For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

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Sirolimus Tablets 1mg

RAPACAN® 1 रेपाकॅन १

Composition:
Each film coated tablet contains:
Sirolimus 1 mg
Excipients q.s.
Colour: Titanium Dioxide IP

Warning:
- Increased susceptibility to infection and the possible development of lymphoma and other malignancies may result from immunosuppression
- The safety and efficacy of ***RAPACAN® 1*** (sirolimus) as immunosuppressive therapy have not been established in liver or lung transplant patients belonging to the class of proliferation signal inhibitor and therefore, such use is not recommended

PHARMACEUTICAL FORM: Film-coated tablet

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic Group: Immunosuppressants

ATC Code: L04AA10

RAPACAN® 1 (Sirolimus) is an immunosuppressant drug, belonging to the class of proliferation signal inhibitor, used to prevent rejection in organ transplantation, and is particularly useful in renal transplants. Sirolimus is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. Its molecular formula is $C_{51}H_{79}NO_{13}$ and its molecular weight is 914.2.

Clinical pharmacology
Mechanism of action
Sirolimus inhibits T-lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (Interleukin [IL]-2, IL-4, and IL-15) stimulation by a mechanism that is distinct from that of other immunosuppressants. Sirolimus also inhibits antibody production. In cells, Sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. The Sirolimus:FKBP-12 complex has no effect on calcineurin activity. This complex binds to and inhibits the activation of the mammalian Target Of Rapamycin (mTOR), a key regulatory kinase. This inhibition suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the G_1 to the S phase of the cell cycle

Pharmacokinetics
Sirolimus is rapidly but poorly absorbed following oral administration with an approximate oral bioavailability of 15%. It reaches maximum blood concentrations in 0.5-2.3 hours after dosing. To minimize variability in Sirolimus concentrations,it should be taken consistently with or without food. Its absorption is affected by high fat meals. The mean (± SD) blood-to-plasma ratio of Sirolimus was 36 ± 18 in stable renal allograft patients, indicating that Sirolimus is extensively partitioned into formed blood elements. The mean volume of distribution (Vss/F) of Sirolimus is 12 ± 8 L/kg. Sirolimus is extensively bound (approximately 92%) to human plasma proteins, mainly serum albumin (97%), α_1-acid glycoprotein and lipoproteins.

Sirolimus is extensively metabolized by the hepatic CYP3A4 system and is also a substrate in the p-glycoprotein pump of the intestinal wall. The clearance of Sirolimus is affected by both of these pathways and displays a large interpatient variability. The majority of the seven metabolites are formed via O-demethylation and hydroxylation. Sirolimus is the major component in human whole blood and contributes to more than 90% of the immunosuppressive activity. The metabolites account for less than 10% of the immunosuppressant activity of Sirolimus. These metabolites are excreted in bile and feces. The half-life of Sirolimus ranges from 57-62 hours, making once daily dosing feasible.

The therapeutic window of Sirolimus may be relatively narrow. Therefore, optimal use of Sirolimus requires careful attention to maintenance of therapeutic levels.

Special Populations:
Hepatic impairment
In patients with mild to moderate hepatic impairment (Child-Pugh class A or B), higher AUC (61%) and half-life (43%) values and lower mean Sirolimus clearance values (33%) were noted as compared to patients with normal hepatic function. The half-life increased from 79 hours in healthy patients to 113 hours in patients with hepatic dysfunction. Dosage adjustments are recommended in patients with liver dysfunction.

Renal impairment
The effect of renal impairment on the pharmacokinetics of Sirolimus is not known. However, there is minimal (2.2%) renal excretion of the drug or its metabolites

Geriatrics
Limited data from elderly patients do not indicate any differences in pharmacokinetic parameters versus young adults.

Gender
Sirolimus clearance is 12% lower in males than females; male patients had a significantly longer half-life than female patients (72.3 hours vs. 61.3 hours). These pharmacokinetic differences do not require dosage adjustments

Indications
Sirolimus is indicated for the prophylaxis of organ rejection in patients receiving renal transplants.

DOSAGE AND ADMINISTRATION
It is recommended that ***RAPACAN® 1*** be used initially in a regimen with other immunosuppressants and corticosteroids. Cyclosporine withdrawal is recommended 2 to 4 months after transplantation in patients at low to moderate immunologic risk.

The safety and efficacy of Cyclosporine withdrawal in high-risk patients have not been adequately studied and it is therefore not recommended. This includes patients with Banff grade III acute rejection or vascular rejection prior to cyclosporine withdrawal, those who are dialysis dependent,or with serum creatinine > 4.5 mg/dL, black patients, re-transplants, multiorgan transplants, patients with high panel of reactive antibodies.

RAPACAN® 1 and cyclosporine combination therapy: The initial dose of ***RAPACAN® 1*** should be administered as soon as possible after transplantation. For *de novo* transplant recipients, a loading dose of ***RAPACAN® 1*** of 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.

RAPACAN® 1 following cyclosporine withdrawal: Initially, patients considered for cyclosporine withdrawal should be receiving ***RAPACAN® 1*** and cyclosporine combination therapy. At 2 to 4 months following transplantation, cyclosporine should be progressively discontinued over 4 to 8 weeks and the ***RAPACAN® 1*** dose should be adjusted to obtain whole blood trough concentrations within the range of 16 to 24 ng/mL (chromatographic method) for the first year following transplantation. Thereafter, the target sirolimus concentrations should be 12 to 20 ng/mL (chromatographic method).

Therapeutic drug monitoring should not be the sole basis for adjusting ***RAPACAN® 1*** therapy. Careful attention should be made to clinical signs/symptoms, tissue biopsy, and laboratory parameters.

Cyclosporine inhibits the metabolism and transport of sirolimus, and consequently, sirolimus concentrations will decrease when cyclosporine is discontinued unless the ***RAPACAN® 1*** dose is increased. The ***RAPACAN® 1***dose will need to be approximately 4-fold higher to account for both the absence of the pharmacokinetic interaction (approximately 2-fold increase) and the augmented immunosuppressive requirement in the absence of cyclosporine (approximately 2- fold increase).

Frequent ***RAPACAN® 1*** dose adjustments based on non-steady-state sirolimus concentrations can lead to overdosing or underdosing because sirolimus has a long half-life. Once ***RAPACAN® 1*** 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.

Sirolimus trough concentrations should be monitored at least 3 to 4 days after a loading dose(s). To minimize the variability of exposure to ***RAPACAN® 1***, this drug should be taken consistently with or without food. Grapefruit juice reduces CYP3A4-mediated drug metabolism and potentially enhances P-gp mediated drug counter-transport from enterocytes of the small intestine. This juice must not be administered with ***RAPACAN® 1*** or used for dilution.

It is recommended that sirolimus be taken 4 hours after administration of cyclosporine oral solution /or cyclosporine capsules.

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

Patients with Hepatic Impairment:
It is recommended that the maintenance dose of ***RAPACAN® 1*** be reduced by approximately one third in patients with hepatic impairment.

Patients with Renal Impairment:
It is not necessary to modify the ***RAPACAN® 1*** loading dose. Dosage need not be adjusted because of impaired renal function.

Blood Concentration Monitoring
Whole blood trough concentrations of Sirolimus should be monitored in patients receiving concentration-controlled ***RAPACAN® 1***. Monitoring is also necessary in pediatric patients, in patients with hepatic impairment, during concurrent administration of CYP3A4 and/or P-gp inducers and inhibitors, and/or if cyclosporine dosage is markedly changed or discontinued.

Contraindications
Sirolimus is contraindicated in patients with a hypersensitivity to Sirolimus or its derivatives or any component of the drug product.

Special Warnings & Precautions for use
Increased susceptibility to infection and the possible development of lymphoma and other malignancies, particularly of the skin, may result from immunosuppression. As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor Oversuppression of the immune system can also increase susceptibility to infection including opportunistic infections, fatal infections and sepsis. Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, and hypersensitivity vasculitis, have been associated with the administration of Sirolimus

The safety and efficacy of Sirolimus as immunosuppressive therapy have not been established in liver transplant patients; therefore, such use is not recommended. The use of Sirolimus has been associated with adverse outcomes in patients following liver transplantation, including excess mortality, graft loss and Hepatic Artery Thrombosis (HAT). 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.The safety and efficacy of Sirolimus as immunosuppressive therapy have not been established in lung transplant patients; therefore, such use is not recommended.

Increased serum cholesterol and triglycerides, that may require treatment, occurred more frequently in patients treated with Sirolimus compared with azathioprine or placebo controls. Sirolimus has been associated with the development of angioedema. The concomitant use of Sirolimus with other drugs known to cause angioedema, such as ACE-inhibitors, may increase the risk of developing angioedema.

There have been reports of impaired or delayed wound healing in patients receiving Sirolimus, including lymphocele and wound dehiscence. mTOR inhibitors such as Sirolimus have been shown *in vitro* to inhibit

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production of certain growth factors that may affect angiogenesis, fibroblast proliferation, and vascular permeability. Lymphocele, a known surgical complication of renal transplantation, occurred significantly more often in a dose-related fashion in patients treated with Sirolimus. Appropriate measures should be considered to minimize such complications. Patients with a BMI greater than 30 kg/m^2 may be at increased risk of abnormal wound healing based on data from the medical literature. There have also been reports of fluid accumulation, including peripheral edema,lymphedema, pleural effusion and pericardial effusions (including hemodynamically significant effusions and tamponade requiring intervention in children and adults), in patients receiving Sirolimus.
Renal function should be closely monitored during the co-administration of Sirolimus with cyclosporine, because long-term administration of the combination has been associated with deterioration of renal function. Patients treated with cyclosporine and Sirolimus were noted to have higher serum creatinine levels and lower glomerular filtration rates compared with patients treated with cyclosporine and placebo or azathioprine controls. Appropriate adjustment of the immunosuppressive regimen, including discontinuation of Sirolimus and/or cyclosporine, should be considered in patients with elevated or increasing serum creatinine levels. In patients at low- to moderate-immunologic risk, continuation of combination therapy with cyclosporine beyond 4 months following transplantation should only be considered when the benefits outweigh the risks of this combination for the individual patients. Caution should be exercised when using agents (e.g., aminoglycosides and amphotericin B) that are known to have a deleterious effect on renal function.In patients with delayed graft function, Sirolimus may delay recovery of renal function.

Periodic quantitative monitoring of urinary protein excretion is recommended. In a study evaluating conversion from calcineurin inhibitors (CNI) to Sirolimus in maintenance renal transplant patients 6-120 months post-transplant, increased urinary protein excretion was commonly observed from 6 through 24 months after conversion to Sirolimus compared with CNI continuation. Patients with the greatest amount of urinary protein excretion prior to Sirolimus conversion were those whose protein excretion increased the most after conversion. New onset nephrotic syndrome was also reported as a treatment-emergent adverse event in 2.2% of the Sirolimus conversion group patients in comparison to 0.4% in the CNI continuation group of patients. Nephrotic range proteinuria (defined as urinary protein to creatinine ratio > 3.5) was also reported in 9.2% in the Sirolimus conversion group of patients in comparison to 3.7% in the CNI continuation group of patients. In some patients, reduction in the degree of urinary protein excretion was observed for individual patients following discontinuation of Sirolimus. The safety and efficacy of conversion from calcineurin inhibitors to Sirolimus in maintenance renal transplant patients have not been established.

Co-administration of Sirolimus with strong inhibitors of CYP3A4 and/or P-gp (such as ketoconazole, voriconazole, itraconazole, erythromycin, telithromycin, or clarithromycin) or strong inducers of CYP3A4 and/or P-gp (such as rifampin or rifabutin) is not recommended.

The concomitant use of Sirolimus with a calcineurin inhibitor may increase the risk of Calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA).

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 disease.

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

Whole blood Sirolimus concentrations should be monitored in patients receiving concentration-controlled Sirolimus. Monitoring is also necessary in patients likely to have altered drug metabolism, in patients **≥ 13** years who weigh less than 40 kg, in patients with hepatic impairment, and during concurrent administration of potent CYP3A4 inducers and inhibitors

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

Carcinogenicity studies were conducted in mice and rats. In an 86-week female mouse study at dosages of 0, 12.5, 25 and 50/6 (dosage lowered from 50 to 6 mg/kg/day at week 31 due to infection secondary to immunosuppression) there was a statistically significant increase in malignant lymphoma at all dose levels. There was no effect on fertility in female & male rats following the administration of Sirolimus .

Pregnancy
Pregnancy Category C
There are no adequate and well controlled studies in pregnant women. Effective contraception must be initiated before , during, and for 12 weeks after therapy has been stopped. Sirolimus should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo/fetus.

Use during lactation
Sirolimus is excreted in trace amounts in milk of lactating rats. It is not known whether Sirolimus is excreted in human milk. The pharmacokinetic and safety profiles of Sirolimus in infants are not known. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from Sirolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use
The safety and efficacy of Sirolimus in pediatric patients below the age of 13 years have not been established.

Geriatric use
Clinical studies of Sirolimus tablets did not include sufficient numbers of patients aged 65 years and over to determine whether safety and efficacy differ in this population from younger patients

Drug Interactions
Sirolimus is extensively metabolized by the cytochrome P450 system. Cyclosporine is a substrate and inhibitor of CYP3A4 and P-gp. Because of the effect of cyclosporine, it is recommended that Sirolimus should be taken 4 hours after administration of cyclosporine.

Co-administration of Sirolimus with strong inhibitors of CYP3A4 and/or P-gp (such as ketoconazole, voriconazole, itraconazole, erythromycin, telithromycin, or clarithromycin) or strong inducers of CYP3A4 and/or P-gp (such as rifampin or rifabutin) is not recommended. Sirolimus is extensively metabolized by the CYP3A4 isoenzyme in the intestinal wall and liver and undergoes counter-transport from enterocytes of the small intestine into the gut lumen by the P-gp drug efflux pump. Sirolimus is potentially recycled between enterocytes and the gut lumen to allow continued metabolism by CYP3A4. Therefore, absorption and the subsequent elimination of systemically absorbed Sirolimus may be influenced by drugs that affect these proteins. Strong inhibitors of CYP3A4 and P-gp significantly decrease the metabolism of Sirolimus and increase Sirolimus concentrations, while strong inducers of CYP3A4 and P-gp significantly increase the metabolism of Sirolimus and decrease Sirolimus concentrations.

Grapefruit Juice
Because grapefruit juice inhibits the CYP3A4-mediated metabolism of Sirolimus, it must not be taken with or be used for dilution of Sirolimus

Inducers or Inhibitors of CYP3A4 and P-gp
Exercise caution when using Sirolimus with drugs or agents that are modulators of CYP3A4 and P-gp. The dosage of Sirolimus and/or the co-administered drug may need to be adjusted
- Drugs that could increase Sirolimus blood concentrations:
  Bromocriptione, cimetidine, cisapride, clotrimazole, danazol, diltiazem, fluconazole, HIV-protease inhibitors (e.g., ritonavir, indinavir), metoclopramide, nicardipine, troleandomycin, verapamil
- Drugs and other agents that could decrease Sirolimus concentrations:
  Carbamazepine, phenobarbital, phenytoin, rifapentine, St. John's Wort (Hypericum perforatum)
- Drugs with concentrations that could increase when given with Sirolimus: Verapamil

Immunosuppressants may affect response to vaccination. Therefore, during treatment with Sirolimus, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to, the following: measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid

Adverse Effects
The most common (≥ 30%) adverse reactions observed with Sirolimus in clinical studies are: peripheral edema, hypertriglyceridemia,hypertension, hypercholesterolemia, increased creatinine, constipation, abdominal pain, diarrhea, headache, fever,urinary tract infection,anemia, nausea, arthralgia, pain and thrombocytopenia.
Abnormal healing events following transplant surgery include fascial dehiscence, incisional hernia, and anastomosis disruption.

Less frequent (>3% but <20%): Sepsis, lymphocele, herpes zoster, herpes simplex. Venous thromboembolism (including pulmonary embolism, deep venous thrombosis), tachycardia, stomatitis, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), leukopenia, abnormal healing, increased lactic dehydrogenase (LDH), hypokalemia, bone necrosis. Pneumonia, epistaxis, melanoma, squamous cell carcinoma, basal cell carcinoma, pyelonephritis. Less frequently (< 3%) occurring adverse reactions included: lymphoma/post-transplant lymphoproliferative disorder, mycobacterial infections (including *M. tuberculosis*), pancreatitis, cytomegalovirus and Epstein- Barr virus.

Over dosage
Reports of overdose with sirolimus have been received; however, experience has been limited. The effects of overdose are similar to those listed in Adverse Effects.

General supportive measures should be followed in all cases of overdose. Based on the poor aqueous solubility and high erythrocyte and plasma protein binding of sirolimus, it is anticipated that sirolimus is not dialyzable to any significant extent.

Incompatibilities: Not applicable

Storage: Store protected from moisture at a temperature not exceeding 30°C.
Keep out of reach of children.

Shelf life: Please refer carton/blister

Special Precautions for Disposal and other handling
Any unused product or waste material should be disposed off in accordance with local requirements.

Presentation
RAPACAN® 1 is available as alu alu blister pack of 10 tablets

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

® - Registered trademark

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To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free No: **1800 102 9465** or e mail us at **drugsafety@biocon.com**

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