Sirolimus Oral Solution

316-2024-05

2102484

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SIROLIMUS ORAL SOLUTION safely and effectively. See full prescribing information for SIROLIMUS ORAL SOLUTION.

SIROLIMUS oral solution

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 sirolimus for prophylaxis of organ rejection in patients receiving renal transplants.**
- **The safety and efficacy of sirolimus 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).**

INDICATIONS AND USAGE

- Sirolimus oral solution is an mTOR inhibitor immunosuppressant 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 to 4 months after transplantation (1.1).
  - Patients at high-immunologic risk: Use in combination with CsA 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).
- Sirolimus oral solution is an mTOR inhibitor indicated for the treatment of patients with lymphangioleiomyomatosis (1.3).

DOSAGE AND ADMINISTRATION

Renal Transplant Patients:

- Administer once daily by mouth, consistently with or without food (2).
- Administer the initial dose as soon as possible after transplantation and 4 hours after CsA (2.1, 7.1).
- Adjust the sirolimus oral solution maintenance dose to achieve sirolimus trough concentrations within the target-range (2.5).
- Hepatic impairment: Reduce maintenance dose in patients with hepatic impairment (2.7, 8.6, 12.3).

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

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

In renal transplant patients at high-immunologic risk:

- Sirolimus Oral Solution and CsA 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).

Lymphangioleiomyomatosis Patients:

- Administer once daily by mouth, consistently with or without food (2).
- Recommended initial sirolimus oral solution dose is 2 mg/day (2.4).
- Adjust the sirolimus oral solution dose to achieve sirolimus trough concentrations between 5 to 15 ng/mL (2.4).
- Hepatic impairment: Reduce maintenance dose in patients with hepatic impairment (2.7, 8.6, 12.3).

Therapeutic drug monitoring is recommended for all patients (2.5, 5.17).

DOSAGE FORMS AND STRENGTHS

- Oral Solution: 60 mg per 60 mL in amber glass bottle (3.1).

CONTRAINDICATIONS

Hypersensitivity to sirolimus (4).

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions (5.4)
- Angioedema (5.5)
- Fluid Accumulation and Impairment of Wound Healing (5.6)
- Hyperlipidemia (5.7)
- Decline in 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 Hemolytic Uremic Syndrome/ Thrombotic Thrombocytopenic Purpura/ Thrombotic Microangiopathy (5.13)
- Embryo-Fetal Toxicity: Can cause fetal harm. Use of highly effective contraception is recommended for females of reproductive potential during treatment and for 12 weeks after final dose of sirolimus (5.15, 8.1)
- Male Infertility: Azoospermia or oligospermia may occur (5.16, 13.1)
- Immunizations: Avoid live vaccines (5.19)

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 (6.6).

To report SUSPECTED ADVERSE REACTIONS, contact Annora Pharma Private Limited at 1-866-495-1995 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).
- Therapeutic drug monitoring and dose reduction for sirolimus should be considered when sirolimus is co-administered with cannabidiol (5.21, 7.5).
- See full prescribing information for complete list of clinically significant drug interactions (12.3).

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data can cause fetal harm (5.15, 8.1).
- Lactation: Potential for serious adverse effects in breastfed infants based on mechanism of action (8.2).
- Females and Males of Reproductive Potential: May impair fertility (8.1, 8.3, 13.1).

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

Revised: 05/2024

FULL PRESCRIBING INFORMATION: CONTENTS *

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

1 INDICATIONS AND USAGE
1.1 Prophylaxis of Organ Rejection in Renal Transplantation
1.2 Limitations of Use in Renal Transplantation
1.3 Treatment of Patients with Lymphangioleiomyomatosis
2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Guidance for Renal Transplant Patients
2.2 Renal Transplant Patients at Low- to Moderate-Immunologic Risk
2.3 Renal Transplant Patients at High-Immunologic Risk
2.4 Dosing in Patients with Lymphangioleiomyomatosis
2.5 Therapeutic Drug Monitoring
2.6 Patients with Low Body Weight
2.7 Patients with Hepatic Impairment
2.8 Patients with Renal Impairment
2.9 Instructions for Dilution and Administration of Sirolimus Oral Solution
3 DOSAGE FORMS AND STRENGTHS
3.1 Sirolimus Oral Solution
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Increased Susceptibility to Infection and the Possible Development of Lymphoma
5.2 Liver Transplantation – Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis
5.3 Lung Transplantation – Bronchial Anastomotic Dehiscence
5.4 Hypersensitivity Reactions
5.5 Angioedema
5.6 Fluid Accumulation and Impairment of Wound Healing
5.7 Hyperlipidemia
5.8 Decline in Renal Function
5.9 Proteinuria
5.10 Latent Viral Infections
5.11 Interstitial Lung Disease/Non-Infectious Pneumonitis
5.12 *De Novo* Use Without Cyclosporine
5.13 Increased Risk of Calcineurin Inhibitor-Induced Hemolytic Uremic Syndrome/Thrombotic Thrombocytopenic Purpura/Thrombotic Microangiopathy
5.14 Antimicrobial Prophylaxis
5.15 Embryo-Fetal Toxicity
5.16 Male Infertility
5.17 Different Sirolimus Trough Concentrations Reported between Chromatographic and Immunoassay Methodologies
5.18 Skin Cancer Events
5.19 Immunizations
5.20 Interaction with Strong Inhibitors and Inducers of CYP3A4 and/or P-gp
5.21 Cannabidiol Drug Interactions
6 ADVERSE REACTIONS
6.1 Clinical Studies Experience in Prophylaxis of Organ Rejection Following Renal Transplantation
6.2 Sirolimus Following Cyclosporine Withdrawal
6.3 High-Immunologic Risk Renal Transplant Patients
6.4 Conversion from Calcineurin Inhibitors to Sirolimus in Maintenance Renal Transplant Population
6.5 Pediatric Renal Transplant Patients
6.6 Patients with Lymphangioleiomyomatosis
6.7 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Use with Cyclosporine
7.2 Strong Inducers and Strong Inhibitors of CYP3A4 and P-gp
7.3 Grapefruit Juice
7.4 Weak and Moderate Inducers or Inhibitors of CYP3A4 and P-gp
7.5 Cannabidiol
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Patients with Hepatic Impairment
8.7 Patients with Renal Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Prophylaxis of Organ Rejection in Renal Transplant Patients
14.2 Cyclosporine Withdrawal Study in Renal Transplant Patients
14.3 High-Immunologic Risk Renal Transplant Patients
14.4 Conversion from Calcineurin Inhibitors to Sirolimus in Maintenance Renal Transplant Patients
14.5 Conversion from a CNI-based Regimen to a Sirolimus-based Regimen in Liver Transplant Patients
14.6 Pediatric Renal Transplant Patients
14.7 Lymphangioleiomyomatosis Patients
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 Sirolimus Oral Solution
17 PATIENT COUNSELING INFORMATION
17.1 Dosage
17.2 Skin Cancer Events
17.3 Pregnancy and Lactation
17.4 Infertility

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

FULL PRESCRIBING INFORMATION

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 sirolimus 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 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 sirolimus 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 sirolimus 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)*].

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... 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 [*see Warnings and Precautions (5.17), Clinical Pharmacology (12.3)*]. 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. A discussion of different assay methods is contained in Clinical Therapeutics, Volume 22, Supplement B, April 2000 [*see References (15)*].

2.6 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.

2.7 Patients with Hepatic Impairment

It is recommended that the maintenance dose of sirolimus oral solution 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 oral solution loading dose [*see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)*].

2.8 Patients with Renal Impairment

Dosage adjustment is not needed in patients with impaired renal function [*see Use in Specific Populations (8.7)*].

2.9 Instructions for Dilution and Administration of Sirolimus Oral Solution

The amber oral dose syringe should be used to withdraw the prescribed amount of sirolimus oral solution from the bottle. Empty the correct amount of sirolimus oral solution from the syringe into only a glass or plastic container holding at least two (2) ounces (1/4 cup, 60 mL) of water or orange juice. No other liquids, including grapefruit juice, should be used for dilution [*see Drug Interactions (7.3), Clinical Pharmacology (12.3)*]. Stir vigorously and drink at once. Refill the container with an additional volume [minimum of four (4) ounces (1/2 cup, 120 mL)] of water or orange juice, stir vigorously, and drink at once.

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

3 DOSAGE FORMS AND STRENGTHS

3.1 Sirolimus Oral Solution

- 60 mg per 60 mL in amber glass bottle.

4 CONTRAINDICATIONS

Sirolimus oral solution is contraindicated in patients with a hypersensitivity to sirolimus [*see Warnings and Precautions (5.4)*].

5 WARNINGS AND PRECAUTIONS

5.1 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 observed in Studies 1 and 2 were 0.7 to 3.2% (for sirolimus -treated patients) versus 0.6 to 0.8% (azathioprine and placebo control) [*see Adverse Reactions (6.1)* and *(6.2)*]. 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 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.

5.2 Liver Transplantation – Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis

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).

In a 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 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 clinical study in stable liver transplant patients 6 to 144 months post-liver transplantation and receiving a CNI-based regimen, an increased number of deaths was observed 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%) [*see Clinical Studies (14.5)*].

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

5.4 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, exfoliative dermatitis and hypersensitivity vasculitis, have been associated with the administration of sirolimus [*see Adverse Reactions (6.7)*].

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5.7 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 [*see Adverse Reactions (6.1)*]. There were increased incidences of hypercholesterolemia (43 to 46%) and/or hypertriglyceridemia (45 to 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. If detected, interventions such as diet, exercise, and lipid-lowering agents should be initiated as outlined by the National Cholesterol Education Program guidelines.

In 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 reactions such as CPK elevations (3%), myalgia (6.7%) and rhabdomyolysis (< 1%). In these 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.

5.8 Decline in Renal Function

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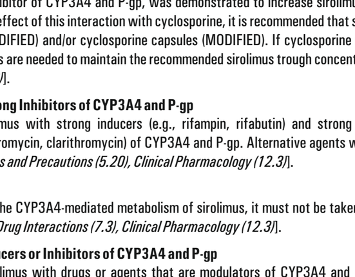

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MEDICATION GUIDE
Sirolimus (sir oh' li mus)
Oral Solution

What is the most important information I should know about sirolimus oral solution?

Sirolimus oral solution can cause serious side effects, including:

1. **Increased risk of getting infections.** Serious infections can happen including infections caused by viruses, bacteria, and fungi (yeast). Your doctor may put you on medicine to help prevent some of these infections.

   Call your doctor right away if you have symptoms of infection including fever or chills while taking sirolimus oral solution.
2. **Increased risk of getting certain cancers.** People who take sirolimus oral solution have a higher risk of getting lymphoma, and other cancers, especially skin cancer. Talk with your doctor about your risk for cancer.

Sirolimus oral solution has not been shown to be safe and effective in people who have had liver or lung transplants. Serious complications and death may happen in people who take sirolimus oral solution after a liver or lung transplant. You should not take sirolimus oral solution if you have had a liver or lung transplant without talking with your doctor.

See the section "What are the possible side effects of sirolimus oral solution?" for information about other side effects of sirolimus oral solution.

What is sirolimus oral solution?

Sirolimus oral solution is a prescription medicine used to prevent rejection (anti-rejection medicine) in people 13 years of age and older who have received a kidney transplant. Rejection is when your body's immune system recognizes the new organ as a "foreign" threat and attacks it.

Sirolimus oral solution is used with other medicines called cyclosporine (Gengraf, Neoral, Sandimmune), and corticosteroids. Your doctor will decide:

- if sirolimus oral solution is right for you, and
- how to best use it with cyclosporine and corticosteroids after your transplant.

It is not known if sirolimus oral solution is safe and effective in children under 13 years of age.

Sirolimus oral solution is a prescription medicine also used to treat lymphangioleiomyomatosis (LAM). LAM is a rare progressive lung disease that affects predominantly women of childbearing age.

Who should not take sirolimus oral solution?

Do not take sirolimus oral solution if you are allergic to sirolimus or any of the other ingredients in sirolimus oral solution. See the end of this leaflet for a complete list of ingredients in sirolimus oral solution.

What should I tell my doctor before taking sirolimus oral solution?

- have liver problems
- have skin cancer or it runs in your family
- have high cholesterol or triglycerides (fat in your blood)
- are pregnant or are a female who can become pregnant. Sirolimus oral solution can harm your unborn baby. You should not become pregnant during treatment with sirolimus oral solution and for 12 weeks after ending treatment with sirolimus oral solution. In order to avoid pregnancy, a female who can get pregnant should use effective birth control during treatment and for 12 weeks after your final dose of sirolimus oral solution. Talk with your doctor about what birth control method is right for you during this time. Tell your doctor right away if you become pregnant or think you are pregnant during treatment with sirolimus oral solution or within 12 weeks after your final dose of sirolimus oral solution.
- It is not known whether sirolimus passes into breast milk; however, there is a risk of serious side effects in breastfed infants. You and your doctor should decide about the best way to feed your baby if you take sirolimus oral solution.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Using sirolimus oral solution with certain medicines may affect each other causing serious side effects.

Sirolimus oral solution may affect the way other medicines work, and other medicines may affect how sirolimus oral solution works.

Especially tell your doctor if you take:

- a medicine to lower your cholesterol or triglycerides
- cyclosporine (including Gengraf, Neoral, Sandimmune) or tacrolimus (Prograf) or other medicines that suppress the immune system
- an antibiotic
- an antifungal medicine
- a medicine for high blood pressure or heart problems
- an anti-seizure medicine
- medicines used to treat stomach acid, ulcers, or other gastrointestinal problems
- bromocriptine mesylate (Parlodel, Cycloset)
- danazol
- letermovir (Prevymis)
- medicines to treat HIV or hepatitis C
- St. John's Wort
- cannabidiol (Epidiolex)

How should I take sirolimus oral solution?

- Read the Instructions for Use that comes with your sirolimus oral solution for information about the right way to take sirolimus oral solution.
- Take sirolimus oral solution exactly as your doctor tells you to take it.
- Your doctor will tell you how much sirolimus oral solution to take and when to take it. Do not change your dose of sirolimus oral solution unless your doctor tells you to.
- If you also take cyclosporine (Gengraf, Neoral, Sandimmune), you should take your sirolimus oral solution and cyclosporine about 4 hours apart.
- Do not stop taking sirolimus oral solution or your other anti-rejection medicines unless your doctor tells you to.
- Your doctor will check the levels of sirolimus oral solution in your blood. Your doctor may change your dose of sirolimus oral solution depending on your blood test results.
- Sirolimus oral solution is taken by mouth 1 time each day.
- Take each dose of sirolimus oral solution the same way, either with or without food. Food can affect the amount of medicine that gets into your bloodstream. Taking each dose of sirolimus oral solution the same way helps keep your blood levels of sirolimus oral solution more stable. Do not take sirolimus oral solution with grapefruit juice.
- Sirolimus oral solution can develop a slight haze when it is refrigerated. If this happens, bring the sirolimus oral solution to room temperature and then gently shake the bottle until the haze goes away.
- If you get sirolimus oral solution on your skin, wash the area with soap and water.
- If you get sirolimus oral solution in your eyes, rinse your eyes with water.
- If you have taken more medicine than you were told, contact a doctor or go to the nearest hospital emergency department right away.

What should I avoid while taking sirolimus oral solution?

- Avoid receiving live vaccines while taking sirolimus oral solution. Some vaccines may not work as well while you are taking sirolimus oral solution.
- Limit your time in sunlight and UV light. Cover your skin with clothing and use a broad spectrum sunscreen with a high protection factor because of the increased risk for skin cancer with sirolimus oral solution.

What are the possible side effects of sirolimus oral solution?

Sirolimus oral solution may cause serious side effects, including:

- See **"What is the most important information I should know about sirolimus oral solution?"**
- **Serious allergic reactions.** Tell your doctor or get medical help right away if you get any of following symptoms of an allergic reaction:
  - swelling of your face, eyes, or mouth
  - trouble breathing or wheezing
  - throat tightness
  - chest pain or tightness
  - feeling dizzy or faint
  - rash or peeling of your skin
- **Swelling (edema).** Fluid may collect in your hands and feet and in various tissues of your body, including in the sac around your heart or lungs. Call your doctor if you have trouble breathing.
- **Poor wound healing.** Sirolimus oral solution may cause your wounds to heal slowly or not heal well. Tell your doctor if you have any redness or drainage, your wound does not heal, or the wound opens up.
- **Increased levels of cholesterol and triglycerides (lipids or fat) in your blood.** Your doctor should do blood tests to check your lipids during treatment with sirolimus oral solution. Your doctor may prescribe treatment with diet, exercise, or medicine if your lipid levels are too high. During treatment with sirolimus oral solution, your blood levels of cholesterol and triglycerides may remain high even if you follow your prescribed treatment plan.
- **Effects on kidney function.** When sirolimus oral solution is taken with cyclosporine (Gengraf, Neoral, Sandimmune), the function of your transplanted kidney may be affected. Your doctor should regularly do tests to check your kidney function while you are taking sirolimus oral solution with cyclosporine (Gengraf, Neoral, Sandimmune).
- **Increased protein in your urine.** Your doctor may regularly test your urine protein.
- **Increased risk for viral infections.**
  - Certain viruses can live in your body and cause active infections when your immune system is weak. BK virus can affect how your kidney works and cause your transplanted kidney to fail.
  - A certain virus can cause a rare serious brain infection called Progressive Multifocal Leukoencephalopathy (PML). PML usually causes death or severe disability. Call your doctor right away if you notice any new or worsening medical problems such as:
    - confusion
    - sudden change in thinking, walking, strength on one side of your body
    - other problems that have lasted over several days
- **Lung or breathing problems.** This can sometimes lead to death. Tell your doctor if you have a new or worsening cough, shortness of breath, difficulty breathing or any new breathing problems. Your doctor may need to stop sirolimus oral solution or lower your dose.
- **Blood clotting problems.** When sirolimus oral solution is taken with cyclosporine or tacrolimus, you may develop a blood clotting problem. Tell your doctor if you get any unexplained bleeding or bruising.
- **Possible harm to your unborn baby.** Sirolimus oral solution can harm your unborn baby. You should not become pregnant during treatment with sirolimus oral solution and for 12 weeks after ending treatment with sirolimus oral solution. See **"What should I tell my doctor before taking sirolimus oral solution?".**

The most common side effects of sirolimus oral solution in people with renal transplant include:

- high blood pressure
- pain (including stomach and joint pain)
- diarrhea
- headache
- fever
- urinary tract infection
- low red blood cell count (anemia)
- nausea
- low platelet count (cells that help blood to clot)
- high blood sugar (diabetes)

The most common side effects of sirolimus oral solution in people with LAM include:

- mouth sores
- diarrhea
- stomach pain
- nausea
- sore throat
- acne
- chest pain
- upper respiratory tract infection
- headache
- dizziness
- sore muscles

Other side effects that may occur with sirolimus oral solution:

- Sirolimus oral solution may affect fertility in females and may affect your ability to become pregnant. Talk to your healthcare provider if this is a concern for you.
- Sirolimus oral solution may affect fertility in males and may affect your ability to father a child. Talk to your healthcare provider if this is a concern for you.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of sirolimus oral solution. For more information ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store sirolimus oral solution?

- Store bottles of sirolimus oral solution in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Protect from light.

Artwork information

Customer	Camber	Market	USA
Dimensions (mm)	480 x 800 mm	Non Printing Colors	Die cut
Pharma Code No.	Front-307& Back-308		
Printing Colours	Black		

Others: Pharma code position and Orientation are tentative, will be changed based on folding size.

- If necessary, bottles of sirolimus oral solution can be stored at room temperature up to 77°F (25°C) for up to 15 days.
- When a bottle of sirolimus oral solution is opened, it should be used within 1 month.
- Use any diluted sirolimus oral solution right away.

Do not use sirolimus oral solution after the expiration date. The expiration date refers to the last day of that month.

Safely throw away medicine that is out of date or no longer needed.

Keep sirolimus oral solution and all medicines out of the reach of children.

General Information about the safe and effective use of sirolimus oral solution.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use sirolimus oral solution for a condition for which it was not prescribed. Do not give sirolimus oral solution to other people even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about sirolimus oral solution. If you would like more information talk to your doctor. You can ask your pharmacist or doctor for information about sirolimus oral solution that is written for health professionals.

For more information, call 1-866-495-1995.

What are the ingredients in sirolimus oral solution?

Active ingredient: sirolimus

Inactive ingredients: Phosal® 50 PG (alcohol, ascorbyl palmitate, phosphatidylcholine, propylene glycol, soy acid, sunflower seed oil glyceride and tocopherol) and polysorbate 80. Sirolimus oral solution contains 1.5% to 2.5% ethanol.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Medication Guide available at http://camberpharma.com/medication-guides.

Manufactured for:
Camber Pharmaceuticals, Inc.
Piscataway, NJ 08854

By: Annora Pharma Pvt. Ltd.
Sangareddy - 502313, Telangana, India.

Revised: 05/2024

INSTRUCTIONS FOR USE

Sirolimus (sir oh' li mus)

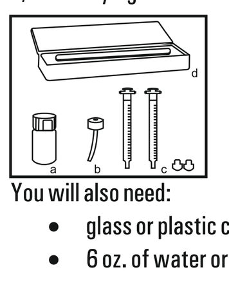
Oral Solution

Be sure that you read and understand the following instructions for the correct way to dilute and take sirolimus oral solution. Ask your pharmacist or doctor if you are not sure. Important:

- Always keep the bottle in an upright position.
- You may store sirolimus oral solution that is in a syringe at room temperature up to 77°F (25°C) or in the refrigerator at 36°F to 46°F (2°C to 8°C) for up to 24 hours. See "How should I store sirolimus oral solution?" at the end of this Instructions for Use.
- Sirolimus oral solution can develop a slight haze when it is refrigerated. If this happens, bring the sirolimus oral solution to room temperature and then gently shake the bottle until the haze goes away.
- Only use a glass or plastic cup to dilute sirolimus oral solution.
- If you are a caregiver, do not let sirolimus oral solution come in contact with your skin or eyes. If you get the oral solution on your skin, wash the area well with soap and water. If you get the oral solution in your eyes, rinse with plain water.
- If you spill sirolimus oral solution, dry the area with a dry paper towel and then wipe the area with a wet paper towel. Throw away the paper towels in the trash and wash your hands well with soap and water.

Each sirolimus oral solution carton contains:

a) a 2 oz. (60 mL fill) amber glass bottle of sirolimus (concentration of 1 mg/mL)
b) 1 oral syringe adapter for fitting into the neck of the bottle
c) enough disposable oral syringes (amber color) and caps for daily dosing
d) 1 carrying case

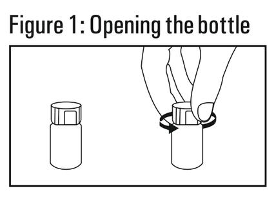


You will also need:

- glass or plastic cup
- 6 oz. of water or orange juice only

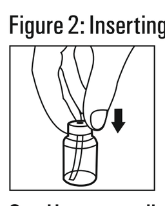
1. Open the solution bottle.
   - Remove the safety cap by squeezing the tabs on each side of the cap and twisting counter clockwise (Figure 1).

Figure 1: Opening the bottle



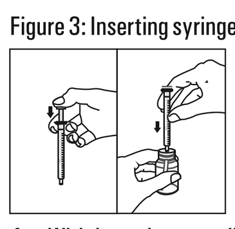
2. The **first time** you use a bottle of sirolimus oral solution:
   - Insert the oral syringe adapter (plastic tube with stopper) tightly into the bottle until it is even with the top of the bottle (Figure 2).
   - Do not remove the oral syringe adapter from the bottle once inserted.

Figure 2: Inserting adapter



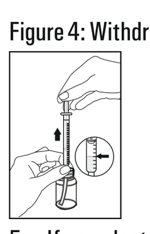
3. Use a new disposable amber oral syringe for each dose of sirolimus oral solution.
   - Fully push down (depress) on the plunger of the disposable amber oral syringe.
   - Then, tightly insert the oral syringe into the opening in the adapter (Figure 3).

Figure 3: Inserting syringe



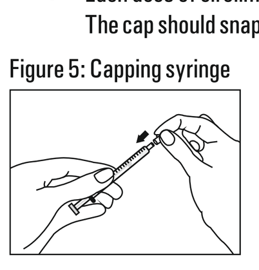
4. Withdraw the prescribed amount of sirolimus oral solution:
   - Gently pull back the plunger of the syringe until the level of the oral solution is even with the marking on the syringe for your prescribed dose.
   - Always keep the bottle in an upright position.
   - If bubbles form within the oral solution in the syringe, empty the syringe into the bottle and repeat step 4 (Figure 4).
   - You may need to repeat step 4 more than once to draw up your prescribed dose.

Figure 4: Withdrawing solution



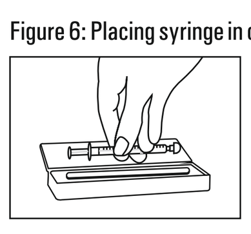
5. If your doctor tells you to carry your medicine with you:
   - Each dose of sirolimus oral solution should be placed in an oral syringe. Place a cap securely on each syringe. The cap should snap into place (Figure 5).

Figure 5: Capping syringe



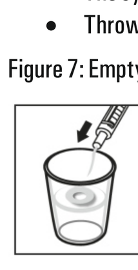
   - Place the capped syringe in the enclosed carrying case (Figure 6). If you need more than 1 carrying case, talk with your doctor or pharmacist.
   - See 'How should I store sirolimus oral solution' for storage instructions.

Figure 6: Placing syringe in carrying case



6. Taking a dose of sirolimus oral solution:
   - Choose a clean flat work surface. Place a clean paper towel on the work surface. Wash and dry your hands.
   - Empty the syringe into a glass or plastic cup containing at least 2 ounces (1/4 cup, 60 mL) of water or orange juice, stir vigorously for 1 minute and drink right away (Figure 7).
   - If more than 1 syringe is needed for your prescribed dose, empty the oral solution from each syringe into the same glass or plastic cup of water or orange juice.
   - Refill the container with at least 4 ounces (1/2 cup, 120 mL) of water or orange juice, stir vigorously again and drink the rinse solution. Do not mix sirolimus oral solution with apple juice, grapefruit juice, or other liquids. Only glass or plastic cups should be used to mix sirolimus oral solution.
   - The syringe and cap should be used only one time and then thrown away.
   - Throw away the paper towel and clean the work surface. Wash your hands.

Figure 7: Emptying syringe into glass



7. Always store the bottles of medication in the refrigerator.

How should I store sirolimus oral solution?

- Store bottles of sirolimus oral solution in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Protect from light.
- Store sirolimus oral solution that is in a syringe at room temperature up to 77°F (25°C) or in the refrigerator at 36°F to 46°F (2°C to 8°C) for up to 24 hours.
- If necessary, bottles of sirolimus oral solution can be stored at room temperature up to 77°F (25°C) for up to 15 days.
- When a bottle of sirolimus oral solution is opened, it should be used within 1 month.
- Use any diluted sirolimus oral solution right away.

Keep sirolimus and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured for:
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Revised: 05/2024

Sirolimus is a white to off white powder. Freely soluble in chloroform, acetone and acetonitrile. Insoluble in water.

Sirolimus is available for administration as an oral solution containing 1 mg/mL sirolimus.

The inactive ingredients in sirolimus oral solution are Phosal® 50 PG (alcohol, ascorbyl palmitate, phosphatidylcholine, propylene glycol, soy acid, sunflower seed oil glyceride and tocopherol) and polysorbate 80. Sirolimus oral solution contains 1.5% to 2.5% ethanol.

12 CLINICAL PHARMACOLOGY

12.1 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. Mammalian target of rapamycin (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.

Studies in experimental models show that sirolimus prolongs allograft (kidney, heart, skin, islet, small bowel, pancreatico-duodenal, and bone marrow) survival in mice, rats, pigs, and/or primates. Sirolimus reverses acute rejection of heart and kidney allografts in rats and prolongs the graft survival in presensitized rats. In some studies, the immunosuppressive effect of sirolimus lasts up to 6 months after discontinuation of therapy. This tolerization effect is alloantigen-specific.

In rodent models of autoimmune disease, sirolimus suppresses immune-mediated events associated with systemic lupus erythematosus, collagen-induced arthritis, autoimmune type I diabetes, autoimmune myocarditis, experimental allergic encephalomyelitis, graft-versus-host disease, and autoimmune uveoretinitis.

Lymphangioleiomyomatosis involves lung tissue infiltration with smooth muscle-like cells that harbor inactivating mutations of the tuberous sclerosis complex (TSC) gene (LAM cells). Loss of TSC gene function activates the mTOR signaling pathway, resulting in cellular proliferation and release of lymphangiogenic growth factors. Sirolimus inhibits the activated mTOR pathway and thus the proliferation of LAM cells.

12.2 Pharmacodynamics

Orally-administered sirolimus, at doses of 2 mg/day and 5 mg/day, 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 [*see Clinical Studies (14.1)*]. There was no demonstrable 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 [*see Dosage and Administration (2.5)*].

12.3 Pharmacokinetics

Sirolimus pharmacokinetics activity have been determined 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 Table 4.

TABLE 4: 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) Solution	Tablets
C_{max} (ng/mL)	14.4 ± 5.3	15.0 ± 4.9
t_{max} (hr)	2.1 ± 0.8	3.5 ± 2.4
AUC (ng•h/mL)	194 ± 78	230 ± 67
C_{min} (ng/mL)[c]	7.1 ± 3.5	7.6 ± 3.1
CL/F (mL/h/kg)	173 ± 50	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 by LC/MS/MS in renal transplant patients, were significantly correlated with $AUC_{\tau,ss}$. Upon repeated, twice-daily administration without an initial loading dose in 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 [*see Dosage and Administration (2.3, 2.5), Warning and Precautions (5.17)*].

Absorption

Following administration of sirolimus oral solution, the mean times to peak concentration (t_{max}) of sirolimus are approximately 1 hour and 2 hours in healthy subjects and renal transplant patients, respectively. The systemic availability of sirolimus is low, and was estimated to be approximately 14% after the administration of sirolimus oral solution. In healthy subjects, the mean bioavailability of sirolimus after administration of the tablet is approximately 27% higher relative to the solution. Sirolimus tablets are not bioequivalent to the solution; however, clinical equivalence has been demonstrated at the 2 mg dose level. Sirolimus concentrations, following the administration of sirolimus oral solution to stable renal transplant patients, are dose-proportional between 3 and 12 mg/m^2.

Food Effects

To minimize variability in sirolimus concentrations, sirolimus oral solution should be taken consistently with or without food [*see Dosage and Administration (2)*]. In 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. The effect of food on the mean sirolimus C_{max} was inconsistent depending on the sirolimus dosage form evaluated.

Distribution

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.

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 [*see Warnings and Precautions (5.20) and Drug Interactions (7)*]. 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 oral solution in healthy volunteers, the majority (91%) of radioactivity was 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) Observed in Phase 3 Clinical Studies

The following sirolimus concentrations (chromatographic equivalent) were observed in phase 3 clinical studies for prophylaxis of organ rejection in *de novo* renal transplant patients [*see Clinical Studies (14)*].

TABLE 5: SIROLIMUS WHOLE BLOOD TROUGH CONCENTRATIONS OBSERVED IN RENAL TRANSPLANT PATIENTS ENROLLED IN PHASE 3 STUDIES

Patient Population (Study number)	Treatment	Year 1 Mean (ng/mL)	Year 1 10th to 90th percentiles (ng/mL)	Year 3 Mean (ng/mL)	Year 3 10th to 90th percentiles ng/mL)
Low-to-moderate risk (Studies 1 & 2)	Sirolimus (2 mg/day) + CsA	7.2	3.6 to 11	–	–
	Sirolimus (5 mg/day) + CsA	14	8 to 22	–	–
Low-to-moderate risk (Study 3)	Sirolimus + CsA	8.6	5 to 13[a]	9.1	5.4 to 14
	Sirolimus alone	19	14 to 22[a]	16	11 to 22
High risk (Study 4)	Sirolimus + CsA	15.7	5.4 to 27.3[b]	–	–
		11.8	6.2 to 16.9[c]		
		11.5	6.3 to 17.3[d]		

a: Months 4 through 12
b: Up to Week 2; observed CsA C_{min} was 217 (56 to 432) ng/mL
c: Week 2 to Week 26; observed CsA C_{min} range was 174 (71 to 288) ng/mL
d: Week 26 to Week 52; observed CsA C_{min} was 136 (54. to 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 sirolimus 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 [*see Dosage and Administration (2.1), Drug Interactions (7.1)*].

Lymphangioleiomyomatosis

In a clinical trial of patients with lymphangioleiomyomatosis, the median whole blood sirolimus trough concentration after 3 weeks of receiving sirolimus tablets at a dose of 2 mg/day was 6.8 ng/mL (interquartile range 4.6 to 9.0 ng/mL; n = 37).

Pharmacokinetics in Specific Populations

Hepatic Impairment

Sirolimus was 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}. 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 [*see Dosage and Administration (2.5)*]. 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 [*see Dosage and Administration (2.7)*].

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 in healthy volunteers. The loading and the maintenance doses of sirolimus need not be adjusted in patients with renal impairment [*see Dosage and Administration (2.6)*].

Pediatric Renal Transplant Patients

Sirolimus pharmacokinetic data were collected 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 to 20 ng/mL for the 21 children receiving tablets, or 5 to 15 ng/mL for the one child receiving oral solution. The children aged 6 to 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 to 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. See Table 6 below.

TABLE 6: 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)	$C_{min,ss}$ (ng/mL)	$AUC_{\tau,ss}$ (ng•h/mL)	CL/F[c] (mL/h/kg)	CL/F[c] (L/h/m^2)
6 to 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 to 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 oral solution [MODIFIED] (e.g., Neoral® Oral Solution) and/or cyclosporine capsules [MODIFIED] (e.g., Neoral® Soft Gelatin Capsules).
b: As measured by Liquid Chromatographic/Tandem Mass Spectrometric Method (LC/MS/MS)
c: Oral-dose clearance adjusted by either body weight (kg) or body surface area (m^2).

Table 7 below summarizes pharmacokinetic data obtained in pediatric dialysis patients with chronically impaired renal function.

TABLE 7: SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN PEDIATRIC PATIENTS WITH END-STAGE KIDNEY DISEASE MAINTAINED ON HEMODIALYSIS OR PERITONEAL DIALYSIS (1, 3, 9, 15 mg/m^2 SINGLE DOSE)*

Age Group (y)	n	t_{max} (h)	$t_{1/2}$ (h)	CL/F/WT(mL/h/kg)
5 to 11	9	1.1 ± 0.5	71 ± 40	580 ± 450
12 to 18	11	0.79 ± 0.17	55 ± 18	450 ± 232

* All subjects received sirolimus oral solution.

Geriatric

Clinical studies of sirolimus did not include a sufficient number of patients > 65 years of age to determine whether they will respond differently than younger patients. After the administration of sirolimus oral solution or 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 phase 3 trials for the prophylaxis of organ rejection following renal transplantation using sirolimus solution or tablets and cyclosporine oral solution [MODIFIED] (e.g., Neoral® Oral Solution) and/or cyclosporine capsules [MODIFIED] (e.g., Neoral® Soft Gelatin Capsules) [*see Clinical Studies (14)*], there were no significant differences in mean trough sirolimus concentrations over time between Black (n = 190) 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 conducted 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 oral solution (MODIFIED) and/or cyclosporine capsules (MODIFIED). Sirolimus concentrations may decrease when cyclosporine is discontinued, unless the sirolimus dose is increased [*see Dosage and Administration (2.2), Drug Interactions (7.1)*].

In a 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 Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). 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.

In a single dose drug-drug interaction study, 24 healthy volunteers were administered 10 mg sirolimus oral solution either simultaneously or 4 hours after a 300 mg dose of Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). For simultaneous administration, the mean C_{max} and AUC of sirolimus, following simultaneous administration were increased by 116% and 230%, respectively, relative to administration of sirolimus alone. However, when given 4 hours after Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]) administration, sirolimus C_{max} and AUC were increased by only 37% and 80%, respectively, compared with administration of sirolimus alone.

In a single-dose cross-over drug-drug interaction study, 33 healthy volunteers received 5 mg sirolimus oral solution alone, 2 hours before, and 2 hours after a 300 mg dose of Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). When given 2 hours before Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]) administration, sirolimus C_{max} and AUC were comparable to those with administration of sirolimus alone. However, when given 2 hours after, the mean C_{max} and AUC of sirolimus were increased by 126% and 141%, respectively, relative to administration of sirolimus alone.

Mean cyclosporine C_{max} and AUC were not significantly affected when sirolimus oral solution was given simultaneously or when administered 4 hours after Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). However, after multiple-dose administration of sirolimus given 4 hours after Neoral® in renal post-transplant patients over 6 months, cyclosporine oral-dose clearance was reduced, and lower doses of Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]) were needed to maintain target cyclosporine concentration.

In a multiple-dose study in 150 psoriasis patients, sirolimus 0.5, 1.5, and 3 mg/m^2/day was administered simultaneously with Sandimmune® Oral Solution (cyclosporine Oral Solution) 1.25 mg/kg/day. The increase in average sirolimus trough concentrations ranged between 67% to 86% relative to when sirolimus was administered without cyclosporine. The intersubject variability (% CV) for sirolimus trough concentrations ranged from 39.7% to 68.7%. There was no significant effect of multiple-dose sirolimus on cyclosporine trough concentrations following Sandimmune® Oral Solution (cyclosporine oral solution) administration. However, the % CV was higher (range 85.9% to 165%) than those from previous studies.

Diltiazem: Diltiazem is a substrate and inhibitor of CYP3A4 and P-gp; sirolimus concentrations should be monitored and a dose adjustment may be necessary [*see Drug Interactions (7.4)*]. 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; co-administration of sirolimus oral solution or tablets and erythromycin is not recommended [*see Warnings and Precautions (5.20), Drug Interactions (7.2)*]. The simultaneous oral administration of 2 mg daily of sirolimus oral solution and 800 mg q 8h of erythromycin as erythromycin ethylsuccinate tablets at steady state to 24 healthy volunteers significantly affected the bioavailability of sirolimus and erythromycin. Sirolimus C_{max} and AUC were increased 4.4- and 4.2-fold respectively and t_{max} was increased by 0.4 hr. Erythromycin C_{max} and AUC were increased 1.6- and 1.7-fold, respectively, and t_{max} was increased by 0.3 hr.

Ketoconazole: Ketoconazole is a strong inhibitor of CYP3A4 and P-gp; co-administration of sirolimus oral solution or tablets and ketoconazole is not recommended [*see Warnings and Precautions (5.20), Drug Interactions (7.2)*]. Multiple-dose ketoconazole administration significantly affected the rate and extent of absorption and sirolimus exposure after administration of sirolimus oral solution, 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 $t_{½}$ 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 oral solution or tablets and rifampin is not recommended. In patients where rifampin is indicated, alternative therapeutic agents with less enzyme induction potential should be considered [*see Warnings and Precautions (5.20), Drug Interactions (7.2)*]. 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 oral solution, greatly decreased sirolimus AUC and C_{max} 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; [*see Drug Interactions (7.4)*]. The simultaneous oral administration of 2 mg daily of sirolimus oral solution and 180 mg q 12h of verapamil at steady state to 25 healthy volunteers significantly affected the bioavailability of sirolimus and verapamil. Sirolimus C_{max} and AUC were increased 2.3- and 2.2-fold, respectively, without substantial change in t_{max}. The C_{max} and AUC of the pharmacologically active S(-) enantiomer of verapamil were both increased 1.5-fold and t_{max} was decreased by 1.2 hr.

Drugs Which May Be Co-administered Without Dose Adjustment

Clinically significant pharmacokinetic drug-drug interactions were not observed 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 (Lo/Ovral®)
- Prednisolone
- Sulfamethoxazole/trimethoprim (Bactrim®)

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 [*see Warnings and Precautions (5.20), Drug Interactions (7.2)*]. 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, letermovir, *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 [*see Dosage and Administration (2.9), Drug Interactions (7.3)*].

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 [*see Drug Interactions (7.4)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were conducted in mice and rats. In an 86-week female mouse study at sirolimus doses 30 to 120 times higher than the 2 mg daily clinical dose (adjusted for body surface area), there was a statistically significant increase in malignant lymphoma at all dose levels compared with controls. In a second mouse study at dosages that were approximately 3 to 16 times the clinical dose (adjusted for body surface area), hepatocellular adenoma and carcinoma in males were considered sirolimus-related. In the 104-week rat study at dosages equal to or lower than the clinical dose of 2 mg daily (adjusted for body surface area), there were no significant findings.

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.

When female rats were treated by oral gavage with sirolimus and mated to untreated males, female fertility was decreased at 0.5 mg/kg (2.5-fold the clinical dose of 2 mg, on a body surface area basis) due to decreased implantation. In addition, reduced ovary and uterus weight were observed. The NOAEL for female rat fertility was 0.1 mg/kg (0.5-fold the clinical dose of 2 mg).

When male rats were treated by oral gavage with sirolimus and mated to untreated females, male fertility was decreased at 2 mg/kg (9.7-fold the clinical dose of 2 mg, on a body surface area basis). Atrophy of testes, epididymides, prostate, seminiferous tubules, and reduced sperm counts were observed. The NOAEL for male rat fertility was 0.5 mg/kg (2.5-fold the clinical dose of 2 mg).

Testicular tubular degeneration was also seen in a 4-week intravenous study of sirolimus in monkeys at 0.1 mg/kg (1-fold the clinical dose of 2 mg, on a body surface area basis).

14 CLINICAL STUDIES

14.1 Prophylaxis of Organ Rejection in Renal Transplant Patients

Sirolimus Oral Solution

The safety and efficacy of sirolimus oral solution for the prevention of organ rejection following renal transplantation were assessed in two randomized, double-blind, multicenter, controlled trials. These studies compared two dose levels of sirolimus oral solution (2 mg and 5 mg, once daily) with azathioprine (Study 1) or placebo (Study 2) when administered in combination with cyclosporine and corticosteroids. Study 1 was conducted in the United States at 38 sites. Seven hundred nineteen (719) patients were enrolled in this trial and randomized following transplantation; 284 were randomized to receive sirolimus oral solution 2 mg/day; 274 were randomized to receive sirolimus oral solution 5 mg/day, and 161 to receive azathioprine 2 to 3 mg/kg/day. Study 2 was conducted in Australia, Canada, Europe, and the United States, at a total of 34 sites. Five hundred seventy-six (576) patients were enrolled in this trial and randomized before transplantation; 227 were randomized to receive sirolimus oral solution 2 mg/day; 219 were randomized to receive sirolimus oral solution 5 mg/day, and 130 to receive placebo. In both studies, the use of antilymphocyte antibody induction therapy was prohibited. In both studies, the primary efficacy endpoint was the rate of efficacy failure in the first 6 months after transplantation. Efficacy failure was defined as the first occurrence of an acute rejection episode (confirmed by biopsy), graft loss, or death.

The tables below summarize the results of the primary efficacy analyses from these trials. Sirolimus oral solution, at doses of 2 mg/day and 5 mg/day, significantly reduced the incidence of efficacy failure (statistically significant at the < 0.025 level; nominal significance level adjusted for multiple [2] dose comparisons) at 6 months following transplantation compared with both azathioprine and placebo.

TABLE 8: INCIDENCE (%) OF EFFICACY FAILURE AT 6 AND 24 MONTHS FOR STUDY 1[a,b]

Parameter	Sirolimus Oral Solution 2 mg/day (n = 284)	Sirolimus Oral Solution 5 mg/day (n = 274)	Azathioprine 2 to 3 mg/kg/day (n = 161)
Efficacy failure at 6 months[c]	18.7	16.8	32.3
Components of efficacy failure			
Biopsy-proven acute rejection	16.5	11.3	29.2
Graft loss	1.1	2.9	2.5
Death	0.7	1.8	0
Lost to follow-up	0.4	0.7	0.6
Efficacy failure at 24 months	32.8	25.9	36.0
Components of efficacy failure			
Biopsy-proven acute rejection	23.6	17.5	32.3
Graft loss	3.9	4.7	3.1
Death	4.2	3.3	0
Lost to follow-up	1.1	0.4	0.6

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.
c: Primary endpoint.

TABLE 9: INCIDENCE (%) OF EFFICACY FAILURE AT 6 AND 36 MONTHS FOR STUDY 2[a,b]

Parameter	Sirolimus Oral Solution 2 mg/day (n = 227)	Sirolimus Oral Solution 5 mg/day (n = 219)	Placebo (n = 130)
Efficacy failure at 6 months[c]	30.0	25.6	47.7
Components of efficacy failure			
Biopsy-proven acute rejection	24.7	19.2	41.5
Graft loss	3.1	3.7	3.9
Death	2.2	2.7	2.3
Lost to follow-up	0	0	0
Efficacy failure at 36 months	44.1	41.6	54.6
Components of efficacy failure			
Biopsy-proven acute rejection	32.2	27.4	43.9
Graft loss	6.2	7.3	4.6
Death	5.7	5.9	5.4
Lost to follow-up	0	0.9	0.8

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.
c: Primary endpoint.

Patient and graft survival at 1 year were co-primary endpoints. The following table shows graft and patient survival at 1 and 2 years in Study 1, and 1 and 3 years in Study 2. The graft and patient survival rates were similar in patients treated with sirolimus and comparator-treated patients.

TABLE 10: GRAFT AND PATIENT SURVIVAL (%) FOR STUDY 1 (12 AND 24 MONTHS) AND STUDY 2 (12 AND 36 MONTHS)[a,b]

Parameter	Sirolimus Oral Solution 2 mg/day	Sirolimus Oral Solution 5 mg/day	Azathioprine 2 to 3 mg/kg/day	Placebo
Study 1	(n = 284)	(n = 274)	(n = 161)	
Graft survival				
Month 12	94.7	92.7	93.8	
Month 24	85.2	89.1	90.1	
Patient survival				
Month 12	97.2	96.0	98.1	
Month 24	92.6	94.9	96.3	
Study 2	(n = 227)	(n = 219)		(n = 130)
Graft survival				
Month 12	89.9	90.9		87.7
Month 36	81.1	79.9		80.8
Patient survival				
Month 12	96.5	95.0		94.6
Month 36	90.3	89.5		90.8

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.

The reduction in the incidence of first biopsy-confirmed acute rejection episodes in patients treated with sirolimus compared with the control groups included a reduction in all grades of rejection.

In Study 1, which was prospectively stratified by race within center, efficacy failure was similar for sirolimus oral solution 2 mg/day and lower for sirolimus oral solution 5 mg/day compared with azathioprine in Black patients. In Study 2, which was not prospectively stratified by race, efficacy failure was similar for both sirolimus oral solution doses compared with placebo in Black patients. The decision to use the higher dose of sirolimus oral solution in Black patients must be weighed against the increased risk of dose-dependent adverse events that were observed with the sirolimus oral solution 5-mg dose [*see Adverse Reactions (6.1)*].

TABLE 11: PERCENTAGE OF EFFICACY FAILURE BY RACE AT 6 MONTHS[a,b]

Parameter	Sirolimus Oral Solution 2 mg/day	Sirolimus Oral Solution 5 mg/day	Azathioprine 2 to 3 mg/kg/day	Placebo
Study 1				
Black (n = 166)	34.9 (n= 63)	18.0 (n = 61)	33.3 (n = 42)	
Non-Black (n = 553)	14.0 (n = 221)	16.4 (n = 213)	31.9 (n = 119)	
Study 2				
Black (n = 66)	30.8 (n = 26)	33.7 (n = 27)		38.5 (n = 13)
Non-Black (n = 510)	29.9 (n = 201)	24.5 (n = 192)		48.7 (n = 117)

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.

Mean glomerular filtration rates (GFR) post-transplant were calculated by using the Nankivell equation at 12 and 24 months for Study 1, and 12 and 36 months for Study 2. Mean GFR was lower in patients treated with cyclosporine and sirolimus oral solution compared with those treated with cyclosporine and the respective azathioprine or placebo control.

TABLE 12: OVERALL CALCULATED GLOMERULAR FILTRATION RATES (Mean ± SEM, cc/min) BY NANKIVELL EQUATION POST-TRANSPLANT[a,b]

[illegible]

events 28/131 (21.4%) versus 4/123 (3.3%) in the sirolimus group compared to the tacrolimus group.

The incidence of biopsy-confirmed acute rejection was higher for patients in the sirolimus group 11/131 (8.4%) compared to the tacrolimus group 2/123 (1.6%) through 2 years post-transplant. The rate of new-onset diabetes mellitus post-randomization, defined as 30 days or longer of continuous or at least 25 days non-stop (without gap) use of any diabetic treatment after randomization, a fasting glucose ≥ 126 mg/dL or a non-fasting glucose ≥ 200 mg/dL, was higher in the sirolimus group 15/82 (18.3%) compared to the tacrolimus group 4/72 (5.6%). A greater incidence of proteinuria, was seen in the sirolimus group 19/131 (14.5%) versus 2/123 (1.6%) in the tacrolimus group.

14.5 Conversion from a CNI-based Regimen to a Sirolimus-based Regimen in Liver Transplant Patients

Conversion from a CNI-based regimen to a sirolimus-based regimen was assessed in stable liver transplant patients 6 to 144 months post-transplant. The clinical study was a 2:1 randomized, multi-center, controlled trial conducted at 82 centers globally, including the US and Europe, and was intended to show that renal function was improved by conversion from a CNI to sirolimus without adversely impacting efficacy or safety. A total of 607 patients were enrolled.

The study failed to demonstrate superiority of conversion to a sirolimus-based regimen compared to continuation of a CNI-based regimen in baseline-adjusted GFR, as estimated by Cockcroft-Gault, at 12 months (62 mL/min in the sirolimus conversion group and 63 mL/min in the CNI continuation group). The study also failed to demonstrate non-inferiority, with respect to the composite endpoint consisting of graft loss and death (including patients with missing survival data) in the sirolimus conversion group compared to the CNI continuation group (6.6% versus 5.6%). The number of deaths in the sirolimus conversion group (15/393, 3.8%) was higher than in the CNI continuation group (3/214, 1.4%), although the difference was not statistically significant. The rates of premature study discontinuation (primarily due to adverse events or lack of efficacy), adverse events overall (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.

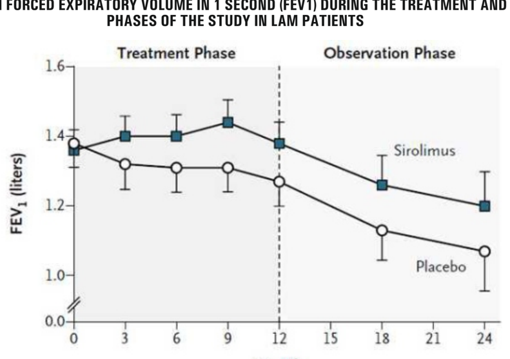
14.6 Pediatric Renal Transplant Patients

Sirolimus was evaluated in a 36-month, open-label, randomized, controlled clinical trial at 14 North American centers in pediatric (aged 3 to < 18 years) renal transplant patients considered to be at high-immunologic risk for developing chronic allograft nephropathy, defined as a history of one or more acute allograft rejection episodes and/or the presence of chronic allograft nephropathy on a renal biopsy. Seventy-eight (78) subjects were randomized in a 2:1 ratio to sirolimus (sirolimus target concentrations of 5 to 15 ng/mL, by chromatographic assay, n = 53) in combination with a calcineurin inhibitor and corticosteroids or to continue calcineurin-inhibitor-based immunosuppressive therapy (n = 25). The primary endpoint of the study was efficacy failure as defined by the first occurrence of biopsy-confirmed acute rejection, graft loss, or death, and the trial was designed to show superiority of sirolimus added to a calcineurin-inhibitor-based immunosuppressive regimen compared to a calcineurin-inhibitor-based regimen. The cumulative incidence of efficacy failure up to 36 months was 45.3% in the sirolimus group compared to 44.0% in the control group, and did not demonstrate superiority. There was one death in each group. The use of sirolimus 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 [*see Warnings and Precautions (5.8)*]. This study does not support the addition of sirolimus to calcineurin-inhibitor-based immunosuppressive therapy in this subpopulation of pediatric renal transplant patients.

14.7 Lymphangioleiomyomatosis Patients

The safety and efficacy of sirolimus for treatment of lymphangioleiomyomatosis (LAM) were assessed in a randomized, double-blind, multicenter, controlled trial. This study compared sirolimus (dose-adjusted to maintain blood trough concentrations between 5 to 15 ng/mL) with placebo for a 12-month treatment period, followed by a 12-month observation period. Eighty-nine (89) patients were enrolled; 43 patients were randomized to receive placebo and 46 patients to receive sirolimus. The primary endpoint was the difference between the groups in the rate of change (slope) per month in forced expiratory volume in 1 second (FEV1). During the treatment period, the FEV1 slope was -12 ± 2 mL per month in the placebo group and 1 ± 2 mL per month in the sirolimus group (treatment difference = 13 mL (95% CI: 7, 18). The absolute between-group difference in the mean change in FEV1 during the 12-month treatment period was 153 mL, or approximately 11% of the mean FEV1 at enrollment. Similar improvements were seen for forced vital capacity (FVC). After discontinuation of sirolimus, the decline in lung function resumed in the sirolimus group and paralleled that in the placebo group (see Figure 1).

FIGURE 1: CHANGE IN FORCED EXPIRATORY VOLUME IN 1 SECOND (FEV1) DURING THE TREATMENT AND OBSERVATION PHASES OF THE STUDY IN LAM PATIENTS



No. of Subjects							
Sirolimus	46	43	41	38	41	21	14
Placebo	43	40	42	39	34	22	13

The rate of change over 12 months of vascular endothelial growth factor-D (VEGF-D), a lymphangiogenic growth factor which has been shown to be elevated in patients with LAM, was significantly different in the sirolimus-treated group (-88.0 ± 16.6 pg/mL/month) compared to placebo (-2.42 ± 17.2 pg/mL/month) with a treatment difference of -86 pg/mL/month (95% CI: -133, -39). The absolute between-group difference in the mean change in VEGF-D during the 12-month treatment period was -1017.2, or approximately 50% of the mean VEGF-D at enrollment.

15 REFERENCES

Clinical Therapeutics, Volume 22, Supplement B, April 2000 [*see Dosage and Administration (2.5)*].

16 HOW SUPPLIED/STORAGE AND HANDLING

Since sirolimus oral solution is not absorbed through the skin, there are no special precautions. However, if direct contact of the oral solution occurs with the skin or eyes, wash skin thoroughly with soap and water; rinse eyes with plain water.

Do not use sirolimus after the expiration date. The expiration date refers to the last day of that month.

16.1 Sirolimus Oral Solution

Sirolimus oral solution, 1 mg/mL is available as clear pale yellow to yellow color viscous solution and free of visible particles.

Each sirolimus oral solution carton, NDC 31722-316-31 contains one 2 oz (60 mL fill) amber glass bottle of sirolimus (concentration of 1 mg/mL), one oral syringe adapter for fitting into the neck of the bottle, sufficient disposable oral syringes (amber color) and caps for daily dosing, and a carrying case.

Sirolimus oral solution bottles should be stored protected from light and refrigerated at 2°C to 8°C (36°F to 46°F). Once the bottle is opened, the contents should be used within one month. If necessary, the patient may store the bottles at room temperatures up to 25°C (77°F) for a short period of time (e.g., not more than 15 days for the bottles).

A syringe (amber color) and cap are provided for dosing, and the product may be kept in the syringe for a maximum of 24 hours at room temperatures up to 25°C (77°F) or refrigerated at 2°C to 8°C (36°F to 46°F). The syringe should be discarded after one use. After dilution, the preparation should be used immediately.

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

17 PATIENT COUNSELING INFORMATION

Advise patients, their families, and their caregivers to read the Medication Guide and Instructions for Use for the Oral Solution and assist them in understanding its contents. The complete text of the Medication Guide and Instructions for Use for the Oral Solution are reprinted at the end of the document.

See FDA-Approved Medication Guide and Instructions for Use for the Oral Solution.

17.1 Dosage

Patients should be given complete dosage instructions [*see FDA-Approved Medication Guide*].

17.2 Skin Cancer Events

Advise patients that exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a broad spectrum sunscreen with a high protection factor because of the increased risk for skin cancer [*see Warnings and Precautions (5.18)*].

17.3 Pregnancy and Lactation

Advise female patients of reproductive potential to avoid becoming pregnant throughout treatment and for 12 weeks after sirolimus therapy has stopped. sirolimus can cause fetal harm if taken during pregnancy. Advise a pregnant woman of the potential risk to her fetus. Before making a decision to breastfeed, inform the patient that the effects of breastfeeding in infants while taking this drug are unknown, but there is potential for serious adverse effects [*see Warnings and Precautions (5.15), Use in Specific Populations (8.1, 8.2, 8.3)*].

17.4 Infertility

Inform male and female patients that sirolimus may impair fertility [*see Warnings and Precautions (5.16), Adverse Reactions (6.7), Use in Specific Populations (8.1, 8.3), Nonclinical Toxicology (13.1)*].

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Revised: 05/2024

2102484