimus trough concentration 1 to 2 weeks later to assure that it remains within recommended target ranges. Also, when switching between different tablet strengths, verification of trough concentrations is recommended.

In 24 healthy volunteers receiving Rapamune tablets with a high-fat meal, C_{max}, t_{max} and AUC showed increases of 65%, 32%, and 23%, respectively. To minimise variability, Rapamune tablets should be taken consistently with or without food. Grapefruit juice affects CYP3A4-mediated metabolism and must, therefore, be avoided.

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

Clinical studies of Rapamune did not include a sufficient number of patients above 65 years of age to determine whether they will respond differently than younger patients. Rapamune tablets administered to 12 renal transplant patients above 65 years of age gave similar results to adult patients (n=167) 18 to 65 years of age.

Initial Therapy (2 to 3 months post-transplant): In most patients receiving Rapamune tablets with a loading dose of 6 mg followed by an initial maintenance dose of 2 mg, whole blood sirolimus trough concentrations rapidly achieved steady-state concentrations within the recommended target range (4 to 12 ng/mL, chromatographic assay). Sirolimus pharmacokinetic parameters following daily doses of 2 mg Rapamune tablets administered in combination with ciclosporin microemulsion (4 hours prior to Rapamune tablets) and corticosteroids in 13 renal transplant patients, based on data collected at months 1 and 3 after transplantation, were: $C_{min,ss}$ 7.39 ± 2.18 ng/mL; $C_{max,ss}$ 15.0 ± 4.9 ng/mL; $t_{max,ss}$ 3.46 ± 2.40 hours; $AUC_{\tau,ss}$ 230 ± 67 ng.h/mL; CL/F/WT, 139 ± 63 mL/h/kg (parameters calculated from LC-MS/MS assay results). The corresponding results for the oral solution in the same clinical study were $C_{min,ss}$ 5.40 ± 2.50 ng/mL, $C_{max,ss}$ 14.4 ± 5.3 ng/mL, $t_{max,ss}$ 2.12 ± 0.84 hours, $AUC_{\tau,ss}$ 194 ± 78 ng.h/mL, CL/F/W 173 ± 50 mL/h/kg. Whole blood trough sirolimus concentrations, as measured by LC/MS/MS, were significantly correlated (r^2=0.85) with $AUC_{\tau,ss}$.

Based on monitoring in all patients during the period of concomitant therapy with ciclosporin, mean (10^{th}, 90^{th} percentiles) troughs (expressed as chromatographic assay values) and daily doses were 8.6 ± 3.0 ng/mL (5.0 to 13 ng/mL) and 2.1 ± 0.70 mg (1.5 to 2.7 mg), respectively (see section 4.2).

Maintenance therapy: From month 3 to month 12, following discontinuation of ciclosporin, mean (10^{th}, 90^{th} percentiles) troughs (expressed as chromatographic assay values) and daily doses were 19 ± 4.1 ng/mL (14 to 24 ng/mL) and 8.2 ± 4.2 mg (3.6 to 13.6 mg), respectively (see section 4.2). Therefore, the sirolimus dose was approximately 4-fold higher to account for both the absence of the pharmacokinetic interaction with ciclosporin (2-fold increase) and the augmented immunosuppressive requirement in the absence of ciclosporin (2-fold increase).

Lymphangioleiomyomatosis (LAM)

In a clinical trial of patients with LAM, the median whole blood sirolimus trough concentration after 3 weeks of receiving sirolimus tablets at a dose of 2 mg/day was 6.8 ng/mL (interquartile range 4.6 to 9.0 ng/mL; n=37). With concentration-control (target concentrations 5 to 15 ng/mL), the median sirolimus concentration at the end of 12 months of treatment was 6.8 ng/mL (interquartile range 5.9 to 8.9 ng/mL; n=37).

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use, were as follows: pancreatic islet cell vacuolation, testicular tubular degeneration, gastrointestinal ulceration, bone fractures and calluses, hepatic haematopoiesis, and pulmonary phospholipidosis.

Sirolimus was not mutagenic in the *in vitro* bacterial reverse mutation assays, the Chinese Hamster Ovary cell chromosomal aberration assay, the mouse lymphoma cell forward mutation assay, or the *in vivo* mouse micronucleus assay.

Carcinogenicity studies conducted in mouse and rat showed increased incidences of lymphomas (male and female mouse), hepatocellular adenoma and carcinoma (male mouse) and granulocytic leukaemia (female mouse). It is known that malignancies (lymphoma) secondary to the chronic use of immunosuppressive agents can occur and have been reported in patients in rare instances. In mouse, chronic ulcerative skin lesions were increased. The changes may be related to chronic immunosuppression. In rat, testicular interstitial cell adenomas were likely indicative of a species-dependent response to lutenising hormone levels and are usually considered of limited clinical relevance.

In reproduction toxicity studies decreased fertility in male rats was observed. Partly reversible reductions in sperm counts were reported in a 13-week rat study. Reductions in testicular weights and/or histological lesions (e.g., tubular atrophy and tubular giant cells) were observed in rats and in a monkey study. In rats, sirolimus caused embryo/foetotoxicity that was manifested as mortality and reduced foetal weights (with associated delays in skeletal ossification) (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate
Macrogol
Magnesium stearate
Talc

Tablet coating:

Rapamune 0.5 mg coated tablets
Macrogol
Glycerol monooleate
Pharmaceutical glaze (shellac)
Calcium sulfate
Microcrystalline cellulose
Sucrose
Titanium dioxide
Yellow iron oxide (E172)
Brown iron oxide (E172)
Poloxamer 188
α-tocopherol
Povidone
Carnauba wax
Printing ink (Shellac, Iron Oxide Red, Propylene Glycol [E1520], Concentrated Ammonia Solution, Simethicone)

Rapamune 1 mg coated tablets
Macrogol
Glycerol monooleate
Pharmaceutical glaze (shellac)
Calcium sulfate
Microcrystalline cellulose
Sucrose
Titanium dioxide
Poloxamer 188
α-tocopherol
Povidone
Carnauba wax
Printing ink (Shellac, Iron Oxide Red, Propylene Glycol [E1520], Concentrated Ammonia Solution, Simethicone)

Rapamune 2 mg coated tablets
Macrogol
Glycerol monooleate
Pharmaceutical glaze (shellac)
Calcium sulfate
Microcrystalline cellulose
Sucrose
Titanium dioxide
Yellow iron oxide (E172)
Brown iron oxide (E172)
Poloxamer 188
α-tocopherol
Povidone
Carnauba wax
Printing ink (Shellac, Iron Oxide Red, Propylene Glycol [E1520], Concentrated Ammonia Solution, Simethicone)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Rapamune 0.5 mg coated tablets
3 years.

Rapamune 1 mg coated tablets
3 years.

Rapamune 2 mg coated tablets
3 years.

6.4 Special precautions for storage

Do not store above 25ºC.

Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

Clear polyvinyl chloride (PVC)/polyethylene (PE)/polychlorotrifluoroethylene (Aclar) aluminium blister packages of 30 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

Rapamune 0.5 mg coated tablets
EU/1/01/171/013-14

Rapamune 1 mg coated tablets
EU/1/01/171/007-8

Rapamune 2 mg coated tablets
EU/1/01/171/009-010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 March 2001
Date of latest renewal: 13 March 2011

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Rapamune 1 mg/mL oral solution:

Pfizer Service Company BV
Hermeslaan 11
1932 Zaventem
Belgium

Rapamune 0.5 mg coated tablets, Rapamune 1 mg coated tablets, Rapamune 2 mg coated tablets:

Pfizer Ireland Pharmaceuticals Unlimited Company
Little Connell, Newbridge, Co. Kildare, W12 HX57
Ireland

Pfizer Manufacturing Deutschland GmbH
Mooswaldallee 1
79108 Freiburg Im Breisgau
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

TEXT FOR 60 mL OUTER CARTON (CONTAINING SYRINGES/BOTTLE IN CARTON)

1. NAME OF THE MEDICINAL PRODUCT

Rapamune 1 mg/mL oral solution
sirolimus

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of Rapamune contains 1 mg sirolimus.
Each 60 mL bottle of Rapamune contains 60 mg sirolimus.

3. LIST OF EXCIPIENTS

Also contains: ethanol, propylene glycol (E1520), soya fatty acids. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution

1 bottle
30 dosing syringes
1 syringe adapter
1 carrying case

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Store in the original bottle in order to protect from light.

Use within 30 days after opening bottle.
Use within 24 hours after filling the dosing syringe.
After dilution, the preparation should be used immediately.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/171/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rapamune 1 mg/mL

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

INTERMEDIATE CARTON: 60 mL BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Rapamune 1 mg/mL oral solution
sirolimus

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of Rapamune contains 1 mg sirolimus.
Each 60 mL bottle of Rapamune contains 60 mg sirolimus.

3. LIST OF EXCIPIENTS

Also contains: ethanol, propylene glycol (E1520), soya fatty acids. See package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution
60 mL bottle

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Store in the original bottle in order to protect from light.

Use within 30 days after opening bottle.
Use within 24 hours after filling the dosing syringe.

After dilution, the preparation should be used immediately.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/171/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL: 60 mL BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Rapamune 1 mg/mL oral solution
sirolimus

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of Rapamune contains 1 mg sirolimus.
Each 60 mL bottle of Rapamune contains 60 mg sirolimus.

3. LIST OF EXCIPIENTS

Also contains: ethanol, propylene glycol (E1520), soya fatty acids. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 mL oral solution.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Date opened

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Store in the original bottle in order to protect from light.

Use within 30 days after opening bottle.
Use within 24 hours after filling the dosing syringe.
After dilution, the preparation should be used immediately.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/171/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTONS – PACK SIZES 30 AND 100 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Rapamune 0.5 mg coated tablets
sirolimus

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each coated tablet contains 0.5 mg sirolimus.

3. LIST OF EXCIPIENTS

Also contains: lactose monohydrate, sucrose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 coated tablets
100 coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Do not crush, chew or split.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25ºC.
Keep the blister in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/171/013 30 tablets
EU/1/01/171/014 100 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rapamune 0.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Rapamune 0.5 mg tablets
sirolimus

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTONS – PACK SIZES 30 AND 100 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Rapamune 1 mg coated tablets
sirolimus

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each coated tablet contains 1 mg sirolimus.

3. LIST OF EXCIPIENTS

Also contains: lactose monohydrate, sucrose. See package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

30 coated tablets
100 coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Do not crush, chew or split
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25˚C.
Keep the blister in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/171/007 30 tablets
EU/1/01/171/008 100 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rapamune 1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Rapamune 1 mg tablets
sirolimus

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTONS – PACK SIZES 30 AND 100 TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Rapamune 2 mg coated tablets
sirolimus

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each coated tablet contains 2 mg sirolimus.

3. LIST OF EXCIPIENTS

Also contains: lactose monohydrate, sucrose. See package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

30 coated tablets
100 coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Do not crush, chew or split
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25˚C.
Keep the blister in the outer carton in order to protect from light.

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11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/171/009 30 tablets
EU/1/01/171/010 100 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rapamune 2 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Rapamune 2 mg tablets
sirolimus

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Rapamune 1 mg/mL oral solution
sirolimus

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rapamune is and what it is used for
2. What you need to know before you take Rapamune
3. How to take Rapamune
4. Possible side effects
5. How to store Rapamune
6. Contents of the pack and other information

1. What Rapamune is and what it is used for

Rapamune contains the active substance sirolimus, which belongs to a group of medicines called immunosuppressants. It helps to control your body's immune system after you have received a kidney transplant.

Rapamune is used in adults to prevent your body from rejecting transplanted kidneys and is normally used with other immunosuppressant medicines called corticosteroids and initially (the first 2 to 3 months) with ciclosporin.

Rapamune is also used for the treatment of patients with sporadic lymphangioleiomyomatosis (S-LAM) with moderate lung disease or declining lung function. S-LAM is a rare progressive lung disease that affects predominantly women of childbearing age. The most common symptom of S-LAM is shortness of breath.

2. What you need to know before you take Rapamune

Do not take Rapamune

- if you are allergic to sirolimus or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to peanut or soya.

Warnings and precautions

Talk to your doctor or pharmacist before taking Rapamune

- If you have any liver problems or have had a disease which may have affected your liver, please tell your doctor as this may affect the dose of Rapamune that you receive and may result in your having additional blood tests.

- Rapamune, like other immunosuppressive medicines, may decrease your body's ability to fight infection, and may increase the risk of developing cancer of the lymphoid tissues and skin.
- If you have a body mass index (BMI) greater than 30 kg/m^2, you may be at increased risk of abnormal wound healing.
- If you are considered to be at high risk for kidney rejection, such as if you had a previous transplant that was lost to rejection.

Your doctor will perform tests to monitor the levels of Rapamune in your blood. Your doctor will also perform tests to monitor your kidney function, your blood fat (cholesterol and/or triglycerides) levels and possibly your liver function, during treatment with Rapamune.

Exposure to sunlight and UV light should be limited by covering your skin with clothing and using a sunscreen with a high protection factor because of the increased risk for skin cancer.

Children and adolescents

There is limited experience on the use of Rapamune in children and adolescents less than 18 years of age. The use of Rapamune is not recommended in this population.

Other medicines and Rapamune

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Some medicines can interfere with the action of Rapamune and, therefore, dose adjustment of Rapamune may be required. In particular, you should inform your doctor or pharmacist if you are taking any of the following:

- any other immunosuppressant medicines.
- antibiotics or antifungal medicines used to treat infection e.g. clarithromycin, erythromycin, telithromycin, troleandomycin, rifabutin, clotrimazole, fluconazole, itraconazole. It is not recommended that Rapamune be taken with rifampicin, ketoconazole or voriconazole.
- any high blood pressure medicines or medicines for heart problems including nicardipine, verapamil and diltiazem.
- anti-epileptic medicines including carbamazepine, phenobarbital, phenytoin.
- medicines used to treat ulcers or other gastrointestinal disorders such as cisapride, cimetidine, metoclopramide.
- bromocriptine (used in the treatment of Parkinson's disease and various hormonal disorders), danazol (used in the treatment of gynaecological disorders), or protease inhibitors (e.g. for HIV and hepatitis C such as ritonavir, indinavir, boceprevir, and telaprevir).
- St. John's Wort (*Hypericum perforatum*).
- letermovir (an antiviral medicine to prevent getting ill from cytomegalovirus).
- cannabidiol (uses amongst others include treatment of seizures).

The use of live vaccines should be avoided with the use of Rapamune. Before vaccinations, please inform your doctor or pharmacist that you are receiving Rapamune.

The use of Rapamune may lead to increased levels of cholesterol and triglycerides (blood fats) in your blood that may require treatment. Medicines known as "statins" and "fibrates" used to treat elevated cholesterol and triglycerides have been associated with an increased risk of muscle breakdown (rhabdomyolysis). Please inform your doctor if you are taking medicines to lower your blood fats.

The combined use of Rapamune with angiotensin-converting enzyme (ACE) inhibitors (a type of medicine used to lower blood pressure) may result in allergic reactions. Please inform your doctor if you are taking any of these medicines.

Rapamune with food and drink

Rapamune should be taken consistently, either with or without food. If you prefer to take Rapamune with food, then you should always take it with food. If you prefer to take Rapamune without food, then you should always take it without food. Food can affect the amount of medicine that gets into your bloodstream, and taking your medicine in a consistent way means that the blood levels of Rapamune remain more stable.

Rapamune should not be taken with grapefruit juice.

Pregnancy, breast-feeding and fertility

Rapamune should not be used during pregnancy unless clearly necessary. You must use an effective method of contraception during treatment with Rapamune and for 12 weeks after treatment has stopped. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

It is not known whether Rapamune passes into breast milk. Patients taking Rapamune should discontinue breast-feeding.

Decreased sperm count has been associated with the use of Rapamune and usually returns to normal once treatment is stopped.

Driving and using machines

Although Rapamune treatment is not expected to affect your ability to drive, if you have any concerns please consult your doctor.

Rapamune contains ethanol (alcohol)

Rapamune contains up to 3.17 vol % ethanol (alcohol). An initial dose of 6 mg contains up to 150 mg of alcohol which is equivalent to 3.80 mL beer or 1.58 mL wine. This amount of alcohol may be harmful for those suffering from alcoholism as well as for pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy. Alcohol may modify or increase the effect of other medicines.

Maintenance doses of 4 mg or less contain small amounts of ethanol (100 mg or less) that are likely to be too low to be harmful.

3. How to take Rapamune

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will decide exactly what dose of Rapamune you must take and how often to take it. Follow your doctor’s instructions exactly, and never change the dose yourself.

Rapamune is for oral use only. Inform your doctor if you have difficulty taking the oral solution.

Rapamune should be taken consistently, either with or without food.

Kidney Transplant
Your doctor will give you an initial dose of 6 mg as soon as possible after the kidney transplant operation. Then you will need to take 2 mg of Rapamune each day, until otherwise directed by your doctor. Your dose will be adjusted depending on the level of Rapamune in your blood. Your doctor will need to perform blood tests to measure Rapamune concentrations.

If you are also taking ciclosporin, then you must take the two medicines approximately 4 hours apart.

It is recommended that Rapamune be used first in combination with ciclosporin and corticosteroids. After 3 months, your doctor may discontinue either Rapamune or ciclosporin, as it is not recommended that these medicines be taken together beyond this period.

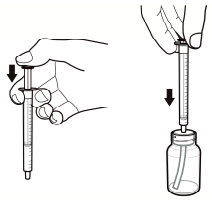
Sporadic Lymphangioleiomyomatosis (S-LAM)
Your doctor will give you 2 mg of Rapamune each day, until otherwise directed by your doctor. Your dose will be adjusted depending on the level of Rapamune in your blood. Your doctor will need to perform blood tests to measure Rapamune concentrations.

Instructions on how to dilute Rapamune

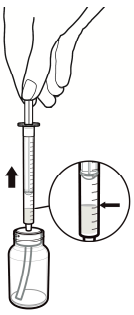
1. Remove the safety cap from the bottle by squeezing the tabs on the cap and twisting. Insert the syringe adapter into the bottle until it is flush with the top of the bottle. Do not attempt to remove the syringe adapter from the bottle once inserted.



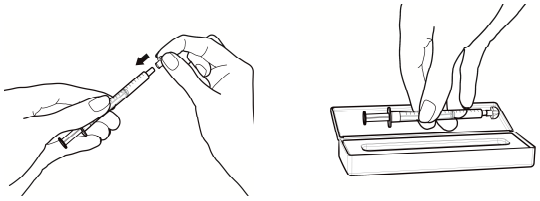
2. With the plunger fully depressed, insert one of the dosing syringes into the opening in the adapter.



3. Withdraw the exact amount of Rapamune oral solution as prescribed by your doctor by gently pulling out the plunger of the dosing syringe until the level of the oral solution is even with the appropriate mark on the dosing syringe. The bottle should remain in an upright position when withdrawing the solution. If bubbles form in the oral solution in the dosing syringe during withdrawal, empty the Rapamune solution back into the bottle and repeat the withdrawal procedure. You may need to repeat step 3 more than once to deliver your dose.



4. You may have been instructed to take your Rapamune oral solution at a particular time of day. If it is necessary to carry your medication with you, fill the dosing syringe to the appropriate mark and place a cap securely on it – the cap should snap into place. Then place the capped dosing syringe in the carrying case provided. Once in the syringe the medication may be kept at room temperature (not exceeding 25°C) or refrigerated and should be used within 24 hours.



5. Empty the contents of the dosing syringe into only a glass or plastic container holding at least 60 mL of water or orange juice. Stir well for one minute and drink immediately at once. Refill the glass with at least 120 mL of water or orange juice, stir well, and drink immediately. No other liquids, including grapefruit juice, should be used for dilution. The dosing syringe and cap are to be used once and then discarded.



When refrigerated the solution in the bottle may develop a slight haze. If this occurs, simply bring your Rapamune oral solution to room temperature and shake gently. The presence of this haze does not affect the quality of Rapamune.

If you take more Rapamune than you should

If you have taken more medicine than you were told contact a doctor or go to the nearest hospital emergency department straight away. Always take the labelled medicine bottle with you, even if it is empty.

If you forget to take Rapamune

If you forget to take Rapamune, take it as soon as you remember, but not within 4 hours of the next dose of ciclosporin. After that, continue to take your medicines as usual. Do not take a double dose to make up for a forgotten dose, and always take Rapamune and ciclosporin approximately 4 hours apart. If you miss a dose of Rapamune completely, you should inform your doctor.

If you stop taking Rapamune

Do not stop taking Rapamune unless your doctor tells you to, as you risk losing your transplant.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions

You should **see your doctor immediately** if you experience symptoms, such as swollen face, tongue and/or back of the mouth (pharynx) and/or difficulties in breathing (angioedema), or a skin condition

whereby the skin can peel off (exfoliative dermatitis). These may be symptoms of a serious allergic reaction.

Kidney damage with low blood cell counts (thrombocytopaenic purpura/haemolytic uraemic syndrome)

When taken with medicines called calcineurin inhibitors (ciclosporin or tacrolimus), Rapamune may increase the risk of kidney damage with low blood platelets and low red blood cell counts, with or without rash (thrombocytopaenic purpura/haemolytic uraemic syndrome). If you experience symptoms, such as bruising or rash, changes in your urine, or changes in behaviour, or any others that are serious, unusual or prolonged, contact your doctor.

Infections

Rapamune reduces your body's own defence mechanisms. Consequently your body will not be as good as normal at fighting infections. So if you are taking Rapamune, you may therefore catch more infections than usual, such as infections of the skin, mouth, stomach and intestines, lungs and urinary tract (see list below). You should contact your doctor if you experience symptoms that are serious, unusual, or prolonged.

Side effect frequencies

Very common: may affect more than 1 in 10 people

- Fluid collection around the kidney
- Swelling of the body including hands and feet
- Pain
- Fever
- Headache
- Increased blood pressure
- Stomach pain, diarrhoea, constipation, nausea
- Low red blood cells, low blood platelets
- Increased fat in the blood (cholesterol and/or triglycerides), increased blood sugar, low blood potassium, low blood phosphorus, increased lactate dehydrogenase in the blood, increased creatinine in the blood
- Joint pain
- Acne
- Urinary tract infection
- Pneumonia and other bacterial, viral, and fungal infections
- A reduced number of infection-fighting cells in the blood (white blood cells)
- Diabetes
- Abnormal tests of liver function, elevated AST and/or ALT liver enzymes
- Rash
- Elevated protein in the urine
- Menstrual disorders (including absent, infrequent or heavy periods)
- Slow healing (this may include separation of the layers of a surgical wound or stitch line)
- Rapid heart rate
- There is a general tendency for fluid to collect in various tissues.

Common: may affect up to 1 in 10 people

- Infections (including life-threatening infections)
- Blood clots in the legs
- Blood clots in the lung
- Mouth sores

- Fluid collection in the abdomen
- Kidney damage with low blood platelets and low red blood cell counts, with or without rash (haemolytic uraemic syndrome)
- Low levels of a type of white blood cells called neutrophils
- Deterioration of bone
- Inflammation that may lead to lung damage, fluid around the lung
- Nose bleeds
- Skin cancer
- Kidney infection
- Ovarian cysts
- Fluid collection in the sac around the heart, that in some cases may decrease the heart's ability to pump blood
- Inflammation of the pancreas
- Allergic reactions
- Shingles
- Cytomegalovirus infection

Uncommon: may affect up to 1 in 100 people

- Cancer of the lymph tissue (lymphoma/post-transplant lympho-proliferative disorder), combined lowering of red blood cells, white blood cells and blood platelets
- Bleeding from the lung
- Protein in the urine, occasionally severe and associated with side effects, such as swelling
- Scarring in the kidney that may reduce kidney function
- Too much fluid collecting in the tissues due to irregular lymph function
- Low blood platelets, with or without rash (thrombocytopaenic purpura)
- Serious allergic reactions that can cause peeling of the skin
- Tuberculosis
- Epstein-Barr virus infection
- Infectious diarrhoea with *Clostridium difficile*
- Serious liver damage

Rare: may affect up to 1 in 1,000 people

- Protein build-up in the air sacs of the lungs that may interfere with breathing
- Serious allergic reactions that can affect blood vessels (see above paragraph on allergic reactions)

Not known: frequency cannot be estimated from the available data

- Posterior reversible encephalopathy syndrome (PRES), a serious nervous system syndrome that has the following symptoms: headache, nausea, vomiting, confusion, seizures, and visual loss. Should any of these occur together, please contact your physician.

S-LAM patients experienced similar side effects to those of kidney transplant patients, with the addition of weight loss, which may affect up to 1 in 10 people.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rapamune

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after “EXP”. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).

Keep Rapamune oral solution in its original bottle in order to protect from light.

Once the bottle has been opened, the contents should be kept refrigerated and used within 30 days. If necessary, you may store the bottle at room temperature up to 25°C for a short period of time, but no longer than 24 hours.

Once the dosing syringe has been filled with Rapamune oral solution, it should be kept at room temperature, but not above 25°C, for maximum 24 hours.

Once the contents of the dosing syringe have been diluted with water or orange juice, the preparation should be drunk immediately.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rapamune contains

The active substance is sirolimus. Each mL of Rapamune oral solution contains 1 mg of sirolimus.

The other ingredients are:

Polysorbate 80 (E433) and phosal 50 PG (phosphatidylcholine, propylene glycol [E1520], mono-and diglycerides, ethanol, soya fatty acids, and ascorbyl palmitate).

This medicine contains approximately 350 mg propylene glycol (E1520) in each mL.

What Rapamune looks like and contents of the pack

Rapamune oral solution is a pale yellow to yellow solution supplied in a 60 mL bottle.

Each pack contains: one bottle (amber glass) containing 60 mL of Rapamune solution, one syringe adapter, 30 dosing syringes (amber plastic) and one syringe carry case.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

Manufacturer:
Pfizer Service Company BV
Hermeslaan 11
1932 Zaventem
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Luxembourg/Luxemburg
Pfizer NV/SA
Tél/Tel: +32 (0)2 554 62 11

България
Пфайзер Люксембург САРЛ, Клон България
Тел: +359 2 970 4333

Česká Republika
Pfizer, spol. s r.o.
Tel: +420 283 004 111

Danmark
Pfizer ApS
Tlf: +45 44 201 100

Deutschland
Pfizer Pharma GmbH
Tel: +49 (0)30 550055-51000

Eesti
Pfizer Luxembourg SARL Eesti filiaal
Tel: +372 666 7500

Ελλάδα
PFIZER ΕΛΛΑΣ A.E.
Τηλ.: +30 210 6785 800

España
Pfizer, S.L.
Télf:+34914909900

France
Pfizer
Tél +33 (0)1 58 07 34 40

Hrvatska
Pfizer Croatia d.o.o.
Tel: + 385 1 3908 777

Lietuva
Pfizer Luxembourg SARL filialas Lietuvoje
Tel. +3705 2514000

Magyarország
Pfizer Kft.
Tel: +36 1 488 3700

Malta
Vivian Corporation Ltd.
Tel: +35621 344610

Nederland
Pfizer bv
Tel: +31 (0)800 63 34 636

Norge
Pfizer AS
Tlf: +47 67 52 61 00

Österreich
Pfizer Corporation Austria Ges.m.b.H.
Tel: +43 (0)1 521 15-0

Polska
Pfizer Polska Sp. z o.o.
Tel.: +48 22 335 61 00

Portugal
Laboratórios Pfizer, Lda.
Tel: +351 21 423 5500

România
Pfizer Romania S.R.L
Tel: +40 (0) 21 207 28 00

Slovenija
Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana
Tel: +386 (0)1 52 11 400

Ireland
Pfizer Healthcare Ireland Unlimited Company
Tel: +1800 633 363 (toll free)
Tel: +44 (0)1304 616161

Ísland
Icepharma hf
Tel: +354 540 8000

Italia
Pfizer S.r.l.
Tel: +39 06 33 18 21

Κύπρος
PFIZER ΕΛΛΑΣ A.E. (Cyprus Branch)
Τηλ: +357 22 817690

Latvija
Pfizer Luxembourg SARL filiāle Latvijā
Tel. +371 67035775

Slovenská Republika
Pfizer Luxembourg SARL, organizačná zložka
Tel: + 421 2 3355 5500

Suomi/Finland
Pfizer Oy
Puh/Tel: +358 (0)9 430 040

Sverige
Pfizer AB
Tel: +46 (0)8 550 520 00

This leaflet was last revised in MM/YYYY

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu

Package leaflet: Information for the user

Rapamune 0.5 mg coated tablets
Rapamune 1 mg coated tablets
Rapamune 2 mg coated tablets
sirolimus

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4

What is in this leaflet

1. What Rapamune is and what it is used for
2. What you need to know before you take Rapamune
3. How to take Rapamune
4. Possible side effects
5. How to store Rapamune
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Rapamune is also used for the treatment of patients with sporadic lymphangioleiomyomatosis (S-LAM) with moderate lung disease or declining lung function. S-LAM is a rare progressive lung disease that affects predominantly women of childbearing age. The most common symptom of S-LAM is shortness of breath.

2. What you need to know before you take Rapamune

Do not take Rapamune

- if you are allergic to sirolimus or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking Rapamune

- If you have any liver problems or have had a disease which may have affected your liver, please tell your doctor as this may affect the dose of Rapamune that you receive and may result in your having additional blood tests.
- Rapamune, like other immunosuppressive medicines, may decrease your body's ability to fight infection, and may increase the risk of developing cancer of the lymphoid tissues and skin.
- If you have a body mass index (BMI) greater than 30 kg/m^2, you may be at increased risk of abnormal wound healing.
- If you are considered to be at high risk for kidney rejection, such as if you had a previous transplant that was lost to rejection.

Your doctor will perform tests to monitor the levels of Rapamune in your blood. Your doctor will also perform tests to monitor your kidney function, your blood fat (cholesterol and/or triglycerides) levels and possibly your liver function, during treatment with Rapamune.

Exposure to sunlight and UV light should be limited by covering your skin with clothing and using a sunscreen with a high protection factor because of the increased risk for skin cancer.

Children and adolescents

There is limited experience on the use of Rapamune in children and adolescents less than 18 years of age. The use of Rapamune is not recommended in this population.

Other medicines and Rapamune

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Some medicines can interfere with the action of Rapamune and, therefore, dose adjustment of Rapamune may be required. In particular, you should inform your doctor or pharmacist if you are taking any of the following:

- any other immunosuppressant medicines.
- antibiotics or antifungal medicines used to treat infection e.g. clarithromycin, erythromycin, telithromycin, troleandomycin, rifabutin, clotrimazole, fluconazole, itraconazole. It is not recommended that Rapamune be taken with rifampicin, ketoconazole or voriconazole.
- any high blood pressure medicines or medicines for heart problems including nicardipine, verapamil and diltiazem.
- anti-epileptic medicines including carbamazepine, phenobarbital, phenytoin.
- medicines used to treat ulcers or other gastrointestinal disorders such as cisapride, cimetidine, metoclopramide.
- bromocriptine (used in the treatment of Parkinson's disease and various hormonal disorders), danazol (used in the treatment of gynaecological disorders), or protease inhibitors (e.g., for HIV and hepatitis C such as ritonavir, indinavir, boceprevir, and telaprevir).
- St. John's Wort (*Hypericum perforatum*).
- letermovir (an antiviral medicine to prevent getting ill from cytomegalovirus).
- cannabidiol (uses amongst others include treatment of seizures).

The use of live vaccines should be avoided with the use of Rapamune. Before vaccinations, please inform your doctor or pharmacist that you are receiving Rapamune.

The use of Rapamune may lead to increased levels of cholesterol and triglycerides (blood fats) in your blood that may require treatment. Medicines known as "statins" and "fibrates" used to treat elevated cholesterol and triglycerides have been associated with an increased risk of muscle breakdown (rhabdomyolysis). Please inform your doctor if you are taking medicines to lower your blood fats.

The combined use of Rapamune with angiotensin-converting enzyme (ACE) inhibitors (a type of medicine used to lower blood pressure) may result in allergic reactions. Please inform your doctor if you are taking any of these medicines.

Rapamune with food and drink

Rapamune should be taken consistently, either with or without food. If you prefer to take Rapamune with food, then you should always take it with food. If you prefer to take Rapamune without food, then you should always take it without food. Food can affect the amount of medicine that gets into your bloodstream, and taking your medicine in a consistent way means that the blood levels of Rapamune remain more stable.

Rapamune should not be taken with grapefruit juice.

Pregnancy, breast-feeding and fertility

Rapamune should not be used during pregnancy unless clearly necessary. You must use an effective method of contraception during treatment with Rapamune and for 12 weeks after treatment has stopped. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

It is not known whether Rapamune passes into breast milk. Patients taking Rapamune should discontinue breast-feeding.

Decreased sperm count has been associated with the use of Rapamune and usually returns to normal once treatment is stopped.

Driving and using machines

Although Rapamune treatment is not expected to affect your ability to drive, if you have any concerns please consult your doctor.

Rapamune contains lactose and sucrose

Rapamune contains 86.4 mg of lactose and up to 215.8 mg of sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Rapamune

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will decide exactly what dose of Rapamune you must take and how often to take it. Follow your doctor’s instructions exactly, and never change the dose yourself.

Rapamune is for oral use only. Do not crush, chew, or split the tablets. Inform your doctor if you have difficulty taking the tablet.

Multiples of 0.5 mg tablets should not be used as a substitute for 1 mg and 2 mg tablets, as the different strengths are not directly interchangeable.

Rapamune should be taken consistently, either with or without food.

<u>Kidney Transplant</u>
Your doctor will give you an initial dose of 6 mg as soon as possible after the kidney transplant operation. Then you will need to take 2 mg of Rapamune each day, until otherwise directed by your

doctor. Your dose will be adjusted depending on the level of Rapamune in your blood. Your doctor will need to perform blood tests to measure Rapamune concentrations.

If you are also taking ciclosporin, then you must take the two medicines approximately 4 hours apart.

It is recommended that Rapamune be used first in combination with ciclosporin and corticosteroids. After 3 months, your doctor may discontinue either Rapamune or ciclosporin, as it is not recommended that these medicines be taken together beyond this period.

Sporadic Lymphangioleiomyomatosis (S-LAM)
Your doctor will give you 2 mg of Rapamune each day, until otherwise directed by your doctor. Your dose will be adjusted depending on the level of Rapamune in your blood. Your doctor will need to perform blood tests to measure Rapamune concentrations.

If you take more Rapamune than you should

If you have taken more medicine than you were told to, contact a doctor or go to the nearest hospital emergency department as soon as possible. Always take the labelled blister with you, even if it is empty.

If you forget to take Rapamune

If you forget to take Rapamune, take it as soon as you remember, but not within 4 hours of the next dose of ciclosporin. After that, continue to take your medicines as usual. Do not take a double dose to make up for a forgotten dose, and always take Rapamune and ciclosporin approximately 4 hours apart. If you miss a dose of Rapamune completely, you should inform your doctor.

If you stop taking Rapamune

Do not stop taking Rapamune unless your doctor tells you to, as you risk losing your transplant.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions

You should **see your doctor immediately** if you experience symptoms, such as swollen face, tongue and/or back of the mouth (pharynx) and/or difficulties in breathing (angioedema), or a skin condition whereby the skin can peel off (exfoliative dermatitis). These may be symptoms of a serious allergic reaction.

Kidney damage with low blood cell counts (thrombocytopaenic purpura/haemolytic uraemic syndrome)

When taken with medicines called calcineurin inhibitors (ciclosporin or tacrolimus), Rapamune may increase the risk of kidney damage with low blood platelets and low red blood cell counts, with or without rash (thrombocytopaenic purpura/haemolytic uraemic syndrome). If you experience symptoms such as bruising or rash, changes in your urine, or changes in behaviour or any others that are serious, unusual or prolonged, contact your doctor.

Infections

Rapamune reduces your body's own defence mechanisms. Consequently your body will not be as good as normal at fighting infections. So if you are taking Rapamune, you may therefore catch more infections than usual, such as infections of the skin, mouth, stomach and intestines, lungs and urinary tract (see list below). You should contact your doctor if you experience symptoms that are serious, unusual, or prolonged.

Side effect frequencies

Very common: may affect more than 1 in 10 people

- Fluid collection around the kidney
- Swelling of the body including hands and feet
- Pain
- Fever
- Headache
- Increased blood pressure
- Stomach pain, diarrhoea, constipation, nausea
- Low red blood cells, low blood platelets
- Increased fat in the blood (cholesterol and/or triglycerides), increased blood sugar, low blood potassium, low blood phosphorus, increased lactate dehydrogenase in the blood, increased creatinine in the blood
- Joint pain
- Acne
- Urinary tract infection
- Pneumonia and other bacterial, viral, and fungal infections
- A reduced number of infection-fighting cells in the blood (white blood cells)
- Diabetes
- Abnormal tests of liver function, elevated AST and/or ALT liver enzymes
- Rash
- Elevated protein in the urine
- Menstrual disorders (including absent, infrequent or heavy periods)
- Slow healing (this may include separation of the layers of a surgical wound or stitch line)
- Rapid heart rate
- There is a general tendency for fluid to collect in various tissues.

Common: may affect up to 1 in 10 people

- Infections (including life-threatening infections)
- Blood clots in the legs
- Blood clots in the lung
- Mouth sores
- Fluid collection in the abdomen
- Kidney damage with low blood platelets and low red blood cell counts, with or without rash (haemolytic uraemic syndrome)
- Low levels of a type of white blood cells called neutrophils
- Deterioration of bone
- Inflammation that may lead to lung damage, fluid around the lung
- Nose bleeds
- Skin cancer
- Kidney infection
- Ovarian cysts
- Fluid collection in the sac around the heart, that in some cases may decrease the heart's ability to pump blood

– Inflammation of the pancreas
– Allergic reactions
– Shingles
– Cytomegalovirus infection

Uncommon: may affect up to 1 in 100 people

– Cancer of the lymph tissue (lymphoma/post-transplant lympho-proliferative disorder), combined lowering of red blood cells, white blood cells and blood platelets
– Bleeding from the lung
– Protein in the urine, occasionally severe and associated with side effects, such as swelling
– Scarring in the kidney that may reduce kidney function
– Too much fluid collecting in the tissues due to irregular lymph function
– Low blood platelets, with or without rash (thrombocytopaenic purpura)
– Serious allergic reactions that can cause peeling of the skin
– Tuberculosis
– Epstein-Barr virus infection
– Infectious diarrhoea with *Clostridium difficile*
– Serious liver damage

Rare: may affect up to 1 in 1,000 people

– Protein build-up in the air sacs of the lungs that may interfere with breathing
– Serious allergic reactions that can affect blood vessels (see above paragraph on allergic reactions)

Not known: frequency cannot be estimated from the available data

– Posterior reversible encephalopathy syndrome (PRES), a serious nervous system syndrome that has the following symptoms: headache, nausea, vomiting, confusion, seizures, and visual loss. Should any of these occur together, please contact your physician.

S-LAM patients experienced similar side effects to those of kidney transplant patients, with the addition of weight loss, which may affect up to 1 in 10 people.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rapamune

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the blister and carton after “EXP”. The expiry date refers to the last day of that month.

Do not store above 25˚C.

Keep the blister in the outer carton in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Rapamune contains

The active substance is sirolimus.
Each Rapamune 0.5 mg coated tablet contains 0.5 mg of sirolimus.
Each Rapamune 1 mg coated tablet contains 1 mg of sirolimus.
Each Rapamune 2 mg coated tablet contains 2 mg of sirolimus.

The other ingredients are:

Tablet core: lactose monohydrate, macrogol, magnesium stearate, talc
Tablet coating: macrogol, glycerol monooleate, pharmaceutical glaze, calcium sulfate, microcrystalline cellulose, sucrose, titanium dioxide, poloxamer 188, α-tocopherol, povidone, carnauba wax, Printing ink (Shellac, Iron Oxide Red, Propylene Glycol [E1520], Concentrated Ammonia Solution, Simethicone). The 0.5 mg and 2 mg tablets also contain yellow iron oxide (E172) and brown iron oxide (E172).

What Rapamune looks like and contents of the pack

Rapamune 0.5 mg is supplied to you as tan-coloured, triangular-shaped, coated tablets marked "RAPAMUNE 0.5 mg" on one side.

Rapamune 1 mg is supplied to you as white-coloured, triangular-shaped, coated tablets marked "RAPAMUNE 1 mg" on one side.

Rapamune 2 mg is supplied to you as yellow to beige-coloured, triangular-shaped, coated tablets marked "RAPAMUNE 2 mg" on one side.

The tablets are supplied in blister packs of 30 and 100 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

Manufacturer:
Pfizer Ireland Pharmaceuticals Unlimited Company
Little Connell
Newbridge
Co. Kildare
W12 HX57
Ireland

Pfizer Manufacturing Deutschland GmbH
Mooswaldallee 1
79108 Freiburg Im Breisgau
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Luxembourg/Luxemburg
Pfizer NV/SA
Tél/Tel: +32 (0)2 554 62 11

Lietuva
Pfizer Luxembourg SARL filialas Lietuvoje
Tel. +3705 2514000

България
Пфайзер Люксембург САРЛ, Клон България
Тел: +359 2 970 4333

Česká Republika
Pfizer, spol. s r.o.
Tel: +420 283 004 111

Danmark
Pfizer ApS
Tlf: +45 44 201 100

Deutschland
Pfizer Pharma GmbH
Tel: +49 (0)30 550055-51000

Eesti
Pfizer Luxembourg SARL Eesti filiaal
Tel: +372 666 7500

Ελλάδα
PFIZER ΕΛΛΑΣ Α.Ε.
Τηλ.: +30 210 6785 800

España
Pfizer, S.L.
Télf:+34914909900

France
Pfizer
Tél +33 (0)1 58 07 34 40

Hrvatska
Pfizer Croatia d.o.o.
Tel: + 385 1 3908 777

Ireland
Pfizer Healthcare Ireland Unlimited Company
Tel: +1800 633 363 (toll free)
Tel: +44 (0)1304 616161

Ísland
Icepharma hf
Tel: +354 540 8000

Italia
Pfizer S.r.l.
Tel: +39 06 33 18 21

Magyarország
Pfizer Kft.
Tel: +36 1 488 3700

Malta
Vivian Corporation Ltd.
Tel: +35621 344610

Nederland
Pfizer bvTel: +31 (0)800 63 34 636

Norge
Pfizer AS
Tlf: +47 67 52 61 00

Österreich
Pfizer Corporation Austria Ges.m.b.H.
Tel: +43 (0)1 521 15-0

Polska
Pfizer Polska Sp. z o.o.
Tel.: +48 22 335 61 00

Portugal
Laboratórios Pfizer, Lda.
Tel: +351 21 423 5500

România
Pfizer Romania S.R.L
Tel: +40 (0) 21 207 28 00

Slovenija
Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana
Tel: +386 (0)1 52 11 400

Slovenská Republika
Pfizer Luxembourg SARL, organizačná zložka
Tel: + 421 2 3355 5500

Suomi/Finland
Pfizer Oy
Puh/Tel: +358 (0)9 430 040

Sverige
Pfizer AB
Tel: +46 (0)8 550 520 00

Κύπρος
PFIZER ΕΛΛΑΣ A.E. (Cyprus Branch)
Τηλ: +357 22 817690

Latvija
Pfizer Luxembourg SARL filiāle Latvijā
Tel. +371 67035775

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Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.