1. NAME OF THE MEDICINAL PRODUCT

Rapamune 1 mg
coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains 1 mg sirolimus.

Excipients with known effect:
Each tablet contains 86.4 mg of lactose monohydrate and 215.8 mg of sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablet (tablet).
White-coloured, triangular-shaped coated tablet marked “RAPAMUNE 1 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).

4.2 Posology and method of administration

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

Posology

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 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.

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. Currently, 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
Co-administration of sirolimus with strong inhibitors of CYP3A4 (such as ketoconazole, voriconazole, itraconazole, telithromycin or clarithromycin) or inducers of CYP3A4 (such as rifampin, rifabutin) is not recommended (see section 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).

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, and danazol.

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)**

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 lymphoproli-ferative disorder		Neuroendocrine carcinoma of the skin*
Blood and lymphatic system disorders	Thrombocyto-paenia, Anaemia, Leucopenia	Haemolytic uraemic syndrome, Neutropaenia	Pancyto-paenia, Thrombotic thrombo-cytopaenic purpura		
Immune system disorders		Hyper-sensitivity (including angioedema, anaphylactic reaction, and anaphylactoid reaction)			
Metabolism and nutrition disorders	Hypokalaemia, Hypophospha-taemia, Hyperlipidaemia (including hypercholeste-rolaemia), Hyperglycaemia, Hypertriglyceri-daemia, Diabetes mellitus				
Nervous system disorders	Headache				Posterior reversible encephalo-

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)
					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	
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).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

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, selective immunosuppressants, ATC code: L04AA10.

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.

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).

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).

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:
Macrogol
Glycerol monooleate
Pharmaceutical glaze (shellac)
Calcium sulfate
Microcrystalline cellulose
Sucrose
Titanium dioxide
Poloxamer 188
α-tocopherol
Povidone
Carnauba wax

Ink red opacode S-1-15095

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials**.**

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. MANUFACTURER
Pfizer Ireland Pharmaceuticals, Ireland
Or
Pfizer Manufacturing Deutschland GmbH, Freiburg, Germany.

8. LICENSE HOLDER

Pfizer Pharmaceuticals Israel Ltd., 9 Shenkar St., Hertzliya Pituach 46725.

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved on February 2016 and updated according to the guidelines of the Ministry of Health, on March 2019