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

TORAFT

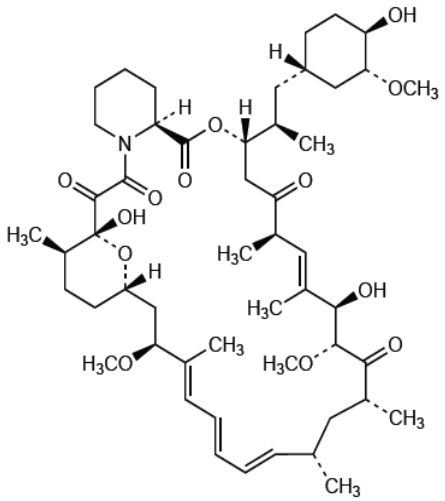
(Sirolimus Tablets)

COMPOSITION:

Each film coated tablet contains
Sirolimus……..1 mg
Colours: Sunset Yellow Lake & Titanium Dioxide I.P.

DESCRIPTION:

Sirolimus is an immunosuppressant drug. It is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. The Chemical name of sirolimus (also known as rapamycin) is (3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,10,12,13,14,21,22,-23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3- {(1R)-2-[(1S,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl}- 10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27- epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclohentriacontine- 1,5,11,28,29-(4H,6H,31H)-pentone. Its empirical formula is $C_{51}H_{79}NO_{13}$ and molecular weight is 914.2. Its chemical structure is:



CLINICAL PHARMACOLOGY:

Pharmacodynamics

Orally-administered sirolimus significantly reduced the incidence of organ rejection in low-to moderate-immunologic risk renal transplant patients at 6 months following transplantation compared with either azathioprine or placebo. There was no reportable efficacy advantage of a daily maintenance dose of 5 mg with a loading dose of 15 mg over a daily maintenance dose of 2 mg with a loading dose of 6 mg. Therapeutic drug monitoring should be used to maintain sirolimus drug levels within the target-range.

Pharmacokinetics

Sirolimus pharmacokinetics activity have been reported following oral administration in healthy subjects, pediatric patients, hepatically impaired patients, and renal transplant patients.

The pharmacokinetic parameters of sirolimus in low-to moderate-immunologic risk adult renal transplant patients following multiple dosing with sirolimus 2 mg daily, in combination with cyclosporine and corticosteroids, is summarized in the following table.

Mean ± SD steady state Sirolimus Pharmacokinetic parameters in Low-to moderate-immunologic risk adult renal transplant Patients following Sirolimus 2 mg daily[a,b]

	Multiple Dose (daily dose)
C_{max} (ng/mL)	15.0 ± 4.9
t_{max} (hr)	3.5 ± 2.4
AUC (ng•h/mL)	230 ± 67
Cmin (ng/mL)[c]	7.6 ± 3.1
CL/F (mL/h/kg)	139 ± 63

[a]: In presence of cyclosporine administered 4 hours before Sirolimus dosing.

[b]: Based on data collected at months 1 and 3 post-transplantation.

[c]: Average C_{min} over 6 months.

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

Absorption

The mean bioavailability of sirolimus after administration of the tablet is approximately 27% higher relative to the solution.

Food Effects

Sirolimus Tablets should be taken consistently with or without food. In reported healthy subjects, a high-fat meal (861.8 kcal, 54.9% kcal from fat) increased the mean total exposure (AUC) of sirolimus by 23 to 35%, compared with fasting.

Distribution

The mean (± SD) blood-to-plasma ratio of sirolimus was reported 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.

Metabolism

Sirolimus is a substrate for both CYP3A4 and P-gp. Sirolimus is extensively metabolized in the intestinal wall and liver and undergoes counter-transport from enterocytes of the small intestine into the gut lumen. Inhibitors of CYP3A4 and P-gp increase sirolimus concentrations. Inducers

of CYP3A4 and P-gp decrease sirolimus concentrations. Sirolimus is extensively metabolized by O-demethylation and/or hydroxylation. Seven (7) major metabolites, including hydroxy, demethyl, and hydroxydemethyl, are identifiable in whole blood. Some of these metabolites are also detectable in plasma, fecal, and urine samples. Sirolimus is the major component in human whole blood and contributes to more than 90% of the immunosuppressive activity.

Excretion

After a single dose of [^{14}C] sirolimus in reported healthy volunteers, the majority (91%) of radioactivity was reportedly recovered from the feces, and only a minor amount (2.2%) was excreted in urine. The mean ± SD terminal elimination half life ($t_{½}$) of sirolimus after multiple dosing in stable renal transplant patients was estimated to be about 62 ± 16 hours.

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

The following sirolimus concentrations (chromatographic equivalent) were reported in phase 3 clinical studies.

Sirolimus whole blood trough concentrations reported in Renal transplant patients enrolled in phase 3 studies

Patient Population(Study number)	Treatment	Year 1		Year 3	
		Mean (ng/mL)	10th – 90th percentiles (ng/mL)	Mean (ng/mL)	10th – 90th percentiles (ng/mL)
Low-to-moderate risk (Studies 1 & 2)	Sirolimus (2 mg/day) + CsA	7.2	3.6-11	-	-
Low-to-moderate risk (Studies 3)	Sirolimus + CsA	8.6	5-13[a]	9.1	5.4-14
	Sirolimus alone	19	14-22[a]	16	11-12
High risk (Study 4)	Sirolimus + CsA	15.7	5.4-27.3 [b]	-	-
		11.8	6.2-16.9[c]		
		11.5	6.3-17.3[d]		

[a]: Months 4 through 12

[b]: Up to Week 2; reported CsA C_{min} was 217 (56 – 432) ng/mL

[c]: Week 2 to Week 26; reported CsA C_{min} range was 174 (71 – 288) ng/mL

[d]: Week 26 to Week 52; reported CsA C_{min} was 136 (54.5 – 218) ng/mL

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

Pharmacokinetics in Specific Populations

Hepatic Impairment

Sirolimus was reportedly administered as a single, oral dose to subjects with normal hepatic function and to patients with Child-Pugh classification A (mild), B (moderate), or C (severe)

hepatic impairment. Compared with the values in the normal hepatic function group, the patients with mild, moderate, and severe hepatic impairment had 43%, 94%, and 189% higher mean values for sirolimus AUC, respectively, with no statistically significant differences in mean C_{max} was reported. As the severity of hepatic impairment increased, there were steady increases in mean sirolimus $t_{1/2}$, and decreases in the mean sirolimus clearance normalized for body weight (CL/F/kg).

The maintenance dose of Sirolimus should be reduced by approximately one third in patients with mild-to-moderate hepatic impairment and by approximately one half in patients with severe hepatic impairment. It is not necessary to modify the sirolimus loading dose in patients with mild, moderate, and severe hepatic impairment. Therapeutic drug monitoring is necessary in all patients with hepatic impairment.

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 was reported in healthy volunteers. The loading and the maintenance doses of sirolimus need not be adjusted in patients with renal impairment.

Pediatric

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

Sirolimus pharmacokinetic parameters (Mean ± SD) in pediatric Renal transplant patients (multiple-dose concentration Control)[a,b]

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

a: Sirolimus co-administered with cyclosporine capsules

b: As measured by Liquid Chromatographic/Tandem Mass Spectrometric Method (LC/MS/MS)

The table below summarizes pharmacokinetic data obtained in pediatric dialysis patients with chronically impaired renal function.

Geriatric

Clinical studies of Sirolimus did not report a sufficient number of patients > 65 years of age to determine whether they will respond differently than younger patients. After the administration

of Sirolimus Tablets, sirolimus trough concentration data in renal transplant patients > 65 years of age were similar to those in the adult population 18 to 65 years of age.

Gender

Sirolimus 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). Dose adjustments based on gender are not recommended.

Race

In the reported phase 3 trials using sirolimus tablets and cyclosporine cyclosporine capsules, there were no reported significant differences in mean trough sirolimus concentrations over time between Black (n = 190) *(The patients at high-immunologic risk defined as Black)* and non-Black (n = 852) patients during the first 6 months after transplantation.

Drug-Drug Interactions

Sirolimus is known to be a substrate for both cytochrome CYP3A4 and P-gp. The pharmacokinetic interaction between sirolimus and concomitantly administered drugs is discussed below. Drug interaction studies have not been reported with drugs other than those described below.

Cyclosporine: Cyclosporine is a substrate and inhibitor of CYP3A4 and P-gp. Sirolimus should be taken 4 hours after administration of cyclosporine capsules. Sirolimus concentrations may decrease when cyclosporine is discontinued, unless the sirolimus dose is increased.

In a reported single-dose drug-drug interaction study, 24 healthy volunteers were administered 10 mg sirolimus Tablets either simultaneously or 4 hours after a 300-mg dose of cyclosporine capsule. For simultaneous administration, mean C_{max} and AUC were increased by 512% and 148%, respectively, relative to administration of sirolimus alone. However, when given 4 hours after cyclosporine administration, sirolimus C_{max} and AUC were both increased by only 33% compared with administration of sirolimus alone.

Diltiazem: Diltiazem is a substrate and inhibitor of CYP3A4 and P-gp; sirolimus concentrations should be monitored and a dose adjustment may be necessary. The simultaneous oral administration of 10 mg of sirolimus oral solution and 120 mg of diltiazem to 18 healthy volunteers significantly affected the bioavailability of sirolimus. Sirolimus C_{max}, t_{max}, and AUC were increased 1.4-, 1.3-, and 1.6-fold, respectively. Sirolimus did not affect the pharmacokinetics of either diltiazem or its metabolites desacetyldiltiazem and desmethyldiltiazem.

Erythromycin: Erythromycin is a substrate and inhibitor of CYP3A4 and P-gp; coadministration of sirolimus tablets and erythromycin is not recommended. Sirolimus Cmax and AUC were increased 4.4-and 4.2-fold respectively and tmax was increased by 0.4 hr. Erythromycin C_{max} and AUC were increased 1.6-and 1.7-fold, respectively, and tmax was increased by 0.3 hr.

Ketoconazole: Ketoconazole is a strong inhibitor of CYP3A4 and P-gp; co-administration of sirolimus tablets and ketoconazole is not recommended. Multiple-dose ketoconazole

administration significantly affected the rate and extent of absorption and sirolimus exposure as reflected by increases in sirolimus C_{max}, t_{max}, and AUC of 4.3-fold, 38%, and 10.9-fold, respectively. However, the terminal t½ of sirolimus was not changed. Single-dose sirolimus did not affect steady-state 12-hour plasma ketoconazole concentrations.

Rifampin: Rifampin is a strong inducer of CYP3A4 and P-gp; co-administration of sirolimus tablets and rifampin is not recommended. In patients where rifampin is indicated, alternative therapeutic agents with less enzyme induction potential should be considered. Pretreatment of 14 healthy volunteers with multiple doses of rifampin, 600 mg daily for 14 days, followed by a single 20-mg dose of sirolimus, greatly decreased sirolimus AUC and Cmax by about 82% and 71%, respectively.

Verapamil: Verapamil is a substrate and inhibitor of CYP3A4 and P-gp; sirolimus concentrations should be monitored and a dose adjustment may be necessary. The simultaneous oral administration of 2 mg daily of sirolimus and 180 mg q 12h of verapamil at steady state to 26 healthy volunteers significantly affected the bioavailability of sirolimus and verapamil. Sirolimus Cmax and AUC were increased 2.3-and 2.2-fold, respectively, without substantial change in tmax. The Cmax and AUC of the pharmacologically active S(-) enantiomer of verapamil were both increased 1.5-fold and tmax was decreased by 1.2 hr.

Drugs which may be co-administered without dose adjustment
Clinically significant pharmacokinetic drug-drug interactions were not reported in studies of drugs listed below. Sirolimus and these drugs may be co-administered without dose adjustments.
Acyclovir
Atorvastatin
Digoxin
Glyburide
Nifedipine
Norgestrel/ethinyl estradiol
Prednisolone
Sulfamethoxazole/trimethoprim

Other Drug-Drug Interactions
Co-administration of Sirolimus with other known strong inhibitors of CYP3A4 and/or P-gp (such as voriconazole, itraconazole, telithromycin, or clarithromycin) or other known strong inducers of CYP3A4 and/or P-gp (such as rifabutin) is not recommended. In patients in whom strong inhibitors or inducers of CYP3A4 are indicated, alternative therapeutic agents with less potential for inhibition or induction of CYP3A4 should be considered.

Care should be exercised when drugs or other substances that are substrates and/or inhibitors or inducers of CYP3A4 are administered concomitantly with sirolimus. Other drugs that have the potential to increase sirolimus blood concentrations include (but are not limited to):
Calcium channel blockers: nicardipine.
Antifungal agents: clotrimazole, fluconazole.
Antibiotics: troleandomycin.
Gastrointestinal prokinetic agents: cisapride, metoclopramide.

Other drugs: bromocriptine, cimetidine, danazol, protease inhibitors (e.g., for HIV and hepatitis C that include drugs such as ritonavir, indinavir, boceprevir, and telaprevir).

Other drugs that have the potential to decrease sirolimus concentrations include (but are not limited to):
Anticonvulsants: carbamazepine, phenobarbital, phenytoin.
Antibiotics: rifapentine.

Other Drug-Food Interactions
Grapefruit juice reduces CYP3A4-mediated drug metabolism. Grapefruit juice must not be taken with or used for dilution of sirolimus.

Drug-Herb Interactions
St. John's Wort (hypericum perforatum) induces CYP3A4 and P-gp. Since sirolimus is a substrate for both cytochrome CYP3A4 and P-gp, there is the potential that the use of St. John's Wort in patients receiving sirolimus could result in reduced sirolimus concentrations

INDICATIONS AND USAGE
Immunosuppressant

DOSAGE AND ADMINISTRATION
Sirolimus is to be administered orally once daily, consistently with or without food.
Tablets should not be crushed, chewed or split. Patients unable to take the tablets should be prescribed the solution and instructed in its use.

The initial dose of sirolimus should be administered as soon as possible after transplantation. It is recommended that sirolimus be taken 4 hours after administration of cyclosporine.

Frequent sirolimus dose adjustments based on non-steady-state sirolimus concentrations can lead to overdosing or underdosing because sirolimus has a long half-life. Once sirolimus maintenance dose is adjusted, patients should continue on the new maintenance dose for at least 7 to 14 days before further dosage adjustment with concentration monitoring. In most patients, dose adjustments can be based on simple proportion: new sirolimus 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 increase sirolimus trough concentrations: sirolimus loading dose = 3 x (new maintenance dose -current maintenance dose). The maximum sirolimus 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).

<u>Patients at Low-to Moderate-Immunologic Risk</u>
Sirolimus and Cyclosporine Combination Therapy
For de novo renal transplant patients, it is recommended that sirolimus Tablets be used initially in a regimen with cyclosporine and corticosteroids. A loading dose of sirolimus equivalent to 3 times the maintenance dose should be given, i.e. a daily maintenance dose of 2 mg should be

preceded with a loading dose of 6 mg. Therapeutic drug monitoring should be used to maintain sirolimus drug concentrations within the target-range.

Sirolimus Following Cyclosporine Withdrawal
At 2 to 4 months following transplantation, cyclosporine should be progressively discontinued over 4 to 8 weeks, and the sirolimus dose should be adjusted to obtain sirolimus whole blood trough concentrations within the target-range. Because cyclosporine inhibits the metabolism and transport of sirolimus, sirolimus concentrations may decrease when cyclosporine is discontinued, unless the sirolimus dose is increased.

Patients at High-Immunologic Risk
In patients with high-immunologic risk, it is recommended that sirolimus be used in combination with cyclosporine and corticosteroids for the first 12 months following transplantation. The safety and efficacy of this combination in high-immunologic risk patients has not been reported beyond the first 12 months. Therefore, after the first 12 months following transplantation, any adjustments to the immunosuppressive regimen should be considered on the basis of the clinical status of the patient.

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

The starting dose of cyclosporine should be up to 7 mg/kg/day in divided doses and the dose should subsequently be adjusted to achieve target whole blood trough concentrations. Prednisone should be administered at a minimum of 5 mg/day.
Antibody induction therapy may be used.

Therapeutic Drug Monitoring
Monitoring of sirolimus trough concentrations is recommended for all patients, especially in those patients likely to have altered drug metabolism, in patients ≥ 13 years who weigh less than 40 kg, in patients with hepatic impairment, when a change in the sirolimus dosage form is made, and during concurrent administration of strong CYP3A4 inducers and inhibitors.
Therapeutic drug monitoring should not be the sole basis for adjusting sirolimus therapy. Careful attention should be made to clinical signs/symptoms, tissue biopsy findings, and laboratory parameters.

When used in combination with cyclosporine, sirolimus trough concentrations should be maintained within the target-range. Following cyclosporine withdrawal in transplant patients at low-to moderate-immunologic risk, the target sirolimus trough concentrations should be 16 to 24 ng/mL for the first year following transplantation. Thereafter, the target sirolimus concentrations should be 12 to 20 ng/mL.

The above recommended 24-hour trough concentration ranges for sirolimus are based on chromatographic methods. Currently in clinical practice, sirolimus whole blood concentrations are being measured by both chromatographic and immunoassay methodologies. Because the

measured sirolimus whole blood concentrations depend on the type of assay used, the concentrations obtained by these different methodologies are not interchangeable. Adjustments to the targeted range should be made according to the assay utilized to determine sirolimus trough concentrations. Since results are assay and laboratory dependent, and the results may change over time, adjustments to the targeted therapeutic range must be made with a detailed knowledge of the site-specific assay used. Therefore, communication should be maintained with the laboratory performing the assay.

Patients with Low Body Weight
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 sirolimus be reduced by approximately one third in patients with mild or moderate hepatic impairment and by approximately one half in patients with severe hepatic impairment. It is not necessary to modify the sirolimus loading dose.

Patients with Renal Impairment
Dosage adjustment is not needed in patients with impaired renal function.

CONTRAINDICATIONS
Toraft is contraindicated in patients with a hypersensitivity to Sirolimus.

WARNINGS AND PRECAUTIONS
Increased Susceptibility to Infection and the Possible Development of Lymphoma
Increased susceptibility to infection and the possible development of lymphoma and other malignancies, particularly of the skin, may result from immunosuppression. The rates of lymphoma/lymphoproliferative disease reported in Studies 1 and 2 were 0.7-3.2% (for sirolimus-treated patients) versus 0.6-0.8% (azathioprine and placebo control). Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections such as tuberculosis, fatal infections, and sepsis. Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should use sirolimus. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

Liver Transplantation – Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis (HAT)
The safety and efficacy of Toraft as immunosuppressive therapy have not been reported in liver transplant patients; therefore, such use is not recommended. The use of Toraft has been associated with adverse outcomes in patients following liver transplantation, including excess mortality, graft loss and Hepatic Artery Thrombosis (HAT).

In a reported study in de novo liver transplant patients, the use of sirolimus in combination with tacrolimus was associated with excess mortality and graft loss (22% in combination versus 9% on tacrolimus alone). Many of these patients had evidence of infection at or near the time of death.

In this and another reported study in de novo liver transplant patients, the use of sirolimus in combination with cyclosporine or tacrolimus was associated with an increase in HAT (7% in combination versus 2% in the control arm); most cases of HAT occurred within 30 days post-transplantation, and most led to graft loss or death.

In a reported clinical study in stable liver transplant patients 6-144 months post-liver transplantation and receiving a CNI-based regimen, an increased number of deaths was reported in the group converted to a sirolimus-based regimen compared to the group who was continued on a CNI-based regimen, although the difference was not statistically significant (3.8% versus 1.4%).

Lung Transplantation – Bronchial Anastomotic Dehiscence

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 reported in lung transplant patients; therefore, such use is not recommended.

Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, exfoliative dermatitis and hypersensitivity vasculitis, have been associated with the administration of Toraft.

Angioedema

Cestel 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.

Fluid Accumulation and Wound Healing

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 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 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 edema, lymphedema, pleural effusion, ascites, and pericardial effusions (including hemodynamically significant effusions and tamponade requiring intervention in children and adults), in patients receiving sirolimus.

Hyperlipidemia

Increased serum cholesterol and triglycerides requiring treatment occurred more frequently in patients treated with sirolimus compared with azathioprine or placebo controls in Studies 1 and

2. There were increased incidences of hypercholesterolemia (43-46%) and/or hypertriglyceridemia (45-57%) in patients receiving sirolimus compared with placebo controls (each 23%). The risk/benefit should be carefully considered in patients with established hyperlipidemia before initiating an immunosuppressive regimen including sirolimus. Any patient who is administered sirolimus should be monitored for hyperlipidemia.

In reported clinical trials of patients receiving sirolimus plus cyclosporine or sirolimus after cyclosporine withdrawal, up to 90% of patients required treatment for hyperlipidemia and hypercholesterolemia with anti-lipid therapy (e.g., statins, fibrates). Despite anti-lipid management, up to 50% of patients had fasting serum cholesterol levels >240 mg/dL and triglycerides above recommended target levels. The concomitant administration of sirolimus and HMG-CoA reductase inhibitors resulted in adverse events such as CPK elevations (3%), myalgia (6.7%) and rhabdomyolysis (<1%). In these reported trials, the number of patients was too small and duration of follow-up too short to evaluate the long-term impact of sirolimus on cardiovascular mortality.

During sirolimus therapy with or without cyclosporine, patients should be monitored for elevated lipids, and patients administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects, as described in the respective labeling for these agents.

Renal Function

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 (Studies 1 and 2). The rate of decline in renal function in these reported studies was greater in patients receiving sirolimus and cyclosporine compared with control therapies.

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.

Proteinuria

Periodic quantitative monitoring of urinary protein excretion is recommended. In a reported 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 nephrosis (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 reported.

Latent Viral Infections

Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include BK virus-associated nephropathy, which has been observed in patients receiving immunosuppressants, including sirolimus. This infection may be associated with serious outcomes, including deteriorating renal function and renal graft loss. Patient monitoring may help detect patients at risk for BK virus-associated nephropathy. Reduction in immunosuppression should be considered for patients who develop evidence of BK virus-associated nephropathy.

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal have been reported in patients treated with immunosuppressants, including sirolimus. PML commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies and ataxia. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated. Consideration should be given to reducing the amount of immunosuppression in patients who develop PML. In transplant patients, physicians should also consider the risk that reduced immunosuppression represents to the graft.

Interstitial Lung Disease

Cases of interstitial lung disease (including pneumonitis, 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.

De Novo Use Without Cyclosporine

The safety and efficacy of de novo use of sirolimus without cyclosporine is not established in renal transplant patients. In a multicenter clinical study, de novo renal transplant patients treated with sirolimus, mycophenolate mofetil (MMF), steroids, and an IL-2 receptor antagonist had significantly higher acute rejection rates and numerically higher death rates compared to patients treated with cyclosporine, MMF, steroids, and IL-2 receptor antagonist. A benefit, in terms of better renal function, was not apparent in the treatment arm with de novo use of sirolimus without cyclosporine. These findings were also reported in a similar treatment group of another clinical trial.

Increased Risk of Calcineurin Inhibitor-Induced Hemolytic Uremic Syndrome/Thrombotic Thrombocytopenic Purpura/Thrombotic Microangiopathy (HUS/TTP/TMA)
The concomitant use of sirolimus with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA).

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 disease.

Assay for Sirolimus Therapeutic Drug Monitoring
Currently in clinical practice, sirolimus whole blood concentrations are being measured by various chromatographic and immunoassay methodologies. Patient sample concentration values from different assays may not be interchangeable.

Skin Cancer Events
Patients on immunosuppressive therapy are at 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.

Interaction with Strong Inhibitors and Inducers of CYP3A4 and/or P-gp
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.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C:
Sirolimus was embryo/fetotoxic in rats when given in doses approximately 0.2 to 0.5 the human doses (adjusted for body surface area). Embryo/fetotoxicity was manifested as mortality and reduced fetal weights (with associated delays in skeletal ossification). However, no teratogenesis was evident. In combination with cyclosporine, rats had increased embryo/feto mortality compared with sirolimus alone. There were no effects on rabbit development at a maternally toxic dosage approximately 0.3 to 0.8 times the human doses (adjusted for body surface area). There are no adequate and well-controlled studies reported in pregnant women. Effective contraception must be initiated before sirolimus therapy, during sirolimus therapy, and for 12 weeks after sirolimus therapy has been stopped. sirolimus should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo/fetus.

Nursing Mothers
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 < 13 years have not been established.
The safety and efficacy of sirolimus Tablets have been reported in children ≥ 13 years judged to be at low-to moderate-immunologic risk.

Safety and efficacy information from a reported controlled clinical trial in pediatric and adolescent (< 18 years of age) renal transplant patients judged to be at high-immunologic risk, defined as a history of one or more acute rejection episodes and/or the presence of chronic allograft nephropathy, do not support the chronic use of Sirolimus Tablets in combination with calcineurin inhibitors and corticosteroids, due to the higher incidence of lipid abnormalities and deterioration of renal function associated with these immunosuppressive regimens compared to calcineurin inhibitors, without increased benefit with respect to acute rejection, graft survival, or patient survival.

Geriatric Use
Reported Clinical studies of Sirolimus Tablets did not include sufficient numbers of patients ≥ 65 years to determine whether they respond differently from younger patients. Data pertaining to sirolimus trough concentrations suggest that dose adjustments based upon age in geriatric renal patients are not necessary. Differences in responses between the elderly and younger patients have not been identified. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, or cardiac function, and of concomitant disease or other drug therapy.

Patients with Hepatic Impairment
The maintenance dose of Toraft should be reduced in patients with hepatic impairment.

Patients with Renal Impairment
Dosage adjustment is not required in patients with renal impairment.

DRUG INTERACTIONS
Sirolimus is known to be a substrate for both cytochrome P-450 3A4 (CYP3A4) and p-glycoprotein (P-gp). Inducers of CYP3A4 and P-gp may decrease sirolimus concentrations whereas inhibitors of CYP3A4 and P-gp may increase sirolimus concentrations.

Use with Cyclosporine
Cyclosporine, a substrate and inhibitor of CYP3A4 and P-gp, was demonstrated to increase sirolimus concentrations when co-administered with sirolimus. In order to diminish the effect of this interaction with cyclosporine, it is recommended that Toraft be taken 4 hours after administration of cyclosporine capsules (MODIFIED). If cyclosporine is withdrawn from

combination therapy with Toraft, higher doses of Toraft are needed to maintain the recommended sirolimus trough concentration ranges.

Strong Inducers and Strong Inhibitors of CYP3A4 and P-gp

Avoid concomitant use of sirolimus with strong inducers (e.g., rifampin, rifabutin) and strong inhibitors (e.g., ketoconazole, voriconazole, itraconazole, erythromycin, telithromycin, clarithromycin) of CYP3A4 and P-gp. Alternative agents with lesser interaction potential with sirolimus should be considered.

Grapefruit Juice

Because grapefruit juice inhibits the CYP3A4-mediated metabolism of sirolimus, it must not be taken with or be used for dilution of Toraft.

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, protease inhibitors (e.g., HIV and hepatitis C that include drugs such as ritonavir, indinavir, boceprevir, and telaprevir), 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

Vaccination

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 REACTIONS

- Increased susceptibility to infection, lymphoma, and malignancy
- Excess mortality, graft loss, and hepatic artery thrombosis in liver transplant patients
- Bronchial anastomotic dehiscence in lung transplant patients
- Hypersensitivity reactions
- Exfoliative dermatitis
- Angioedema
- Fluid Accumulation and Wound Healing
- Hypertriglyceridemia, hypercholesterolemia
- Decline in renal function in long-term combination of cyclosporine with Toraft
- Proteinuria
- Interstitial lung disease
- Increased risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA)

The most common (≥ 30%) adverse reactions observed with sirolimus in clinical studies reported are: peripheral edema, hypertriglyceridemia, hypertension, hypercholesterolemia, creatinine increased, constipation, abdominal pain, diarrhea, headache, fever, urinary tract infection, anemia, nausea, arthralgia, pain, and thrombocytopenia.

The following adverse reactions reported in a rate of discontinuation of > 5% in clinical trials: creatinine increased, hypertriglyceridemia, and thrombotic thrombocytopenic purpura (TTP).

Increased Serum Cholesterol and Triglycerides

The use of sirolimus in renal transplant patients was associated with increased serum cholesterol and triglycerides that may require treatment.

Abnormal Healing

Abnormal healing events following transplant surgery include fascial dehiscence, incisional hernia, and anastomosis disruption (e.g., wound, vascular, airway, ureteral, biliary).

Sirolimus Following Cyclosporine Withdrawal

The incidence of adverse reactions was reported through 36 months in a randomized, multicenter, controlled trial in which 215 renal transplant patients received Sirolimus as a maintenance regimen following cyclosporine withdrawal, and 215 patients received Sirolimus with cyclosporine therapy. All patients were treated with corticosteroids.

Following randomization (at 3 months), patients who had cyclosporine eliminated from their therapy reported higher incidences of the following adverse reactions: abnormal liver function tests (including increased AST/SGOT and increased ALT/SGPT), hypokalemia, thrombocytopenia, and abnormal healing. Conversely, the reporting of the following adverse events was higher in patients who remained on cyclosporine than those who had cyclosporine withdrawn from therapy: hypertension, cyclosporine toxicity, increased creatinine, abnormal kidney function, toxic nephropathy, edema, hyperkalemia, hyperuricemia, and gum hyperplasia. Mean systolic and diastolic blood pressure improved significantly following cyclosporine withdrawal.

Malignancies

The incidence of malignancies in reported Study is presented in the table following.

In reported Study, the incidence of lymphoma/lymphoproliferative disease was similar in all treatment groups. The overall incidence of malignancy was higher in patients receiving sirolimus plus cyclosporine compared with patients who had cyclosporine withdrawn. Conclusions regarding these differences in the incidence of malignancy could not be made because Study was not designed to consider malignancy risk factors or systematically screen subjects for malignancy. In addition, more patients in the sirolimus with cyclosporine group had a pretransplantation history of skin carcinoma.

Incidence (%) of malignancies in study 3 (cyclosporine withdrawal study) at 36 months post-transplant[a,b]

Malignancy	Nonrandomized (n = 95)	Sirolimus with Cyclosporine Therapy (n = 215)	Sirolimus Following Cyclosporine Therapy (n = 215)
Lymphoma/lymphoproliferative disease	1.1	1.4	0.5
Skin Carcinoma			
Any Squamous Cell[c]	3.2	3.3	2.3
Any Basal Cell[c]	3.2	6.5	2.3
Melanoma	0.0	0.0	0.0
Miscellaneous/Not Specified	1.1 0	0.9	0.0
Total	4.2	7.9	3.7
Other Malignancy	3.2	3.3	1.9

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.
c: Patients may be counted in more than one category.

High-Immunologic Risk Patients

Safety was reported in 224 patients who received at least one dose of sirolimus with cyclosporine. Overall, the incidence and nature of adverse events was similar to those seen in previous combination studies with sirolimus. The incidence of malignancy was 1.3% at 12 months.

Conversion from Calcineurin Inhibitors to sirolimus in Maintenance Renal Transplant Population

The safety and efficacy of conversion from calcineurin inhibitors to sirolimus in maintenance renal transplant population have not been REPORTED. In a reported study evaluating the safety and efficacy of conversion from calcineurin inhibitors to sirolimus (initial target sirolimus concentrations of 12-20 ng/mL, and then 8-20 ng/mL, by chromatographic assay) in maintenance renal transplant patients, enrollment was stopped in the subset of patients (n = 87) with a baseline glomerular filtration rate of less than 40 mL/min. There was a higher rate of serious adverse events, including pneumonia, acute rejection, graft loss and death, in this stratum of the sirolimus treatment arm.

The subset of patients with a baseline glomerular filtration rate of less than 40 mL/min had 2 years of follow-up after randomization. In this population, the rate of pneumonia was 15/58 vs. 4/29, graft loss (excluding death with functioning graft loss) was 13/58 vs. 9/29, and death was 9/58 vs. 1/29 in the sirolimus conversion group and CNI continuation group, respectively.
In the subset of patients with a baseline glomerular filtration rate of greater than 40 mL/min, there was no reported benefit associated with conversion with regard to improvement in renal function and a greater incidence of proteinuria in the sirolimus conversion arm.
Overall in reported study, a 5-fold increase in the reports of tuberculosis among sirolimus (11/551) and comparator (1/273) treatment groups was observed with 2:1 randomization scheme.

Pediatrics

Safety was reported in a controlled clinical trial in pediatric (< 18 years of age) renal transplant patients considered at 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 sirolimus in combination with calcineurin inhibitors and corticosteroids was associated with a higher incidence of deterioration of renal function (creatinine increased) compared to calcineurin inhibitor-based therapy, serum lipid abnormalities (including, but not limited to, increased serum triglycerides and cholesterol), and urinary tract infections.

Postmarketing Experience

The following adverse reactions have been reported during post-approval use of sirolimus. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Body as a Whole* – Lymphedema.
- *Cardiovascular* – Pericardial effusion (including hemodynamically significant effusions and tamponade requiring intervention in children and adults) and fluid accumulation.
- *Digestive System* – Ascites.
- *Hematological/Lymphatic* – The concomitant use of sirolimus with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced HUS/TTP/TMA; pancytopenia, neutropenia.
- *Hepatobiliary Disorders* – Hepatotoxicity, including fatal hepatic necrosis, with elevated sirolimus trough concentrations.
- *Immune System* – Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, and hypersensitivity vasculitis.
- *Infections* - Tuberculosis. BK virus associated nephropathy has been observed in patients receiving immunosuppressants, including sirolimus. This infection may be associated with serious outcomes, including deteriorating renal function and renal graft loss. Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with immunosuppressants, including sirolimus. Clostridium difficile enterocolitis.
- *Metabolic/Nutritional* - Liver function test abnormal, AST/SGOT increased, ALT/SGPT increased, hypophosphatemia, hyperglycemia.
- *Respiratory* - Cases of interstitial lung disease (including pneumonitis, 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 sirolimus trough concentration increases; pulmonary hemorrhage; pleural effusion; alveolar proteinosis.
- *Skin* – Exfoliative dermatitis
- *Urogenital* – Nephrotic syndrome, proteinuria, focal segmental glomerulosclerosis, ovarian cysts, menstrual disorders (including amenorrhea and menorrhagia). Azoospermia has been reported with the use of sirolimus and has been reversible upon discontinuation of sirolimus in most cases.

OVERDOSAGE
Reports of overdose with sirolimus have been reported; however, experience has been limited. In general, the adverse effects of overdose are consistent with those listed in the adverse reactions section.
General supportive measures should be followed in all cases of overdose. Based on the low aqueous solubility and high erythrocyte and plasma protein binding of sirolimus, it is anticipated that sirolimus is not dialyzable to any significant extent. In mice and rats, the acute oral LD_{50} was greater than 800 mg/kg.

EXPIRY DATE
Do not use later than the date of expiry

STORAGE
Store at a temperature not exceeding 30°C, protected from light and moisture

PRESENTATIONS
Toraft is available in blister pack of 10 tablets.

MARKETED BY
TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA