APPROVED PACKAGE INSERT

SCHEDULING STATUS:

S4

PROPRIETARY NAME (and dosage form):

RAPAMUNE® 1 mg Tablets

COMPOSITION:

Each tablet contains 1 mg sirolimus.

The other ingredients are:
Tablet core: lactose monohydrate, macrogol, magnesium stearate, talc.
Tablet coating: macrogol, glycerol monooleate, pharmaceutical glaze, calcium sulphate, microcrystalline cellulose, sucrose, titanium dioxide, poloxamer 188, α-tocopherol, povidone, carnauba wax.

PHARMACOLOGICAL CLASSIFICATION:

A 34 Other

PHARMACOLOGICAL ACTION:

Sirolimus inhibits T cell activation and proliferation that occurs in response to antigenic and cytokine (Interleukin 2, 4 and 15) stimulation by blocking calcium dependent and calcium independent intracellular signal transduction. Sirolimus also inhibits antibody production.

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 direct effect on T and B cell activation suppressing immune mediated reactions such as allograft rejection, collagen-induced arthritis, experimental allergic encephalomyelitis, graft versus host disease and experimental uveitis.

Pharmacokinetics

Absorption:

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

The systemic availability (F) of sirolimus from the oral solution was estimated to be approximately 14 %. After sirolimus administration by tablet, F was estimated to be approximately 17 %. Sirolimus concentrations are dose proportional between 3 and 12 mg/m^2 after administration of the sirolimus oral solution in stable renal transplant patients, and between 5 and 40 mg after administration by sirolimus tablet in healthy volunteers.

Distribution:

The mean (± SD) blood-to-plasma ratio (B/P) of sirolimus was 36 (± 17,9) in stable renal allograft recipients after administration of the oral solution, indicating that sirolimus is extensively partitioned into formed blood products.

The mean volume of distribution (V_{ss}/F) of sirolimus when administered as the oral solution is 12 ± 7,52 l/kg. Sirolimus is extensively bound (approximately 92 %) to human plasma proteins.

Metabolism:

Sirolimus is a substrate for both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein. Sirolimus is extensively metabolised by O-demethylation and/or hydroxylation. Seven major metabolites, including hydroxy-, demethyl- and hydroxydemethyl, are identifiable in whole blood. Some of these metabolites were also detectable in plasma, faecal and urine samples. Glucuronide and sulphate conjugates were not present in any of the biologic matrices.

Sirolimus is the major component in human blood and contributes to greater than 90 % of the immunosuppressive activity.

Elimination:

After a single dose of ^{14}C sirolimus by oral solution in healthy volunteers, the majority (91,1 %) of radioactivity was recovered from the faeces, and only a minor amount (2,2 %) was excreted in urine.

The terminal half-life in stable renal transplant patients after multiple oral doses of the oral solution was estimated to be about 62 ± 16 h.

The effective half-life, however, is shorter and mean steady-state concentrations were achieved after 5 to 7 days.

Effect of Food:

In healthy volunteers, a high-fat meal altered the bioavailability characteristics of sirolimus after administration of the oral solution. There was a 34 % decrease in the peak blood sirolimus concentration (C_{max}), a 3,5-fold increase in the time to peak concentration (t_{max}), and a 35 % increase in total exposure (AUC). After administration of the tablets and a high-fat meal in healthy volunteers, $C_{max,}$ t_{max}, and AUC showed increases of 65 %, 32 % and 23 % respectively.

It is recommended that Rapamune be taken consistently either with or without food.

The use of orange juice and water to dilute Rapamune were equivalent with respect to $C_{max,}$, and AUC. Grapefruit juice reduces CYP3A4-mediated drug metabolism and potentially enhances P-gp mediated drug counter-transport from enterocytes of the small intestine and must not be used for dilution or taken with Rapamune.

Initial Therapy with cyclosporin (2 to 4 months post-transplant):

In most patients receiving sirolimus 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 sirolimus tablets administered in combination with cyclosporin micro-emulsion (4 hours prior to sirolimus 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 h; $AUC_{\tau,ss,}$ 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 trial 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 h, $AUC_{\tau,ss}$ 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 cyclosporin, mean (10th, 90th percentiles) troughs (by immunoassay) and daily doses were 10,8 (6,3 to 15,8) ng/ml and 2,09 (1,5 to 2,7) mg/day, respectively.

Maintenance Therapy following cyclosporin (CsA) withdrawal:

Therapy from month 3 to month 12:

Following discontinuation of cyclosporin, mean (10th, 90th percentiles) troughs (by immunoassay) and daily doses were 23,3 (16,9 to 29,6) ng/ml and 8,2 (3,8 to 13,6) mg/day respectively.
Therefore, the sirolimus dose was approximately 4-fold higher to account for both the absence of the pharmacokinetic interaction with cyclosporin (2-fold increase) and the augmented immunosuppressive requirement in the absence of cyclosporin (2-fold increase).

Kinetics in special clinical situations*:*

Elderly: Clinical studies with sirolimus did not include a sufficient number of patients > 65 years of age to determine whether they will respond differently than younger patients. Sirolimus trough concentration data after sirolimus oral solution in 35 renal transplant patients > 65 years of age were similar to those in the adult population (n = 822) from 18 to 65 years of age.
Children: 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, there were no statistically significant differences due to age in t½, V_{ss}/F, or B/P. However, values of AUC tended to show less than proportional increases with dose, and the mean weight normalised CL/F was larger for younger paediatric patients (544 ml/h/kg) than for older paediatric patients (443 ml/h/kg).

A meta-analysis comparing paediatric patients with healthy adults revealed that mean CL/F in young paediatric patients were also significantly greater than those in healthy adults (287 ml/h/kg).

Sirolimus pharmacokinetic data were collected in concentration-controlled trials of paediatric renal transplant patients who were also receiving cyclosporin and corticosteroids. The target ranges for trough concentrations were either 10-20 ng/ml for the 21 children receiving tablets, or 5-15 ng/ml for the one child receiving oral solution. The children aged 6-11 years (n = 8) received mean ± SD doses of 1,75 ± 0,71 mg/day (0,064 ± 0,018 mg/kg, 1,65 ± 0,43 mg/m^2). The children aged 12-18 years (n = 14) received mean ± SD doses of 2,79 ± 1,25 mg/day (0,053 ± 0,0150 mg/kg, 1,86 ± 0,61 mg/m^2). At the time of sirolimus blood sampling for pharmacokinetic evaluation, the majority (80 %) of these paediatric patients received the sirolimus dose at 16 hours after the once daily cyclosporin dose.

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN PAEDIATRIC RENAL TRANSPLANT PATIENTS (MULTIPLE DOSE CONCENTRATION CONTROL)

Age (y)	n	Body weight (kg)	$C_{max,ss}$ (ng/ml)	$t_{max,ss}$ (h)	$C_{min,ss}$ (ng/ml)	$AUC_{\tau,ss}$ (ng•h/ml)	CL/F[c] (ml/h/kg)	CL/F[c] (l/h/m^2)
6-11	8	27 ± 10	22,1 ± 8,9	5,88 ± 4,05	10,6 ± 4,3	356 ± 127	214 ± 129	5,4 ± 2,8
12-18	14	52 ± 15	34,5 ± 12,2	2,7 ± 1,5	14,7 ± 8,6	466 ± 236	136 ± 57	4,7 ± 1,9

a: Sirolimus co-administered with cyclosporin oral solution and/or cyclosporin capsules.
b: As measured by Liquid Chromatographic/Tandem Mass Spectrometric Method (LC/MS/MS)
c: Oral-dose clearance adjusted by either body weight (kg) or body surface area (m^2).

Liver insufficiency: In mild and moderate hepatically impaired patients (Child-Pugh classification of A or B), mean values for sirolimus AUC and $t_{½}$ were increased 61 % and 43 % respectively and CL/F was decreased 33 % compared to normal healthy subjects. There were no statistically significant differences between the two populations in $C_{max,}$ $t_{max,}$ V_{ss}/F and B/P.

The mean $t_{½}$ increased from 79 ± 12 hours in subjects with normal hepatic function to 113 ± 41 hours in patients with impaired hepatic function.
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 67 % compared to normal healthy subjects. There were no statistically significant differences between the two populations in C_{max}, t_{max}, or V_{ss}/F. The mean $t_{i/2}$ increased from 80 ± 5 hours in subjects with normal hepatic function to 214 ± 69 hours in patients with severe impairment of hepatic function.

Renal insufficiency: The pharmacokinetics of sirolimus are very similar in various populations with renal function ranging from normal to absent (dialysis patients). Metabolic studies show that there is very minimal renal excretion of the drug or its metabolites.

Renal transplant patients: Mean (±SD) pharmacokinetic parameters for sirolimus given daily by oral solution in combination with CsA and corticosteroids in renal transplant patients were determined at months 1, 3 and 6 after transplantation. There were no significant differences in $C_{max,}$ t_{max}, AUC and CL/F with respect to treatment group or month. After daily administration of sirolimus in renal transplant patients by oral solution and tablet, estimates of $C_{max,}$ AUC and CL/F did not appear to be different; but t_{max} was significantly different.
Mean whole blood sirolimus trough concentrations in patients receiving either sirolimus by oral solution or tablet with a loading dose of three times the maintenance dose achieved steady-state concentrations within 24 hours after the start of dose administration.

Gender: After the administration of sirolimus oral solution, the clearance in males was 12 % lower than that in females; male subjects had a significantly longer $t_{1/2}$ than did female subjects (72,3 hours versus 61,3 hours). A similar trend in the effect of gender on sirolimus oral dose clearance and $t_{1/2}$ was observed after the administration of sirolimus tablets. Dose adjustments based on gender are not recommended.

INDICATIONS:
Rapamune is indicated for the prophylaxis of organ rejection in patients receiving renal transplants.

Rapamune should be used initially in a regimen with cyclosporin (CsA) micro-emulsion and corticosteroids. CsA withdrawal could be considered 2 to 4 months after transplantation in patients at low to moderate immunological risk of graft loss, and the Rapamune dose should be increased to reach recommended blood concentrations (see Dosage and Directions for Use). Cyclosporin withdrawal has not been studied in patients with Banff 93 grade III acute rejection or vascular rejection prior to CsA withdrawal, those who are dialysis-dependent, or with serum creatinine > 0,25 mmol/l, black patients, renal re-transplants, multi-organ transplants, or patients with high-panel reactive antibodies. (See Dosage and Directions for Use)

CONTRA-INDICATIONS:

Rapamune is contra-indicated in patients with a hypersensitivity to sirolimus or any of the excipients.
Pregnancy and lactation.
De novo liver or lung transplantation.
Concomitant use with grapefruit juice.

WARNINGS:

Immunosuppression increases the susceptibility to infection and the development of lymphoma and other malignancies, particularly of the skin. Oversuppression of the immune system can also increase susceptibility to opportunistic infections, sepsis, and fatal infections (see Precautions and Side-effects).

Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, exfoliative dermatitis and hypersensitivity vasculitis have been associated with the administration of sirolimus (See Side-effects).

The safety and efficacy of Rapamune as immunosuppressive therapy have not been established in *de novo* liver or lung transplant patients, and is therefore contra-indicated.

Liver Transplantation – Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis (HAT): The use of Rapamune in combination with tacrolimus was associated with excess

mortality and graft loss in a study in *de novo* liver transplant recipients. Many of these patients had evidence of infection at or near the time of death.

In this and another study in *de novo* liver transplant recipients, the use of Rapamune in combination with CsA or tacrolimus was associated with an increase in HAT; most cases of HAT occurred within 30 days post-transplantation and most led to graft loss or death.

A clinical study in liver transplant patients randomised to conversion to a Rapamune-based regimen versus continuation of a calcineurin inhibitors (CNI)-based regimen 6 -144 months post-liver transplantation demonstrated an increased number of deaths in the Rapamune conversion group compared to the CNI continuation group.

Lung Transplantation – Bronchial Anastomotic Dehiscence:
Cases of bronchial anastomotic dehiscence, most fatal, have been reported in *de novo* lung transplant patients when Rapamune has been used as part of an immunosuppressive regimen.

Co-administration of Rapamune with strong inhibitors of CYP3A4 and/or P-gp (such as ketoconazole, voriconazole, itraconazole, telithromycin, or clarithromycin) or strong inducers of CYP3A4 and/or P-gp (such as rifampin or rifabutin) is not recommended. Rapamune is extensively metabolised by the CYP3A4 isozyme in the intestinal wall and liver. Inhibitors of CYP3A4 decrease the metabolism of Rapamune and increase Rapamune levels. Inducers of CYP3A4 increase the metabolism of Rapamune and decrease Rapamune levels (See Interactions).

INTERACTIONS:

1) Inhibitors and Inducers of Cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp):
Co-administration of Rapamune with strong inhibitors of CYP3A4 (such as ketoconazole, voriconazole, itraconazole, telithromycin, or clarithromycin) or inducers of CYP3A4 (such as rifampin or rifabutin) is not recommended (See Warnings).
Rapamune is extensively metabolised by the CYP3A4 isozyme in the gut wall and liver and undergoes counter-transport from enterocytes of the small intestine by the P-glycoprotein (P-gp) drug-efflux pump. Therefore, absorption and the subsequent elimination of systemically

absorbed Rapamune may be influenced by agents that affect these proteins. **Inhibitors of CYP3A4 and P-gp may increase Rapamune levels. Inducers of CYP3A4 and P-gp may decrease Rapamune levels.**

In patients in whom strong inhibitors or inducers of CYP3A4 and P-gp are indicated, alternative therapeutic agents with less potential for inhibition or induction of CYP3A4 and P-gp should be considered.

Medicines that inhibit CYP3A4 include but are not limited to:	**Medicines that induce CYP3A4 include but are not limited to:**
Calcium channel blockers: nicardipine, verapamil,diltiazem Antifungal agents: clotrimazole, fluconazole, itraconazole, ketoconazole, voriconazole Antibiotics: clarithromycin, erythromycin, telithromycin, troleandomycin Gastrointestinal prokinetic agents: cisapride, metoclopramide Other medicines: bromocriptine, cimetidine, CsA, danazol, HIV-protease inhibitors (e.g. ritonavir, indinavir) Grapefruit juice	Anticonvulsants: carbamazepine, phenobarbital, phenytoin Antibiotics: rifabutin, rifampicin, rifapentine Herbal preparations: St. John's Wort (Hypericum perforatum, hypericin)

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

a) ***Diltiazem:***

Diltiazem is a substrate and inhibitor of CYP3A4 and P-gp. If diltiazem is administered, Rapamune blood levels should be monitored and a dose reduction may be necessary.

The simultaneous oral administration of 10 mg of Rapamune oral solution and 120 mg of diltiazem to 18 healthy volunteers significantly increased the bioavailability of Rapamune.

Rapamune $C_{max,}$ $t_{max,}$ and AUC were increased 1,4-, 1,3-, and 1,6-fold respectively. Rapamune did not affect the pharmacokinetics of either diltiazem or its metabolites desacetyldiltiazem and desmethyldiltiazem.

b) ***Verapamil:***

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

Multiple-dose administration of verapamil and Rapamune oral solution significantly affected the rate and extent of absorption of both medicines. Whole blood Rapamune $C_{max,}$ $t_{max,}$ 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 %.

c) ***Erythromycin:***

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

Multiple-dose administration of erythromycin ethylsuccinate and Rapamune oral solution significantly increased the rate and extent of absorption of both medicines. Whole blood Rapamune $C_{max,}$ $t_{max,}$ 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.

d) ***Ketoconazole:***

Ketoconazole is a strong inhibitor of CYP3A4 and P-gp. Co-administration of Rapamune and ketoconazole is not recommended.
Multiple-dose ketoconazole administration significantly affected the rate and extent of absorption and sirolimus exposure after administration of Rapamune oral solution, as reflected by increases in sirolimus $C_{max,}$ $t_{max,}$ and AUC of 4,4 fold (332 %), 1,4 fold (38 %), and 10,9 fold (990 %), respectively. However, the terminal $t_{½}$ of sirolimus was not changed.

Single-dose Rapamune did not affect steady-state 12-hour plasma ketoconazole concentrations.

e) ***Rifampicin:***

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

Pre-treatment of 14 healthy volunteers with multiple doses of rifampicin, 600 mg daily for 14 days, followed by a single 20 mg-dose of Rapamune by oral solution, greatly increased Rapamune oral-dose clearance by 5,5 fold (range = 2,8 to 10) which represents mean decreases in AUC and C_{max} of about 82 % and 71 %, respectively.

2) Cyclosporin (CsA):

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

Patients administered Rapamune with CsA should be monitored for the development of rhabdomyolysis.

Cyclosporin micro-emulsion:

It is recommended that Rapamune be taken 4 hours after cyclosporin (micro-emulsion) administration.

3) HMG-CoA Reductase Inhibitors, Fibrates:

Patients administered Rapamune with HMG-CoA reductase inhibitors and/or fibrates should be monitored for the development of rhabdomyolysis.

4) Calcineurin Inhibitors:

Calcineurin inhibitor-reduced haemolytic uraemic syndrome/thrombotic thrombocytopaenic purpura/ thrombotic microangiopathy (HUS/TTP/TMA) has been reported in patients receiving Rapamune with a calcineurin inhibitor.

5) Vaccinations:

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

6) Food:

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

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

PREGNANCY AND LACTATION:

See Contra-indications.

There are no studies of Rapamune use in pregnant women.

In animal studies, embryo/foetal toxicity was manifested as mortality and reduced foetal weights (with associated delays in skeletal ossification). However, no teratogenesis was evident. In combination with cyclosporin, rats had increased embryo/feto mortality compared to Rapamune alone. There were no effects on rabbit development at the maternally toxic dosage of 0,05 mg/kg (approximately 0,3 to 0,8 times the clinical doses adjusted for body surface area).

Rapamune should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo/ foetus (see Precautions).

Effective contraception must be used before and during Rapamune therapy and for 12 weeks after Rapamune has been stopped.

It is not known whether Rapamune is excreted in human milk. A decision should be made whether to discontinue breast feeding or to discontinue Rapamune therapy.

DOSAGE AND DIRECTIONS FOR USE:

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

Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Rapamune. Patients receiving Rapamune should be managed in facilities equipped and staffed with adequate laboratory and supportive medical

resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

Rapamune and CsA combination therapy

For *de novo* transplant recipients, a loading oral dose of Rapamune corresponding to 3 times the maintenance dose should be given.

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

It is recommended that Rapamune be used initially in a regimen with CsA and corticosteroids. CsA could be withdrawn 2 to 4 months after renal transplantation in patients at low to moderate immunologic risk, and the Rapamune dose should be increased to reach the recommended blood concentrations. Cyclosporin withdrawal has not been studied in patients with Banff 93 grade III acute rejection or vascular rejection prior to CsA withdrawal, those who are dialysis-dependent, or with serum creatinine > 0,25 mmol/l, black patients, renal re-transplants, multi-organ transplants, or patients with high-panel reactive antibodies. (See Dosage and Directions for Use).

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

Initially, patients should be receiving Rapamune and CsA combination therapy. At 2 to 4 months following transplantation, CsA should be progressively discontinued over 4 to 8 weeks and the Rapamune dose should be adjusted to obtain whole blood trough concentrations within the range of 16 to 24 ng/ml (chromatographic method) for the first year following transplantation. Thereafter, the target Rapamune concentrations should be 12 to 20 ng/ml (chromatographic method). The actual observations at year 1 and 5 (see below) were close to these ranges.

CsA inhibits the metabolism and transport of Rapamune, and consequently, Rapamune levels will decrease when cyclosporin is discontinued unless the Rapamune dose is increased. On average, the Rapamune dose will need to be 4-fold higher to account for both the absence of

the pharmacokinetic interaction (approximately 2-fold increase) and the augmented immunosuppressive requirement in the absence of cyclosporin (approximately 2-fold increase).

The rate at which the dose of Rapamune is increased should correspond to the rate of CsA elimination.

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

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

It is recommended that Rapamune be taken 4 hours after cyclosporine microemulsion administration.

Use in children below 13 years: The safety and efficacy of Rapamune in paediatric patients below the age of 13 years have not been established.

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

Safety and efficacy information from a controlled clinical trial in paediatric and adolescent (<18 years of age) renal transplant recipients judged to be at high immunologic risk, defined as a history of one or more acute rejections episodes and/or the presence of chronic allograft nephropathy, do not support the chronic use of Rapamune oral solution or tablets in combination with calcineurin inhibitors and corticosteroids, due to the increased risk of lipid abnormalities and deterioration of renal function associated with these immunosuppressive regimens, without increased benefit with respect to acute rejection, graft survival, or patient survival.
The safety and efficacy of Rapamune oral solution and Rapamune tablets have not been studied in children aged 13 or older judged to be at low to moderate immunologic risk. Use of Rapamune oral solution and Rapamune tablets in this subpopulation of children aged 13 or older is supported by evidence from adequate and well-controlled trials of Rapamune oral solution in adults with additional pharmacokinetic data in paediatric renal transplantation recipients.

Use in elderly patients: No dosage adjustment is required in elderly patients.
Clinical studies of Rapamune did not include a sufficient number of patients > 65 years of age to determine whether they will respond differently than younger patients. Rapamune trough concentration data after oral solution in 35 renal transplant patients > 65 years of age were similar to those in the adult population (n = 822) from 18 to 65 years of age.

Patients with renal dysfunction: No dosage adjustment required (See Pharmacokinetic properties).

Patients with hepatic impairment:
The maintenance dose of Rapamune should be approximately one third in patients with mild to moderate hepatic impairment and by approximately a half in patients with severe hepatic impairment.

Dosage should also be adjusted in patients who experience acute hepatic impairment post-transplantation. It is not necessary to modify the Rapamune loading dose (see Pharmacokinetic properties). In patients with hepatic impairment, it is recommended that Rapamune whole blood trough levels be monitored.

Rapamune whole blood trough level monitoring: (See Assay Methodology section below)
Blood sirolimus trough levels should be monitored:

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

Therapeutic drug monitoring should not be the sole basis for adjusting Rapamune therapy. Careful attention should be made to clinical signs/symptoms, tissue biopsy, and laboratory parameters.
It is recommended that patients switched from the solution to the tablet formulation on a mg per mg basis have a trough concentration taken 1 or 2 weeks after switching formulations to confirm that the trough concentration is within the recommended target range.

Assay methodology:
The recommended 24-hour trough concentration ranges for Rapamune are based on chromatographic methods. Several assay methodologies have been used to measure the whole blood concentrations of Rapamune. Currently in clinical practice, Rapamune whole blood concentrations are being measured by both chromatographic and immunoassay methodologies. The concentration values obtained by these different methodologies are not interchangeable. Adjustments to the targeted range should be made according to the assay being utilised to determine the Rapamune trough concentration. Since results are assay and laboratory dependent, and the results may change over time, adjustment to the targeted therapeutic range must be made with a detailed knowledge of the site-specific assay method used.
Instructions for handling and use:

Oral Solution:
Since Rapamune is not absorbed through the skin, there are no special precautions. However, if direct contact with the skin or mucous membranes occurs, wash thoroughly with soap and water, rinse eyes with plain water.
At the time of use, an adapter and a dip tube should be inserted into the neck of the bottle and the prescribed amount of Rapamune should be withdrawn using the oral dosing syringe supplied.
Empty the correct amount of Rapamune from the syringe into a glass or plastic container with at least 60 ml of water or orange juice.
Do not use any liquids other than water or orange juice for dilution. **Grapefruit juice must not be used.** Stir vigorously and drink at once.

Refill the glass container with an additional volume (minimum of 120 ml) of water or orange juice, stir vigorously, and drink at once.
Discard the syringe after one use.

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

Rapamune oral solution contains polysorbate-80, which is known to increase the rate of di-(2-ethylhexyl) phthalate (DEHP) extraction from polyvinyl chloride (PVC). This should be considered during the preparation and administration of Rapamune oral solution. It is important that the recommendations in Dosage and Directions for Use be followed closely.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects

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

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

Adverse reactions are listed in the table in CIOMS frequency categories:

Very Common: ≥ 10 %

Common: ≥ 1 % and < 10 %

Uncommon: ≥ 0,1 % and < 1 %

Rare: ≥ 0,01 % and < 0,1 %

Very Rare: < 0,01 %

Body System	***Adverse Reaction***
BODY AS A WHOLE	
Very common:	Lymphocele, peripheral oedema, fever, headache, pain
Common:	Abnormal wound healing; oedema; fungal, viral, and bacterial infections (such as mycobacterial infections including tuberculosis, Epstein-Barr virus, CMV, and Herpes Zoster); herpes simplex; sepsis
Rare:	Lymphoedema
CARDIOVASCULAR	
Very common:	Hypertension
Common:	Tachycardia; venous thromboembolism (including pulmonary embolism, deep vein thrombosis)
Rare:	Pericardial effusion (including haemodynamically significant effusions in children and adults
DIGESTIVE	
Very common:	Abdominal pain; diarrhoea, constipation, nausea
Common:	Stomatitis, ascites
Uncommon:	Pancreatitis
HAEMATOLOGICAL/LYMPHATIC	

Very common:	Particularly at higher doses: Anaemia; thrombocytopenia;
Common:	Leukopenia; neutropenia; thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome
Uncommon:	Lymphoma/post-transplant lymphoproliferative disorder; Pancytopenia

IMMUNE SYSTEM

Rare:	Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, and hypersensitivity vasculitis have been associated with the administration of Rapamune (see Warnings).

METABOLIC/NUTRITIONAL

Very common:	Hypertriglyceridaemia (hyperlipaemia); hypercholesterolaemia; hyperphosphataemia; hyperglycaemia; hypokalaemia; increased lactic dehydrogenase (LDH), increased creatinine
Common:	Abnormal liver function tests, increased ALT; increased AST, fluid accumulation

MUSCULOSKELETAL

Very common:	Arthralgia
Common:	Bone necrosis

RESPIRATORY (see also text below for pneumonitis)

Common:	Epistaxis; pneumonia, pneumonitis, pleural effusion
Uncommon:	Pulmonary haemorrhage
Rare:	Alveolar proteinosis

SKIN

Very common:	Acne
Common:	Rash, squamous cell carcinoma, basal cell carcinoma
Uncommon:	Melanoma

Rare:	Exfoliative dermatitis (see Warnings)

UROGENITAL

Very common:	Urinary tract infection
Common:	Pyelonephritis, proteinuria
Uncommon:	Nephrotic syndrome

Adverse events in which frequencies are unknown: Focal segmental glomerulosclerosis

Rapamune following CsA withdrawal: The incidence of adverse reactions was determined through 60 months in a randomised, multicentre controlled trial in which 215 renal transplant patients received Rapamune as a maintenance regimen following CsA withdrawal, and 215 patients received Rapamune with CsA therapy. All patients were treated with corticosteroids. The safety profile prior to randomisation (start of CsA withdrawal) was similar to that of the 2-mg Rapamune groups in studies of Rapamune in combination with CsA. Following randomisation (at 3 months), patients who had CsA eliminated from their therapy experienced significantly higher incidences of increased AST and increased ALT, liver damage, hypokalaemia, thrombocytopenia, abnormal healing, acne, ileus, and joint disorder. Conversely, the incidence of acidosis, hypertension, CsA toxicity, increased creatinine, abnormal kidney function, toxic nephropathy, oedema, hyperuricaemia, gout, and gum hyperplasia was significantly higher in patients who remained on CsA than those who had CsA withdrawn from therapy. Mean systolic and diastolic blood pressure improved significantly following CsA withdrawal.

Following CsA withdrawal, (at 60 months), the incidence of Herpes zoster infection was significantly lower in patients receiving Rapamune following CsA withdrawal, compared with patients who continued to receive Rapamune and CsA.
The incidence of malignancies following CsA withdrawal based upon distinct categories, is presented in the following table.
The incidence of lymphoma/ lymphoproliferative disease was similar in all treatment groups.
The overall incidence of malignancy, based upon the number of patients who had one or more malignancy, was lower in patients who had CsA withdrawn than in patients receiving Rapamune plus CsA (10,7 % versus 15,8 %, respectively).

INCIDENCE (%) OF MALIGNANCIES AT 60 MONTHS POST-TRANSPLANT[a]			
Malignancy[d]	**Non-randomised**[b] **(n = 95)**	**Rapamune with CsA Therapy**[c] **(n = 215)**	**Rapamune following CsA Withdrawal**[c] **(n = 215)**
Lymphoma/ lymphoproliferative disease	1,1	1,4	0,5
Skin Carcinoma			
Non-melanoma skin carcinoma	5,3	8,8	7,0
Melanoma	0,0	0,5	0,5
Other Malignancy	5,3	7,0	3,3
a: Includes patients who prematurely discontinued treatment.			
b: Patients received Rapamune, CsA and corticosteroids.			
c: Patients received Rapamune and corticosteroids.			
d: Patients may be counted in more than one category.			

By 60 months, the incidence of nonskin malignancies (lymphoma/ lymphoproliferative disease plus other malignancy from the table above), was significantly higher in the cohort who continued CsA as compared with the cohort who had CsA withdrawn (8,4 % vs 3,8 %, respectively). For skin cancer, the median time to first occurrence was significantly delayed (491 vs 1 126 days) and when taking into account that a patient may have multiple skin cancers the relative risk (RR = 0,346) for developing skin cancer was significantly lowered in the CsA withdrawal group as compared with the group that continued CsA.

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

Conversion to Rapamune in patients with Glomerular Filtration Rate < 40 mL/min
The safety and efficacy of conversion from calcineurin inhibitors to Rapamune in maintenance renal transplant patients have not been established.
In a study evaluating conversion from calcineurin inhibitors to Rapamune (target levels of 12-20 ng/ml by chromatographic assay) in maintenance renal transplant patients 6 -120 months post-transplant (see Pharmacodynamics) in a stratum of the Rapamune treatment arm with a calculated glomerular filtration rate of less than 40 ml/min, there was a higher rate of serious side-effects including pneumonia, acute rejection, graft loss and death in this Rapamune treatment arm (n = 60, median time post-transplant 36 months).

The concomitant use of sirolimus with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA) (see Special Precautions).
In patients with delayed graft function, Rapamune may delay recovery of renal function (See Special Precautions, Renal Function).

- *Interstitial Lung Disease*:

Cases of interstitial lung disease (including pneumonitis, and infrequently bronchiolitis obliterans organizing pneumonia (BOOP) and pulmonary fibrosis), some fatal, with no identified infectious 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 Rapamune level increases (see Precautions, “Interstitial Lung Disease”).

- *Latent Viral Infections:*

BK virus associated nephropathy has been observed in patients receiving immunosuppressants, including Rapamune. This infection may be associated with serious outcomes, including renal graft loss (See Special Precautions, Latent Viral Infections).

- *Hepatotoxicity:*

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

- *Abnormal Healing:*

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

Clinical Trial Adverse Events reported in ≥ 20 % of patients for which causality cannot be determined

Adverse reactions reported in ≥ 20 % of patients treated with Rapamune and cyclosporin in controlled studies for prevention of rejection, but for which causality cannot be determined, are:

BODY AS A WHOLE: abdominal pain, asthenia, fever, headache, pain
CARDIOVASCULAR SYSTEM: hypertension
DIGESTIVE SYSTEM: constipation, dyspepsia, nausea
METABOLIC AND NUTRITIONAL: urea and increased creatinine, oedema, hypercholesterolaemia, hyperlipaemia, hypophosphataemia
NERVOUS SYSTEM: tremor
RESPIRATORY SYSTEM: dyspnoea, pharyngitis

There were no significant differences in the incidence rates for clinically important opportunistic or common transplant-related infections across treatment groups, with the exception of mucosal infections with *Herpes simplex*, which occurred at a significantly greater rate in patients treated with Rapamune 5 mg/day.

Clinical Trial Adverse Events reported in < 20% of patients for which causality cannot be determined

The following adverse events, not mentioned above, were reported in less than 20 % of patients treated with Rapamune or control therapy during clinical trials but causality cannot be determined:

BODY AS A WHOLE: abdomen enlarged, accidental injury, back pain, chest pain, chills, face oedema, generalised oedema, peritonitis
CARDIOVASCULAR SYSTEM: haemorrhage, hypervolaemia, hypotension
DIGESTIVE SYSTEM: anorexia, flatulence, oral moniliasis, vomiting
ENDOCRINE SYSTEM: Cushing's syndrome, diabetes mellitus
HAEMIC AND LYMPHATIC SYSTEM: ecchymosis, leukocytosis
METABOLIC AND NUTRITIONAL: acidosis, creatine phosphokinase increased, dehydration, hypercalcaemia, hyperglycaemia, hyperkalaemia, hypocalcaemia, hypomagnesaemia, weight gain
MUSCULOSKELETAL SYSTEM: tetany
NERVOUS SYSTEM: agitation, anxiety, confusion, depression, dizziness, hypoaesthesia, hypotonia, insomnia, paraesthesia, somnolence
RESPIRATORY SYSTEM: increased cough, pleural effusion, pulmonary physical finding, rhinitis
SKIN AND APPENDAGES: hirsutism, pruritus, skin disorder, sweating
SPECIAL SENSES: abnormal vision
UROGENITAL SYSTEM: albuminuria, bladder pain, dysuria, haematuria, hydronephrosis, kidney tubular necrosis, oliguria, scrotal oedema, toxic nephropathy, urinary frequency, urinary incontinence, urinary retention

- *Other clinical experience*

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

Special precautions

Rapamune is for oral administration only.

Rapamune has been administered concurrently with the following agents in clinical studies: cyclosporin, azathioprine, mycophenolate mofetil, corticosteroids, and cytotoxic antibodies.

The efficacy and safety of Rapamune in combination with other immunosuppressive agents has not been determined.

Wound Healing and Fluid Accumulation:

mTOR inhibitors such as Rapamune has been shown *in vitro* to inhibit production of certain growth factors that may affect angiogenesis, fibroblast proliferation and vascular permeability. There have been reports of impaired or delayed wound healing in patients receiving Rapamune, including lymphocele and wound dehiscence. 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 (See Side Effects and Special Precautions)

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

Skin malignancies:

Immunosuppression increases the susceptibility to the development of lymphoma and other malignancies, particularly of the skin. Therefore patients taking Rapamune should limit exposure to sunlight and UV light by wearing protective clothing and using a sunscreen with a high protective factor (see Warnings and Side effects).

Lymphocele:

Lymphocele, a known surgical complication of renal transplantation, occurred significantly more often in a dose-related fashion in Rapamune treated patients. Appropriate post-operative measures should be considered to minimise this complication.

Hyperlipidaemia:

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

Rhabdomyolysis:
In clinical trials, the concomitant administration of Rapamune and HMG-CoA reductase inhibitors and/or fibrates was well tolerated. During Rapamune therapy, patients should be monitored for elevated lipids, and patients administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects as described in the respective labelling for these agents.

Renal Function:
Patients treated with CsA and Rapamune had higher serum creatinine levels and lower glomerular filtration rates compared to patients treated with CsA and placebo or azathioprine controls.
The rate of decline in renal function was greater in patients receiving Rapamune and CsA compared with control therapies.
Therefore, renal function should be monitored and appropriate adjustment of the immunosuppressive regimen should be considered in patients with elevated serum creatinine levels.
In a study that compared a regimen of Rapamune and CsA to one in which CsA was withdrawn 2-4 months post-transplantation, those in whom CsA was not withdrawn had significantly higher serum creatinine levels and significantly lower glomerular filtration rates at 12 months through 60 months, and significantly lower graft survival at 48 months, the point at which it was decided by the sponsor to discontinue subjects from assigned therapy in the Rapamune and CsA arm. When the protocol was amended all subjects had reached 48 months and some completed the 60 months of the study.
In patients at low to moderate immunologic risk, continuation of combination therapy with CsA beyond 4 months following transplantation should only be considered when the benefits outweigh the risks of this combination for individual patients (see Precautions).
In patients with delayed graft function, Rapamune may delay the recovery of renal function.

Proteinuria:
Periodic quantitative monitoring of urinary protein excretion is recommended. In a study evaluating conversion from calcineurin inhibitors (CNI) to Rapamune in maintenance renal transplant patients 6 –120 months post-transplant, increased urinary protein excretion was

commonly observed from the 6 through 24 month after conversion to Rapamune compared with CNI continuation (23,6 % versus 12,8 %, respectively) see SIDE EFFECTS. Those patients in the highest quartile of urinary protein excretion prior to Rapamune conversion (urinary protein to creatinine ratio ≥ 0,27) were those whose protein excretion increased the most after conversion. New-onset nephrosis (nephrotic syndrome) was also reported in 2 % of the patients in the study. Reduction in the degree of urinary protein excretion was observed for individual patients following discontinuation of Rapamune. The safety and efficacy of conversion from calcineurin inhibitors to Rapamune in maintenance renal transplant patients have not been established.

De novo use without calcineurin inhibitor (CNI)
The safety and efficacy of the *de novo* use of Rapamune without a calcineurin inhibitor (CNI) is not established in renal transplant patients. In two multi-center clinical studies, *de novo* renal transplant patients treated with Rapamune, MMF, steroids, and an IL-2 receptor antagonist had significantly higher acute rejection rates and numerically higher death rates compared to patients treated with a calcineurin inhibitor, MMF, steroids and IL-2 receptor antagonist. A benefit, in terms of better renal function, was not apparent in the treatment arms with *de novo* use of Rapamune without a CNI. It should be noted that an abbreviated schedule of administration of daclizumab was employed in one of the studies.

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

Concomitant use of angiotensin – converting enzyme (ACE) inhibitors:
The concomitant administration of Rapamune and ACE inhibitors has resulted in angioneurotic oedema-type reactions.

Interstitial Lung Disease:
Cases of interstitial lung disease (including pneumonitis, and frequently bronchiolitis obliterans with organizing pneumonia (BOOP) and pulmonary fibrosis), some fatal, with no identified infectious aetiology have occurred in patients receiving immunosuppressive regimens including

Rapamune. In some cases, the interstitial lung disease has resolved upon discontinuation or dose reduction of Rapamune. The risk may be increased as the trough sirolimus level increases (See Side-effects, Interstitial Lung disease).

Latent Viral Infections:
Patients treated with immunosuppressants, including Rapamune, are at risk for opportunistic infections, including activation of latent viral infections. Among these conditions is BK virus associated nephropathy. This infection is often related to a high total immunosuppressive burden and may lead to serious outcomes, including graft loss. Physicians should consider this in the differential diagnosis in immunosuppressed patients with deteriorating renal function (See Side Effects, Latent Viral Infections).

Antimicrobial Prophylaxis:
Cases of *Pneumocystis carinii* pneumonia have been reported in patients not receiving antimicrobial prophylaxis. Therefore, antimicrobial prophylaxis for *Pneumocystis carinii* pneumonia should be administered for 1 year following transplantation.

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

Paediatric Use:
Safety and efficacy of Rapamune in paediatric patients below the age of 13 years have not been established. It is recommended that Rapamune whole blood trough levels be monitored if used in paediatric patients < 13 years of age (see Dosage and Directions for Use).

Contraception:
Effective contraception must be initiated before Rapamune therapy, and maintained during Rapamune therapy for 12 weeks after Rapamune therapy has been stopped (see Pregnancy and Lactation).

Use in high risk patients:

The safety and efficacy of CsA withdrawal in high-risk renal transplant patients have not been adequately studied and such use is therefore not recommended. This includes patients with Banff 93 grade III acute rejection or vascular rejection prior to CsA withdrawal, those who are dialysis-dependent, or with serum creatinine > 0,25 mmol/l, black patients, renal re-transplants, multi-organ transplants, and patients with a high panel of reactive antibodies.

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

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
At present, there is limited experience with overdose. One patient experienced an episode of atrial fibrillation after ingestion of 150 mg of Rapamune.
Treatment should be supportive and symptomatic in all cases of overdose.
In general, the adverse effects of overdosage are consistent with those listed in the Side-effect section (See Side-effects and Special Precautions).
Based on the poor aqueous solubility and high erythrocyte and plasma protein binding of Rapamune, it is anticipated that Rapamune is not dialyzable to any significant extent.

IDENTIFICATION:
1 mg Tablet: White, triangular-shaped, sugar-coated tablets, branded Rapamune 1 mg in red ink.

PRESENTATION:
1 mg Tablet: Blister packs of 30's.

STORAGE INSTRUCTIONS:
1 mg Tablet:
Store below 25 ^{o}C. Protect from light.
Do not remove the blisters from the carton until required for use.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBERS:

1 mg Tablet: 35/34/0009

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pfizer Laboratories (Pty) Ltd
85 Bute Lane
Sandton, 2196
SOUTH AFRICA

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

20 April 2012