HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Rapamune safely and effectively. See full prescribing information for Rapamune.

RAPAMUNE (sirolimus) ORAL SOLUTION AND TABLETS
Initial U.S. Approval: 1999

WARNING: IMMUNOSUPPRESSION, USE IS NOT RECOMMENDED IN LIVER OR LUNG TRANSPLANT PATIENTS
See Full Prescribing Information for complete Boxed Warning.

- **Increased susceptibility to infection and the possible development of lymphoma and other malignancies may result from immunosuppression (5.1). Only physicians experienced in immunosuppressive therapy and management of renal transplant patients should use Rapamune for prophylaxis of organ rejection in patients receiving renal transplants.**
- **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 (5.2, 5.3).**
  - **Liver Transplantation – Excess mortality, graft loss, and hepatic artery thrombosis (5.2).**
  - **Lung Transplantation – Bronchial anastomotic dehiscence (5.3).**

RECENT MAJOR CHANGES

Indications and Usage, Treatment of Patients with Lymphangioleiomyomatosis (1.3)	5/2015
Dosing in Patients with Lymphangioleiomyomatosis (2.4)	5/2015
Warnings and Precautions, Interstitial Lung Disease/Non-Infectious Pneumonitis (5.11)	11/2015

INDICATIONS AND USAGE

Rapamune is indicated:

- **As an immunosuppressive agent indicated for the prophylaxis of organ rejection in patients aged ≥13 years receiving renal transplants.**
  - Patients at low- to moderate-immunologic risk: Use initially with cyclosporine (CsA) and corticosteroids. CsA withdrawal is recommended 2-4 months after transplantation (1.1).
  - Patients at high-immunologic risk: Use in combination with cyclosporine and corticosteroids for the first 12 months following transplantation (1.1). Safety and efficacy of CsA withdrawal has not been established in high risk patients (1.1, 1.2, 14.3).
  - Therapeutic drug monitoring is recommended for all patients (2.5,5.15).
- **For the treatment of patients with lymphangioleiomyomatosis.**
  - Therapeutic drug monitoring is recommended for all patients (2.5,5.15).

DOSAGE AND ADMINISTRATION

In renal transplant patients

- Take once daily by mouth, consistently with or without food. Take the initial dose as soon as possible after transplantation and 4 hours after CsA (2, 7.1). Adjust the Rapamune maintenance dose to achieve sirolimus trough concentrations within the target-range (2.5).

In renal transplant patients at low-to moderate-immunologic risk

- Rapamune and Cyclosporine Combination Therapy: One loading dose of 6 mg on day 1, followed by daily maintenance doses of 2 mg (2.2).
- Rapamune Following Cyclosporine Withdrawal: 2-4 months post-transplantation, withdraw CsA over 4-8 weeks (2.2).

In renal transplant patients at high-immunologic risk

- Rapamune and Cyclosporine Combination Therapy (for the first 12 months post-transplantation): One loading dose of up to 15 mg on day 1, followed by daily maintenance doses of 5 mg (2.3).

In lymphangioleiomyomatosis patients

- Take once daily by mouth, consistently with or without food. The initial Rapamune dose should be 2 mg/day. Adjust the Rapamune dose to achieve sirolimus trough concentrations between 5-15 ng/mL (2.4).

DOSAGE FORMS AND STRENGTHS

- **Rapamune Oral Solution:** 60 mg per 60 mL in amber glass bottle (3.1).
- **Rapamune Tablets:** 0.5 mg, tan; 1 mg, white; 2 mg, yellow-to-beige (3.2).

CONTRAINDICATIONS

Hypersensitivity to Rapamune (4).

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions (5.4)
- Angioedema (5.5)
- Fluid Accumulation and Wound Healing (5.6)
- Hyperlipidemia (5.7)
- Renal Function (5.8)
- Proteinuria (5.9)
- Latent Viral Infections (5.10)
- Interstitial Lung Disease/Non-Infectious Pneumonitis (5.11)
- *De Novo* Use Without Cyclosporine (5.12)
- Increased Risk of Calcineurin Inhibitor-induced HUS/TTP/TMA (5.13)

ADVERSE REACTIONS

Prophylaxis of organ rejection in patients receiving renal transplants: Most common adverse reactions (incidence ≥ 30%) are peripheral edema, hypertriglyceridemia, hypertension, hypercholesterolemia, creatinine increased, abdominal pain, diarrhea, headache, fever, urinary tract infection, anemia, nausea, arthralgia, pain, and thrombocytopenia (6).

Lymphangioleiomyomatosis: Most common adverse reactions (incidence ≥ 20%) are stomatitis, diarrhea, abdominal pain, nausea, nasopharyngitis, acne, chest pain, peripheral edema, upper respiratory tract infection, headache, dizziness, myalgia, and hypercholesterolemia.

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Avoid concomitant use with strong CYP3A4/P-gp inducers or strong CYP3A4/P-gp inhibitors that decrease or increase sirolimus concentrations (7.4, 12.3).
- Exercise caution when administering with drugs that are inhibitors/inducers of CYP3A4/P-gp (7.4, 12.3).

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use only if the potential benefit outweighs the potential risk to the embryo/fetus (8.1).
- Hepatic impairment: Reduce maintenance dose in patients with hepatic impairment (2.7, 8.6, 12.3).

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide

Revised: 11/2015

FULL PRESCRIBING INFORMATION: CONTENTS *

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

BOX WARNING: IMMUNOSUPPRESSION, USE IS NOT RECOMMENDED IN LIVER OR LUNG TRANSPLANT PATIENTS

- **Increased susceptibility to infection and the possible development of lymphoma and other malignancies may result from immunosuppression**

Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of renal transplant patients should use Rapamune® for prophylaxis of organ rejection in patients receiving renal transplants. 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 [see *Warnings and Precautions (5.1)*].

- **The safety and efficacy of Rapamune (sirolimus) as immunosuppressive therapy have not been established in liver or lung transplant patients, and therefore, such use is not recommended [see *Warnings and Precautions (5.2, 5.3)*].**
- **Liver Transplantation – Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis (HAT)**

The use of Rapamune in combination with tacrolimus was associated with excess mortality and graft loss in a study in *de novo* liver transplant patients. Many of these patients had evidence of infection at or near the time of death.

In this and another study in *de novo* liver transplant patients, the use of Rapamune in combination with cyclosporine or tacrolimus was associated with an increase in HAT; most cases of HAT occurred within 30 days post-transplantation and most led to graft loss or death [see *Warnings and Precautions (5.2)*].

- **Lung Transplantation – Bronchial Anastomotic Dehiscence**

Cases of bronchial anastomotic dehiscence, most fatal, have been reported in *de novo* lung transplant patients when Rapamune has been used as part of an immunosuppressive regimen [*see Warnings and Precautions (5.3)*].

1 INDICATIONS AND USAGE

1.1 Prophylaxis of Organ Rejection in Renal Transplantation

Rapamune (sirolimus) is indicated for the prophylaxis of organ rejection in patients aged 13 years or older receiving renal transplants. Therapeutic drug monitoring is recommended for

all patients receiving Rapamune [see *Dosage and Administration (2.5), Warnings and Precautions (5.15)*].

In patients at low-to moderate-immunologic risk, it is recommended that Rapamune be used initially in a regimen with cyclosporine and corticosteroids; cyclosporine should be withdrawn 2 to 4 months after transplantation [see *Dosage and Administration (2.2)*].

In patients at high-immunologic risk (defined as Black recipients and/or repeat renal transplant recipients who lost a previous allograft for immunologic reason and/or patients with high panel-reactive antibodies [PRA; peak PRA level > 80%]), it is recommended that Rapamune be used in combination with cyclosporine and corticosteroids for the first year following transplantation [see *Dosage and Administration (2.3), Clinical Studies (14.3)*].

1.2 Limitations of Use in Renal Transplantation

Cyclosporine withdrawal has not been studied in patients with Banff Grade 3 acute rejection or vascular rejection prior to cyclosporine withdrawal, those who are dialysis-dependent, those with serum creatinine > 4.5 mg/dL, Black patients, patients of multi-organ transplants, secondary transplants, or those with high levels of panel-reactive antibodies [see *Clinical Studies (14.2)*].

In patients at high-immunologic risk, the safety and efficacy of Rapamune used in combination with cyclosporine and corticosteroids has not been studied beyond one year; 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 [see *Clinical Studies (14.3)*].

In pediatric patients, the safety and efficacy of Rapamune have not been established in patients < 13 years old, or in pediatric (< 18 years) renal transplant patients considered at high-immunologic risk [see *Adverse Reactions (6.5), Clinical Studies (14.6)*]. The safety and efficacy of *de novo* use of Rapamune without cyclosporine have not been established in renal transplant patients [see *Warnings and Precautions (5.12)*].

The safety and efficacy of **conversion from calcineurin inhibitors to Rapamune** in maintenance renal transplant patients have not been established [see *Clinical Studies (14.4)*].

1.3 Treatment of Patients with Lymphangioleiomyomatosis

Rapamune (sirolimus) is indicated for the treatment of patients with lymphangioleiomyomatosis. Therapeutic drug monitoring is recommended for all patients receiving Rapamune [see *Dosage and Administration (2.5), Warnings and Precautions (5.15)*].

2 DOSAGE AND ADMINISTRATION

Rapamune is to be administered orally once daily, consistently with or without food [see *Dosage and Administration (2.5), Clinical Pharmacology (12.3)*].

Tablets should not be crushed, chewed or split. Patients unable to take the tablets should be prescribed the solution and instructed in its use.

2.1 General Dosing Guidance for Renal Transplant Patients

The initial dose of Rapamune should be administered as soon as possible after transplantation. It is recommended that Rapamune be taken 4 hours after administration of cyclosporine oral solution (MODIFIED) and or/cyclosporine capsules (MODIFIED) [see *Drug Interactions (7.2)*].

Frequent Rapamune dose adjustments based on non-steady-state sirolimus concentrations can lead to overdosing or underdosing because sirolimus has a long half-life. Once Rapamune maintenance dose is adjusted, patients should continue on the new maintenance dose for at least 7 to 14 days before further dosage adjustment with concentration monitoring. In most patients, dose adjustments can be based on simple proportion: new Rapamune dose = current dose x (target concentration/current concentration). A loading dose should be considered in addition to a new maintenance dose when it is necessary to 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).

Two milligrams (2 mg) of Rapamune Oral Solution have been demonstrated to be clinically equivalent to 2 mg Rapamune Tablets; hence, are interchangeable on a mg-to-mg basis. However, it is not known if higher doses of Rapamune Oral Solution are clinically equivalent to higher doses of Rapamune Tablets on a mg-to-mg basis [see *Clinical Pharmacology (12.3)*].

2.2 Renal Transplant Patients at Low- to Moderate-Immunologic Risk

Rapamune and Cyclosporine Combination Therapy

For *de novo* renal transplant patients, it is recommended that Rapamune Oral Solution and Tablets be used initially in a regimen with cyclosporine and corticosteroids. A loading dose of Rapamune 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 [see *Dosage and Administration (2.5)*].

Rapamune Following Cyclosporine Withdrawal

At 2 to 4 months following transplantation, cyclosporine should be progressively discontinued over 4 to 8 weeks, and the Rapamune dose should be adjusted to obtain sirolimus whole blood trough concentrations within the target-range [see *Dosage and Administration (2.5)*]. Because cyclosporine inhibits the metabolism and transport of sirolimus, sirolimus concentrations may decrease when cyclosporine is discontinued, unless the Rapamune dose is increased [see *Clinical Pharmacology (12.3)*].

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