#### patients should use sirolimus for prophylaxis of organ rejection in patients receiving renal transp 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). icroangiopathy (5.13) .....INDICATIONS AND USAGE---Sirolimus oral solution is an mTOR inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in patients aged $\geq$ 13 year: 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). www.fda.gov/medwatch. 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: concentrations (7.4, 12.3). 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). WARNING: IMMUNOSUPPRESSION, USE IS NOT RECOMMENDED IN LIVER OR LUNG TRANSPLANT PATIENTS

- 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 Thrombotic Purpura/ Thrombotic Embryo-Fetal Toxicity: Can cause fetal harm. Use of highly effective contraception is recommended for females of reproductive potential g 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  $\geq$  30%) are peripheral edema, terolemia, creatinine increased, abdominal pain, diarrhea, headache, fever, urinar anemia, nausea, arthralgia, pain, and thrombocytopenia (6). hatosis: Most common adverse reactions (incidence  $\geq$  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 --- DRUG INTERACTIONS----Avoid concomitant use with strong CYP3A4/P-gp inducers or strong CYP3A4/P-gp inhibitors that decrease or increase sirolimus Therapeutic drug monitoring and dose reduction for sirolimus should be considered when sirolimus is co-administered with cannabidiol (5.21, 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). echanism of action (8.2). Lactation: Potential for serious adverse effects in breastfed infants h 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 Conversion from Calcineurin Inhibitors to Sirolimus in Maintenance Renal Transplant Popul 6.5 Pediatric Renal Transplant Patients 6.6 Patients with Lymphangioleior 6.7 Postmarketing Experience 7 DRUG INTERACTIONS Use with Cyclosporin
- with azathioprine and placebo controls. Treatment of new-onset hypercholesterolemia with lipid-lowering agents was required in 42 to 52% of patients enrolled in the sirolimus arms of Studies 1 and 2 compared with 16% of patients in the placeboarm and 22% of patients in the azathoprine arms. In other sciolinus renal transplant studies, 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 see Warnings and Precautions (5.7) normal Healing Abnormal healing events following transplant surgery include fascial dehiscence, incisional hernia, and anastomosis disruption (e.g., wound, vascular, airway, ureteral, biliary). Malignancies Fable 2 below summarizes the incidence of malignancies in the two controlled trials (Studies 1 and 2) for the prevention of acute rejection [se Clinical Studies (14.1)]. At 24 months (Study 1) and 36 months (Study 2) post-transplant, there were no significant differences among treatment groups TABLE 2: INCIDENCE (%) OF MALIGNANCIES IN STUDY 1 (24 MONTHS) AND STUDY 2 (36 MONTHS) POST-TRANSPLANT<sup>1,1</sup> Sirolimus Oral Solution Sirolimus Oral Solution Azathioprine Placebo 2 to 3 mg/kg/day 2 mg/day 5 mg/day Study 1 Study 2 Study 1 Study 2 Study 1 Study 2 Malignancy (n = 284) (n = 227) (n = 274) (n = 219) (n = 161) (n = 130) Lymphoma/lymphoproliferative disease 0.7 1.8 1.1 3.2 0.6 0.8 Skin Carcinoma Any Squamous Cell<sup>c</sup> 0.4 2.7 2.2 0.9 3.8 3.0 2.2 1.5 Any Basal Cell<sup>c</sup> 0.7 1.8 2.5 5.3 Melanoma 0.0 0.4 0.0 1.4 0.0 0.0 Miscellaneous/Not Specified 0.0 0.0 0.0 0.0 0.0 0.8 Total 1.1 4.4 3.3 4.1 4.3 7.7 1.1 2.2 1.5 Other Malignancy 1.4 0.6 2.3 a: Patients received cyclosporine and corticosteroids. b: Includes patients who prematurely discontinued treatment c: Patients may be counted in more than one category. 6.2 Sirolimus Following Cyclosporine Withdrawa The incidence of adverse reactions was determined through 36 months in a randomized, multicenter, controlled trial (Study 3) in which 215 renal transplant patients received sirolimus as a maintenance regimen following cyclosporine withdrawal, and 215 patients received sirolimus with cyclosporine therapy [see Clinical Studies (14.2]]. All patients were treated with corticosteroids. The safety profile prior to randomization (start of cyclosporine withdrawal) was similar to that of the 2 mg sirolimus groups in Studies 1 and 2.

Less frequently (<3%) occurring adverse reactions included: lymphoma/post-transplant lymphoproliferative disorder, mycobacterial infections

In Studies 1 and 2, in *de novo* renal transplant patients who began the study with fasting, total serum cholesterol < 200 mg/dL or fasting, total

serum triglycerides < 200 mg/dL, there was an increased incidence of hypercholesterolemia (fasting serum cholesterol > 240 mg/dL) or

hypertrialyceridemia (fasting serum trialycerides > 500 ma/dL), respectively, in patients receiving both sirolimus 2 mg and sirolimus 5 mg compared

(including M. tuberculosis), nancreatitis, cytomegalovirus (CMV), and Enstein-Barr virus,

Increased Serum Cholesterol and Triglycerides

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

[he incidence of malignancies in Study 3 [see Clinical Studies (14.2/] is presented in Table 3.

In Study 3, the incidence of lymphoma/lymphoproliferative disease was similar in all treatment groups. The overall incidence of malignancy was higher in patients receiving sirolimus plus cyclosporine compared with patients who had cyclosporine withdrawn. Conclusions regarding these lifferences in the incidence of malignancy could not be made because Study 3 was not designed to consider malignancy risk factors or systematically screen subjects for malignancy. In addition, more patients in the sirolimus with cyclosporine group had a pre-transpl

**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:

. 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.

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

breastfed infants. You and your doctor should decide about the best way to feed your baby if you take

• It is not known whether sirolimus passes into breast milk; however, there is a risk of serious side effects in

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

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

cyclosporine (including Gengraf, Neoral, Sandimmune) or tacrolimus (Prograf) or other medicines that

Read the Instructions for Use that comes with your sirolimus oral solution for information about the right

Your doctor will tell you how much sirolimus oral solution to take and when to take it. Do not change your

If you also take cyclosporine (Gengraf, Neoral, Sandimmune), you should take your sirolimus oral solution

• Do not stop taking sirolimus oral solution or your other anti-rejection medicines unless your doctor tells you

• Your doctor will check the levels of sirolimus oral solution in your blood. Your doctor may change your dose

• Take each dose of sirolimus oral solution the same way, either with or without food. Food can affect the

• Sirolimus oral solution can develop a slight haze when it is refrigerated. If this happens, bring the sirolimus

If you have taken more medicine than you were told, contact a doctor or go to the nearest hospital

Avoid receiving live vaccines while taking sirolimus oral solution. Some vaccines may not work as well while

• Limit your time in sunlight and UV light. Cover your skin with clothing and use a broad spectrum sunscreen

Serious allergic reactions. Tell your doctor or get medical help right away if you get any of following

Swelling (edema). Fluid may collect in your hands and feet and in various tissues of your body, including in

Poor wound healing. Sirolimus oral solution may cause your wounds to heal slowly or not heal well. Tell

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

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,

Certain viruses can live in your body and cause active infections when your immune system is weak. BK

• A certain virus can cause a rare serious brain infection called Progressive Multifocal

• 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

Blood clotting problems. When sirolimus oral solution is taken with cyclosporine or tacrolimus, you may

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?".

nausea

chest pain

headache

dizziness

o sore muscles

Sirolimus oral solution may affect fertility in females and may affect your ability to become pregnant. Talk

• Sirolimus oral solution may affect fertility in males and may affect your ability to father a child. Talk to your

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

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

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

urinary tract infection

blood to clot)

low platelet count (cells that help

high blood sugar (diabetes)

upper respiratory tract infection

develop a blood clotting problem. Tell your doctor if you get any unexplained bleeding or bruising.

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

○ pain (including stomach and joint pain) ○ low red blood cell count (anemia)

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

Other side effects that may occur with sirolimus oral solution:

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.

healthcare provider if this is a concern for you.

How should I store sirolimus oral solution?

Leukoencephalopathy (PML). PML usually causes death or severe disability. Call your doctor right away

Effects on kidney function. When sirolimus oral solution is taken with cyclosporine (Gengraf, Neoral,

your doctor if you have any redness or drainage, your wound does not heal, or the wound opens up

• feeling dizzy or faint

• rash or peeling of your skin

with a high protection factor because of the increased risk for skin cancer with sirolimus oral solution.

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

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.

swelling of your face, eyes, or mouth
 chest pain or tightness

the sac around your heart or lungs. Call your doctor if you have trouble breathing.

• Increased protein in your urine. Your doctor may regularly test your urine protein.

if you notice any new or worsening medical problems such as:

other problems that have lasted over several days

need to stop sirolimus oral solution or lower your dose.

sudden change in thinking, walking, strength on one side of your body

virus can affect how your kidney works and cause your transplanted kidney to fail.

• If you get sirolimus oral solution in your eyes, rinse your eyes with water.

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

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

within 12 weeks after your final dose of sirolimus oral solution.

have liver problems

have high cholesterol or triglycerides (fat in your blood)

a medicine to lower your cholesterol or triglycerides

• a medicine for high blood pressure or heart problems

bromocriptine mesylate (Parlodel, Cycloset)

medicines to treat HIV or hepatitis C

How should I take sirolimus oral solution?

way to take sirolimus oral solution

and cyclosporine about 4 hours apart.

• medicines used to treat stomach acid, ulcers, or other gastrointestinal problems

• Take sirolimus oral solution exactly as your doctor tells you to take it.

dose of sirolimus oral solution unless your doctor tells you to.

of sirolimus oral solution depending on your blood test results.

• Sirolimus oral solution is taken by mouth 1 time each day.

have skin cancer or it runs in your family

sirolimus oral solution.

Especially tell your doctor if you take:

• an antifungal medicine

• an anti-seizure medicine

letermovir (Prevymis)

cannabidiol (Epidiolex)

with grapefruit juice.

emergency department right away.

you are taking sirolimus oral solution.

symptoms of an allergic reaction:

• trouble breathing or wheezing

throat tightness

prescribed treatment plan.

Neoral, Sandimmune).

confusion

high blood pressure

o diarrhea

fever

headache

mouth sores

stomach pain

sore throat

diarrhea

o nausea

o acne

Sirolimus oral solution:

Protect from light.

pharmacist

1088.

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• Increased risk for viral infections.

What should I avoid while taking sirolimus oral solution?

What are the possible side effects of sirolimus oral solution?

Sirolimus oral solution may cause serious side effects, including:

• St. John's Wort

suppress the immune system

serious side effects.

• an antibiotic

danazol

to

solution works.

# -- DOSAGE FORMS AND STRENGTHS--• Oral Solution: 60 mg per 60 mL in amber plass bottle (3.1). These highlights do not include all the information needed to use SIROLIMUS ORAL SOLUTION safely and effectively. See full --- CONTRAINDICATIONS Hypersensitivity to sirolimus (4).

Angioedema (5.5)

Hyperlipidemia (5.7)

Proteinuria (5.9)

Hypersensitivity Reactions (5.4)

Decline in Renal Function (5.8)

Fluid Accumulation and Impairment of Wound Healing (5.6

# Sirolimus Oral Solution 316-2024-05

---WARNINGS AND PRECAUTIONS--

# FULL PRESCRIBING INFORMATION: CONTENTS \*

HIGHLIGHTS OF PRESCRIBING INFORMATION

SIROLIMUS or al solution

Initial U.S. Approval: 1999

rmation for SIROLIMUS ORAL SOLUTION.

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 (5.1). Only physicians experienced in immunosuppressive therapy and management of renal transplant

See full prescribing information for complete boxed warning.

- INDICATIONS AND USAGE
- 1.1 Prophylaxis of Organ Rejection in Renal Transplantation
- 1.2 Limitations of Use in Renal Transplantation Treatment of Patients with Lymphangiolei
- DOSAGE AND ADMINISTRATION
- General Dosing Guidance for Renal Transplant Patients
- Renal Transplant Patients at Low- to Moderate-Im 2.3 Renal Transplant Patients at High-Immunologic Risk
- 2.4 Dosing in Patients with Lymphangioleiomy
- Therapeutic Drug Monitoring
- 7.5 Cannabidiol
  - 8 USE IN SPECIFIC POPULATIONS 8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Patients with Henatic Impairmer

- Strong Inducers and Strong Inhibitors of CYP3A4 and  $P\mbox{-}gp$
- 7.3 Grapefruit Juice 7.4 Weak and Moderate Inducers or Inhibitors of CYP3A4 and P-gp

8.3 Females and Males of Reproductive Potential

s was associated with increased serum cholesterol and triglycerides that may require tre

2.6 Patients with Low Body Weigh

DOSAGE FORMS AND STRENGTHS

5.4 Hypersensitivity Reactions

Fluid Accumulation and Im

5.12 De Novo Use Without Cyclosporine

icroangiopath

5.17 Different Sirolimus Trough Cor

5.21 Cannabidiol Drug Interaction

6.2 Sirolimus Following Cyclosporine Withdrawal 6.3 High-Immunologic Risk Renal Transplant Patients

5.14 Antimicrobial Prophylaxis

5.15 Embryo-Fetal Toxicity

5.16 Male Infertility

5.18 Skin Cancer Events

5.19 Immunizations

ADVERSE REACTIONS

3.1 Sirolimus Oral Solution

4 CONTRAINDICATIONS WARNINGS AND PRECAUTIONS

5.5 Angioedema

5.7 Hyperlipidemia 5.8 Decline in Renal Function

Proteinuria 5.10 Latent Viral Infections

3

5

- Patients with Hepatic Impairme Patients with Renal Impairment

Lung Transplantation – Bronchial Anastomotic De

5.11 Interstitial Lung Disease/Non-Infectious Pneumonitis

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

6.1 Clinical Studies Experience in Prophylaxis of Organ Rejection Following Renal Transplantation

5.1 Increased Susceptibility to Infection and the Possible Development of Lymphoma
 5.2 Liver Transplantation – Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis

ment of Wound Healin

nunologic Risk

- 2.9 Instructions for Dilution and Administration of Sirolimus Oral Solution
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        - 11 DESCRIPTION
        - 12 CLINICAL PHARMACOLOGY
        - 12.1 Mechanism of Action 12.2 Pharmacodynamics
        - 2.3 Pharmacokinetic
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        - 14.1 Prophylaxis of Organ Rejection in Renal Transplant Patients 14.2 Cyclosporine Withdrawal Study in Renal Transplant Patient:
        - I.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 Patient
        - 14.6 Pediatric Renal Transplant Patients

Increased serum cholesterol and triglycerides requiring treatment occurred more frequently in patients treated with sirolimus compared with azthioprine 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

Any patient who is administered sirolimus should be monitored for hyperlipidemia. If detected, interventions such as diet, exercise, and lipid-lowering

In clinical trials of patients receiving sirolimus plus cyclosporine or sirolimus after cyclosporine withdrawal, up to 90% of patients required treatmen

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%), mvaloia (6,7%) and rhabdomvolvsis (<1%). In these

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 rhabdomvolvsis and other adverse effects, as described in the

Renal function should be closely monitored during the co-administration of sirolimus with cyclosporine, because long-term administration of the

combination has been associated with deterioration of renal function. Patients treated with cyclosporine and sirolimus were noted to have higher

serum creatinine levels and lower glomerular filtration rates compared with patients treated with cyclosporine and placebo or azathioprine control

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

Appropriate adjustment of the immunosuppressive regimen, including discontinuation of sirolimus and/or cyclosporine, should be considered in

cyclosporine beyond 4 months following transplantation should only be considered when the benefits outweigh the risks of this combination for

patients with elevated or increasing serum creatinine levels. In patients at low- to moderate-immunologic risk, continuation of combination therapy

the individual patients. Caution should be exercised when using agents (e.g., aminoglycosides and amphotericin B) that are known to have a

eriodic quantitative monitoring of urinary protein excretion is recommended. In a study evaluating conversion from calcineurin inhibitors (CNI) to

sirolimus in maintenance renal transplant patients 6 to 120 months post-transplant, increased urinary protein excretion was commonly observe

from 6 through 24 months after conversion to sirolimus compared with CNI continuation [see Clinical Studies (14.4), Adverse Reactions (6.4)].

after conversion. New onset nephrosis (nephrotic syndrome) was also reported as a treatment-emergent adverse reaction in 2.2% of the sirolimus

conversion group patients in comparison to 0.4% in the CNI continuation group of patients. Nephrotic range proteinuria (defined as urinary protein creatinine ratio > 3.5) was also reported in 9.2% in the sirolimus conversion group of patients in comparison to 3.7% in the CNI continuation group

olimus. The safety and efficacy of conversion from calcineurin inhibitors to sirolimus in maintenance renal transplant patients have not bee

associated nephropathy, which has been observed in renal transplant patients receiving immunosuppressants, including sirolimus. This infectior

may be associated with serious outcomes, including deteriorating renal function and renal graft loss [see Adverse Reactions (6.7)]. Patient

including sirolimus. PML commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies and ataxia. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically

indicated. Consideration should be given to reducing the amount of immunosuppression in patients who develop PML. In transplant patients

uation or dose reduction of sirolimus. The risk may be increased as the trough sirolimus concentration in

afety and efficacy of *de novo* use of sirolimus without cyclosporine is not established in renal transplant patients. In a multicenter clinical study

de novo renal transplant patients treated with sirolimus, mycophenolate mofetil (MMF), steroids, and an IL-2 receptor antagonist had significantly

higher acute rejection rates and numerically higher death rates compared to patients treated with cyclosporine, MMF, steroids, and IL-2 receptor antagonist. A benefit, in terms of better renal function, was not apparent in the treatment arm with *de novo* use of sirolimus without cyclosporine.

5.13 Increased Risk of Calcineurin Inhibitor.Induced Hemolytic Ilremic Syndrome/Thromhotic Thromhocytonenic Purnura/Thromhoti

The concomitant use of sirolimus with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced hemolytic uremic syndrome/

Cases of Pneumocystis carinii pneumonia have been reported in transplant patients not receiving antimicrobial prophylaxis. Therefore, antimicrobial

negalovirus (CMV) prophylaxis is recommended for 3 months after transplantation, particularly for patients at increased risk for CMV disease.

Based on animal studies and the mechanism of action [see Clinical Pharmacology (12.1)], sirolimus can cause fetal harm when administered to a pregnant woman. In animal studies, sirolinus caused embryo-fetal toxicity when administered during the period of organogenesis at maternal exposures that were equal to or less than human exposures at the recommended lowest starting dose. Advise pregnant women of the potential risk

to a fetus. Advise female patients of reproductive potential to avoid becoming pregnant and to use highly effective contraception while using

Currently in clinical practice, sirolimus whole blood concentrations are being measured by various chromatographic and immunoassay

methodologies. Patient sample concentration values from different assays may not be interchangeable [see Dosage and Administration (2.5]].

permia or oligospermia may be observed [see Adverse Reactions (6.7), Nonclinical Toxicology (13.1)]. Sirolimus is an anti-proliferative drug

botic microangiopathy (HUS/TTP/TMA) [see Adverse Reactions (6. 7/1.

sed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include BK virus

of patients. In some patients, reduction in the degree of urinary protein excretion was observed for individual patients following discontinuation of

tients with the greatest amount of urinary protein excretion prior to sirolimus conversion were those whose protein excret

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal have been reported in patients treated with imr

trials, the number of patients was too small and duration of follow-up too short to evaluate the long-term impact of sirolimus on cardiov

olemia with anti-lipid therapy (e.g., statins, fibrates). Despite anti-lipid management, up to 50% of patients had

carefully considered in patients with established hyperlipidemia before initiating an immunosuppressive regimen including sirolimus.

ts should be initiated as outlined by the National Cholesterol Education Program guidelin

In patients with delayed graft function, sirolimus may delay recovery of renal function

nonitoring may help detect patients at risk for BK virus-associated nephropathy. Redu

physicians should also consider the risk that reduced immunosuppression represents to the graft.

These findings were also observed in a similar treatment group of another clinical trial.

irolimus and for 12 weeks after ending treatment [see Use in Specific Populati

prophylaxis for Pneumocystis carinii pneumonia should be administered for 1 year following transplantation

who develop evidence of BK virus-associated nephropathy.

5.11 Interstitial Lung Disease/Non-Infectious Pneumonitis

- 14.7 Lymphangio sis Patients 15 REFERENCES
- 16 HOW SUPPLIED/STORAGE AND HANDLING
- 16.1 Sirolimus Oral Solution
- 17 PATIENT COUNSELING INFORMATION
- 7.1 Dosage 17.2 Skin Cancer Events

5.7 Hyperlipidemia

mortality.

or hyperlipidemia and hypercholes

respective labeling for these agents.

5.8 Decline in Renal Function

deleterious effect on renal function

5.10 Latent Viral Infections

eactions (6.7)].

5.12 De Novo Use Without Cyclosporine

5.14 Antimicrobial Prophylaxis

5.15 Embryo-Fetal Toxicity

5.16 Male Infertility

5.18 Skin Cancer Events

Patients on immu

5.19 Immunizations

and affects rapidly dividing cells like the germ cells.

5.9 Proteinuria

- 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 ncreased susceptibility to infection and the possible development of lymphoma and other malignancies may result fror Increased susceptibility to infection and the possible development of lymphoma may result from immunos

5.13 Increased Risk of Calcineurin Inhibitor-Induced Hemolytic Uremic Syndrome/Thrombotic Thrombocytopenic Purpura/Thromboti

centrations Reported between Chromatographic and Immunoassay Methodologie

- 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 oped and staffed with adequate laboratory and supportive medical resources. The physician responsible for m prapy 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 tacrolimu 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 motic dehiscence, most fatal, have been reported in de novo lung transplant patients when sirolimus has been used as part of an immunosuppressive regimen [see Warnings and Precautions (5.3)].

# INDICATIONS AND USAGE

Prophylaxis of Organ Rejection in Renal Transplantation Sirolimus oral solution is indicated for the prophylaxis of organ rejection in patients aged 13 years or older receiving renal transplants.

In patients at low-to moderate-immunologic risk, it is recommended that sirolimus oral solution be used initially in a regimen with cyclosporine and eroids; 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 fo reason and/or patients with high panel-reactive antibodies (PRA; peak PRA level > 80%)), it is recommended that sirolimus oral tion 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 sirolimus oral solution 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 immu 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 sirolimus oral solution have not been established in patients < 13 years old, or in pediatric (< 18 sidered at high-immunologic risk [see Adverse Reactions (6.5), Clinical Studies (14.6)

The safety and efficacy of de novo use of sirolimus oral solution 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 sirolimus oral solution in maintenance renal transplant patients have not been established [see Clinical Studies (14.4]]

#### 1.3 Treatment of Patients with Lymphangiole

on is indicated for the treatment of patients with lymphangiole 2 DOSAGE AND ADMINISTRATION

Sirolimus oral solution is to be administered orally once daily, consistently with or without food [see Dosage and Administration (2.5), Clinical cology (12.3/].

#### 2.1 General Dosing Guidance for Renal Transplant Patients

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

osis (LAM)

Frequent sirolimus oral solution dose adjustments based on non-steady-state sirolimus concentrations can lead to overdosing or underdosing because Trequent anomals on a bottom tope adjustments based on nor steary states anomals of concentrations can also to versional of an also between the states and the states of t sirolimus oral solution dose = current dose x (target concentration/current concentration). A loading dose should be considered in addition to a new straintenance dose when it is necessary to increase sirolinus trough concentrations, in local dose induces concentrations and the straintenance dose increase dose increases indicates and the straintenance dose increases and the straintenance dose. The maximum sirolinus oral solution 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

Two millionames (2 mo) of sirolimus oral solution have been demonstrated to be clinically equivalent to 2 mo sirolimus tablets; hence, at this dose these two formulations are interchangeable. However, it is not known if higher doses of sirolimus oral solution are clinically equivalent to higher doses of sirolimus tablets on a mo-to-mo basis [see Clinical Pharmacology (12.3)].

#### 2.2 Renal Transplant Patients at Low- to Moderate-Immunologic Ris

Sirolimus Oral Solution and Cyclosporine Combination Therapy

For de novo renal transplant patients, it is recommended that sirolimus oral solution and tablets be used initially in a regimen with cyclosporine and To be provide that the provide the providet the providet the providet the the target-range [see Dosage and Administration (2.5/].

#### Sirolimus Oral Solution Following Cyclosporine Withdrawal

At 2 to 4 months following transplantation, cyclosporine should be progressively discontinued over 4 to 8 weeks, and the sirolimus oral solution 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 sirolimus oral solution dose is increased [see Clinical Pharmacology (12.3)].

#### 2.3 Renal Transplant Patients at High-Immunologic Risk

In patients with high-immunologic risk, it is recommended that sirolimus oral solution be used in combination with cyclosporine and corticosteroids for the first 12 months following transplantation [see Clinical Studies (14.3]]. The safety and efficacy of this combination in high-immunologic risk patients has not been studied beyond the first 12 months. Therefore, after the first 12 months following transplantation, any adjustments to the ered on the basis of the clinical status of the patient

For patients receiving singlinus and solution with cyclosporine, singlinus and solution therapy should be initiated with a loading dose of up to 15 mg. on day 1 post-transplantation. Beginning on day 2, an initial maintenance dose of 5 mg/day should be given. A trough level should be obtained between days 5 and 7, and the daily dose of sirolimus oral solution should thereafter be adjusted [see Dosage and Administration (2.5/].

The starting dose of cyclosporine should be up to 7 mg/kg/day in divided doses and the dose should subsequently be adjusted to achieve target whole tion (2.5/). Prednisone should be administered at a mini entrations [see Dosane and Adm

TABLE 3: INCIDENCE (%) OF MALIGNANCIES IN STUDY 3 (CYCLOSPORINE WITHDRAWAL STUDY) AT 36 MONTHS POST-TRANSPLANT

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

#### a: Patients received cyclosporine and corticosteroids.

b: Includes patients who prematurely discontinued treatmen c: Patients may be counted in more than one category.

# 6.3 High-Immunologic Risk Renal Transplant Patients

Safety was assessed in 224 nationts who received at least one dose of sirolimus with cyclosporine [see Clinical Studies (14,3)]. Overall, the cidence and nature of adverse reactions was similar to those seen in previo 1.3% at 12 months.

#### 6.4 Conversion from Calcineurin Inhibitors to Sirolimus in Maintenance Renal Transplant Population

The safety and efficacy of conversion from calcineurin inhibitors to sirolimus in maintenance renal transplant population have not been established Isee Clinical Studies (14,47). In a study evaluating the safety and efficacy of conversion from calcineurin inhibitors to sirolimus (initial target sirolimus (see climical statues (1-4-4)). In a study evaluating the safety and entracty of conversion from cancient minutors to showing similar larger showing concentrations of 12 to 20 ng/mL, and then 8 to 20 ng/mL, by chromatographic assay in maintenance renal transplant patients, enrollment was stopped in the subset of patients (n = 87) with a baseline glomerular filtration rate of less than 40 mL/min. There was a higher rate of serious adverse vents, including pneumonia, acute rejection, graft loss and death, in this stratum of the sirolir The subset of nations with a baseline plomerular filtration rate of less than 40 mL/min had 2 years of follow-up after randomization. In this

propulation, the rate of pneumonia was 25.5.% (9)58) versus 3.4% (1/29) in the sirolimus conversion group and CNI continuation grant loss (section) and the sirolimus conversion group and CNI continuation grant loss (section) and the sirolimus conversion group and CNI continuation group.

In the subset of patients with a baseline glomerular filtration rate of greater than 40 mL/min, there was no benefit associated with conversion with ent in renal function and a greater incidence of proteinuria in the s Overall in this study, a 5-fold increase in the reports of tuberculosis among sirolimus 2.0% (11/551) and comparator 0.4% (1/273) treatment arouns

In a second study evaluating the safety and efficacy of conversion from tacrolimus to sirolimus 3 to 5 months post-kidney transplant, a higher rate of adverse events, discontinuations due to adverse events, acute rejection, and new onset diabetes mellitus was observed following conversion to sirolimus. There was also no benefit with respect to renal function and a greater incidence of proteinuria was observed after conversion to sirolimus

#### 6.5 Pediatric Renal Transplant Patient

Safety was assessed in a controlled clinical trial in pediatric (< 18 years of age) renal transplant patients considered at high-immunologic risk defined as a history of one or more acute allograft rejection episodes and/or the presence of chronic allograft nephropathy on a renal biopsy [see Clinical Studies (14.6/]. The use of sirolimus in combination with calcineurin inhibitors and corticosteroids was associated with a higher incidence of deterioration of renal function (creating in a forces and contraction with continuous minutus and contractions was associated with a night includince of deterioration of renal function (creating in a forces and) compared to calcineum inhibitor-based therapy, serum lipid abnormalities (including, but not limited to, increased serum triglycerides and cholesterol), and urinary tract infections.

#### 6.6 Patients with Lymphangioleiomyomatosis

Safety was assessed in a controlled trial involving 89 patients with lymphangioleiomyomatosis, 46 of whom were treated with sirolimus [see Clinical Studies (14.7]). The adverse drug reactions observed in this trial were consistent with the known safety profile for renal transplant patients receiving sirolimus, with the addition of weight decreased which was reported at a greater incidence with sirolimus when compared to placebo Adverse reactions occurring at a frequency of  $\geq$  20% in the sirolimus treatment group and greater than placebo include stomatitis, diarrhea, abdominal pain, nausea, nasopharyngitis, acne, chest pain, peripheral edema, upper respiratory tract infection, headache, dizziness, myalgia, and

#### Postmarketing Expe

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

#### Body as a Whole - Lymphedema

- Cardiovascular Pericardial effusion (including hemodynamically significant effusions and tamponade requiring intervention in children and adults) and fluid accumulation
- Digestive System Ascites.
- Hematological/Lymphatic Pancytopenia, neutropenia. Hepatobiliary Disorders - Hepatotoxicity, including fatal hepatic necrosis, with elevated sirolimus trough concentrations
- Immune System Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, and hypersensitivity vasculitis [see Warnings and Precautions (5.4/).
- Infections Tuberculosis, BK virus associated neohropathy has been observed in patients receiving immunosuppressants, including sirolimus. This infection may be associated with serious outcomes, including deteriorating renal function and renal graft loss. Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with

ssants, including sirolimus lsee Warnings and Precautions (5, 10), Clostridium difficile ente Metabolic/Nutritional - Liver function test abnormal, AST/SGOT increased, ALT/SGPT increased, hypophosphatemia hyperglycemia, diabetes mellitus.

#### Nervous system – Posterior reversible encephalopathy syndrome

Respiratory - Cases of interstitial lung disease (including pneumonitis, bronchiolitis obliterans organizing pneumonia [BOOP], and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving imm ncluding sirolimus. In some cases, the interstitial lung disease has resolved upon discontinuation or dose reduction of sirolimus. The risk may be increased as the sirolimus trough concentration increases [see Warnings and Precautions (5.11)]; pulmonary hemorrhage pleural effusion; alveolar proteinosis.

Skin - Neuroendocrine carcinoma of the skin (Merkel cell carcinoma) [see Warnings and Precautions (5.18)], exfoliative dermatitis [see Warnings and Precautions (5.4)].

Urogenital – Nephrotic syndrome, proteinuria, focal segmental glomerulosclerosis, ovarian cysts, menstrual disorders (including amenorrhea and menorrhagia). Azoospermia has been reported with the use of sirolimus and has been reversible upon discontinuation of sirolimus in most case

#### DRUG INTERACTIONS

Cases of interstitual lung disease (ILD) (including pneumonitis, branchiolitis obliterans organizing pneumonia (BOOP), and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving immunosuppressive regimens including sirolimus. In some cases, the ILD was reported with pulmonary hypertension (including pulmonary arterial hypertension (PAHI) as a secondary event. In some cases, the ILD has Sirolimus is known to be a substrate for both cytochrome P-450 3A4 (CYP3A4) and p-glycoprotein (P-gp). Inducers of CYP3A4 and P-gp may as inhihitors of CYP3A4 and P-gp may increase 7.1 Use with Cyclosporine

cyclosporine, a substrate and inhibitor of CYP3A4 and P-gp, was demonstrated to increase sirolimus concentrations when co-administered with

or cooperating a submitted in a minimum of the second region of the seco sirolimus, higher doses of sirolimus are needed to maintain the recommended sirolimus trough concentration ranges [see Dosage and Administration (2.2), Clinical Pharmacology (12.3)].

# 7.2 Strong Inducers and Strong Inhibitors of CYP3A4 and P-gp

administered drug may need to be adjusted [see Clinical Pharmacology (12.3]].

Drugs and other agents that could decrease sirolin

Drugs with concentrations that could increase when given with sirolimu

Avoid concomitant use of sirolimus with strong inducers (e.g., rifampin, rifabutin) and strong inhibitors (e.g., ketoconazole, voriconazole cin) of CYP3A4 and P-gp. Alternative agents with itraconazole, erythromycin, tellthromycin, clarithromycin) of CYP3A4 and P-gp. Alternativ should be considered [*see Warnings and Precautions (5.20), Clinical Pharmacology (12.3/*]. 7.3 Grapefruit Juice

#### Because grapefruit juice inhibits the CYP3A4-mediated metabolism of sirolimus, it must not be taken with or be used for dilution of sirolimus (see Dosage and Administration (2.9), Drug Interactions (7.3), Clinical Pharmacology (12.3)

Drugs that could increase similarity blood concentrations: Bromocriptine, cimetidine, cisapride, clotrimazole, danazol, diltiazem, fluconazole, letermovir, protease inhibitors (e.g., HIV and hepatitis C

that include drugs such as ritonavir, indinavir, boceprevir, and telaprevir), metoclopramide, nicardipine, troleandomycin, verapamil

e blood levels of sirolimus may increase upon concomitant use with cannabidiol. When cannabidiol and sirolimus are co-administered, closely monito

for an increase in sirolimus blood levels and for adverse reactions suggestive of sirolimus toxicity. A dose reduction of sirolimus should be considered as

7 4 Weak and Moderate Inducers or Inhibitors of CYP3A4 and P-gp Exercise caution when using sirolimus with drugs or agents that are modulators of CYP3A4 and P-gp. The dosage of sirolimus and/or the co-

#### Antibody induction therapy may be used

2.4 Dosing in Patients with Lymphangi natosis, the initial sirolimus oral solution dose should be 2 mg/day. Sirolimus whole blood trough For patients with lymphangioleiom ntrations should be measured in 10 to 20 days, with dosage adjustment to maintain concentrations between 5 to 15 ng/mL [see Dosage and dministration (2.5/]. In most patients, dose adjustments can be based on simple proportion: new sirolimus oral solution dose = current dose (target concentration/current concentration). Frequent sirolimus oral solution dose adjustments based on non-steady-state sirolimus concentration tage concentration concentration, request a normal of a solution tage appartiest based on those seary state a normal concentrations can lead to overdosing or under dosing because sirolinum has a long half life. Once sirolinums call solution maintenance dose a dijusted, patients should continue on the new maintenance dose for at least 7 to 14 days before further dosage adjustment with concentration monitoring. Once a stable dose is achieved, therapeutic drug monitoring should be performed at least every three months

#### 2.5 Therapeutic Drug Monitoring

nended for all patients, especially in those patients likely to have altered drug metabolism, ir Monitoring of sirolimus trough concen patients > 13 years who weigh less than 40 kg, in patients with benatic impairment, when a change in the sirolimus oral solution dosage form is CVP3AA inducers and inhibitors [see Warnin autions (5.20, 5.21), Drug Inte

Therapeutic drug monitoring should not be the sole basis for adjusting sirolimus oral solution therapy. Careful attention should be made to clinical signs/symptoms, tissue bionsy findings, and laboratory parameters.

When used in combination with cyclosporine, sirolimus trough concentrations should be maintained within the target-range [see Clinical Studies (14)] Clinical Pharmacology (12.3)]. Following cyclosporine withdrawal in transplant patients at low- to moderate-im ologic risk, the target sirolim trough concentrations should be 16 to 24 ng/mL for the first year following transplantation. Thereafter, the target sirolimus concentrations should be 12 to 20 ng/mL.

The above recommended 24-hour trough concentration ranges for sirolimus are based on chromatographic methods. Currently in clinical practice, srolimus whole blood concentrations are being measured by both chromatographic and immunoassay methodologies. Because the measurer sirolimus whole blood concentrations depend on the type of assay used, the concentrations obtained by these different methodologies are no 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 natients > 13 years who weigh less than 40 kg should be adjusted based on body surface area to 1 mg/m<sup>2</sup>/day. The loading dose should be 3 mg/n

#### 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 nately 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 or all does syring eshould 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 polyvin chloride (PVC). This should be considered during the preparation and administration of sirolimus oral solution. It is important that these recommendation

- 3 DOSAGE FORMS AND STRENGTHS
- 3.1 Sirolimus Oral Solution
- 60 mg per 60 mL in amber glass bottle
- CONTRAINDICATIONS
- nus 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 Lymphome

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 incre susceptibility to infection, including opportunistic infections such as tuberculosis, fatal infections, and sepsis. Only physicians experienced in ve therapy and management of organ transplant patients should use sirolimus for prophylaxis of organ rejection in patients receivin renal transplants. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medica

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 <i>de novo</i> 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 <i>de novo</i> 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 <i>Clinical Studies</i> (14.5/].
5.3 June Transplantation - Bronchial Anastomotic Dahisconce

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 imr suppressive therapy have not been established in lung transplant patients; therefore, such use is not

# 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]].

#### 5.5 Angioedema

Sirolimus has been associated with the development of angioedema. The concomitant use of sirolimus with other drugs known to cause angioedema such as angiotensin-converting enzyme (ACE) inhibitors, may increase the risk of developing angioedema. Elevated sirolimus levels (with/withou nitant ACE inhibitors) may also potentiate angioedema [see Drug Interactions (7.2/]. In some cases, the angioedema has resolved upor discontinuation or dose reduction of sirolimus.

#### 5.6 Fluid Accumulation and Impairment of Wound Healing

There have been reports of impaired or delayed wound healing in patients receiving sirolimus, including lymphocele and wound dehiscence [see Adverse Reactions (6.1)]. 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. Lymphocele, a known surgical complication of renal transplantation, occurred significantly more often in a dose-related fashion in patients treated with sirolimus [see Adverse Reactions (6.1]]. Appropriate measures should be considered to minimize such complications. Patients with a body mass index (BMI) greater than 30 kg/m<sup>2</sup> may be at d risk of abnormal wound healing based on data from the medical liter

There have also been reports of fluid accumulation, including peripheral edema, lymphedema, pleural effusion, ascites, and pericardial effusions ant effusions and tamponade requiring intervention in children and adults), in patients receiving sirolimu:

Artwork information Market Customer Cambe USA Non Printing Colors Die cut Dimensions (mm) 480 x 800 mm 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.

# essive therapy are at increased risk for skin cancer. Exposure to sunlight and ultraviolet (UV) light should be limited by

[see Boxed Warning, Warnings and Precautions (5.2)]

wearing protective clothing and using a broad spectrum sunscreen with a high protection factor [see Adverse Reactions (6.1, 6.2, 6.7]].

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

5.20 Interaction with Strong Inhibitors and Inducers of CYP3A4 and/or P-gp Avoid concomitant use of sirolimus with strong inhibitors of CYP3A4 and/or P-op (such as ketoconazole, voriconazole, itraconazole, erythromycin,

5.17 Different Sirolimus Trough Concentration Reported between Chromatographic and Immunoassay Methodologies

nromycin, or clarithromycin) or strong inducers of CYP3A4 and/or P-gp (such as rifampin or rifabutin) [see Drug Interactions (7.2]] 5.21 Cannabidiol Drug Interactions When cannabidiol and sirolimus are co-administered, closely monitor for an increase in sirolimus blood levels and for adverse reactions suggestive of

#### sirolimus toxicity. A dose reduction of sirolimus should be considered as needed when sirolimus is co-administered with cannabidiol [see Dosage and istration (2.5) and Drug Interactions (7.5/).

- ADVERSE REACTIONS
- reactions are discussed in greater detail in other sections of the label

Increased susceptibility to infection, lymphoma, and malignancy [see Boxed Warning, Warnings and Precautions (5.1)] ess mortality, graft loss, and hepatic artery thrombosis in liver transplant patien

- Bronchial anastomotic dehiscence in lung transplant patients [see Boxed Warning, Warnings and Precautions (5.3/]
- Hypersensitivity reactions [see Warnings and Precautions (5.4/] Exfoliative dermatitis [see Warnings and Precautions (5.4)]
- Angioedema [see Warnings and Precautions (5.5/]
- Fluid accumulation and impairment of wound healing [see Warnings and Precautions (5.6)] Hypertriglyceridemia, hypercholesterolemia [see Warnings and Precautions (5.7)]
- Decline in renal function in long-term combination of cyclosporine with sirolimus [see Warnings and Precautions (5.8)]
  - Proteinuria [see Warnings and Precautions (5.9/] Interstitial lung disease [see Warnings and Precautions (5.11)]
  - Increased risk of calcineurin inhibitor-induced HUS/TTP/TMA [see Warnings and Precautions (5.13/]
  - Embryo-fetal toxicity [see Warnings and Precautions (5, 15]]
- Male infertility [see Warnings and Precautions (5.16/] The most common (≥30%) adverse reactions observed with sirolimus in clinical studies for organ rejection prophylaxis in recipients of rena

transplantation are: peripheral edema, hypertriglyceridemia, hypertension, hypercholesterolemia, creatinine increased, constipation, abdomina pain, diarrhea, headache, fever, urinary tract infection, anemia, nausea, arthraloia, pain, and thrombocytopenia, The most common ( $\geq$  20%) adverse reactions observed with sirolimus in the clinical study for the treatment of LAM are: stomatitis, diarrhea, abdominal pain, nausea, nasopharyngitis, acne, chest pain, peripheral edema, upper respiratory tract infection, headache, dizziness, myalgia, and

**Contraception** The following adverse reactions resulted in a rate of discontinuation of >5% in clinical trials for renal transplant rejection prophylaxis: creatinin

increased, hypertriglyceridemia, and TTP. In patients with LAM, 11% of subjects discontinued due to adverse reactions, with no single adverse reaction leading to discontinuation in more than one patient being treated with sirolimus 6.1 Clinical Studies Experience in Prophylaxis of Organ Rejection Following Renal Transplant

The safety and efficacy of sirolimus oral solution for the prevention of organ rejection following renal transplantation were assessed in two andomized, double-blind, multicenter, controlled trials [see Clinical Studies (14.1/]. The safety profiles in the two studies were simila

The incidence of adverse reactions in the randomized, double-blind, multicenter, placebo-controlled trial (Study 2) in which 219 renal transplan patients received sirolimus oral solution 2 mg/day, 208 received sirolimus oral solution 5 mg/day, and 124 received placebo is presented in Table 1 below. The study population had a mean age of 46 years (range 15 to 71 years), the distribution was 67% male, and the composition by race was White (78%), Black (11%), Asian (3%), Hispanic (2%), and Other (5%), All patients were treated with cyclosporine and corticosteroids, Data (  $\geq$  12 nonths post-transplant) presented in the following table show the adverse reactions that occurred in at least one of the sirolimus treatment groups

with an incidence of  $\geq 20\%$ . The safety profile of the tablet did not differ from that of the oral solution formulation [see Clinical Studies (14.1)]. In general, adverse reactions related to the administration of sirolimus were dependent on dose/concentration. Although a daily maintenance dose 5 mg, with a loading dose of 15 mg, was shown to be safe and effective, no efficacy advantage over the 2 mg dose could be established for rena

ransplant patients. Patients receiving 2 mg of sirolimus oral solution per day demonstrated an overall better safety profile than did patient receiving 5 mg of sirolimus oral solution per day. ecause clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly

compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice. TABLE 1: ADVERSE REACTIONS OCCURRING AT A FREQUENCY OF > 20% IN AT LEAST ONE OF THE SIROLIMUS TREATMENT

GROUPS IN A STUDY OF PROPHYLAXIS OF ORGAN REJECTION FOLLOWING RENAL TRANSPLANTATION (%) AT  $\geq 12$  months POST-TRANSPLANTATION (STUDY 2)<sup>a</sup>

	Sirolimus	Ural Solution ——		
Adverse Reaction	2 mg/day (n = 218)	5  mg/day (n = 208)	Placebo $(n = 124)$	
Peripheral edema	54	58	48	_
Hypertriglyceridemia	45	57	23	
Hypertension	45	49	48	
Hypercholesterolemia	43	46	23	
Creatinine increased	39	40	38	
Constipation	36	38	31	
Abdominal pain	29	36	30	
Diarrhea	25	35	27	
Headache	34	34	31	
Fever	23	34	35	
Urinary tract infection	26	33	26	
Anemia	23	33	21	
Nausea	25	31	29	
Arthralgia	25	31	18	
Thrombocytopenia	14	30	9	
Pain	33	29	25	
Acne	22	22	19	
Rash	10	20	6	
Edema	20	18	15	

a: Patients received cyclosporine and corticosteroids.

The following adverse reactions were reported less frequently (  $\geq$  3%, but < 20%) Body as a Whole - Sepsis, lymphocele, herpes zoster, herpes simple

Edema

- Cardiovascular Venous thromboembolism (including pulmonary embolism, deep venous thrombosis), tachycardia.
- Digestive System Stomatitis.
- tologic and Lymphatic System Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), leukopenia
- Metabolic/Nutritional Abnormal healing, increased lactic dehydrogenase (LDH), hypokalemia, diabetes mellitus,
- sculoskeletal System Bone necrosis. Respiratory System - Pneumonia, epistaxis,
- Skin Melanoma, squamous cell carcinoma, basal cell carcinoma.
- Urogenital System Pyelonephritis, decline in renal function (creatinine increased) in long-term combination of cyclosporine with sirolimus ee Warnings and Precautions (5.8)], ovarian cysts, menstrual disorders (including amer

**Risk Summary** Based on animal studies and the mechanism of action, sirolimus can cause fetal harm when administered to a pregnant woman [see Data, Clinical macology (12.1/). There are limited data on the use of sirolimus during pregnancy; however, these data are insufficient to inform a drug associated risk of adverse developmental outcomes. In animal studies, sirolimus was embryo/fetotoxic in rats at sub-therapeutic doses [see Data] Advise pregnant women of the potential risk to a fetus

needed when sirolimus is co-administered with cannabidiol [see Dosage and Administration (2.5) and Warnings and Precautions (5.21)].

Carbamazepine, phenobarbital, phenytoin, rifapentine, St. John's Wort (Hypericum perforatum

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the ted background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respec

Animal Data Sirolimus crossed the placenta and was toxic to the conceptus.

Verapamil

8 USE IN SPECIFIC POPULATIONS

7.5 Cannahidiol

8.1 Pregnanc

In rat embryo-fetal development studies, pregnant rats were administered sirolimus orally during the period of organogenesis (Gestational Day 6 to 15). Sirolimus produced embryo-fetal lethality at 0.5 mg/kg (2.5-fold the clinical dose of 2 mg, on a body surface area basis) and reduced fetal weigh d 1 mg/kg/5 fold the clinical dose of 2 mg). The no observed adverse effect level (NOAEL) for fetal toxicity in rats was 0.1 mg/kg (0.5-fold the clinical dose of 2 mg). The no observed adverse effect level (NOAEL) for fetal toxicity in rats was 0.1 mg/kg (0.5-fold the clinical dose of 2 mg). Maternal toxicity (weight loss) was observed at 2 mg/kg (10-fold the clinical dose of 2 mg). The NOAEL for maternal toxicity was 1 mg/kg. In combination with cyclosporine, rats had increased embryo-fetal mortality compared with sirolimus alone.

n rabbit embryo-fetal development studies, pregnant rabbits were administered sirolimus orally during the period of organogenesis (Gestational Day 6 to 18). There were no effects on embryo-fetal development at doses up to 0.05 mg/kg (0.5-fold the clinical dose of 2 mg, on a body surface area basis); however, at doses of 0.05 mg/kg and above, the ability to sustain a successful pregnancy was impaired (i.e., embryo-fetal abortion or early resorption). Maternal toxicity (decreased body weight) was observed at 0.05 mg/kg. The NOAEL for maternal toxicity was 0.025 mg/kg (0.25-fold the clinical dose of 2 mg).

In a nee- and nost-natal development study in rats, preparant females were dosed during pestation and lactation (Gestational Day 6 through Lactation Day 20). An increased incidence of dead pups, resulting in reduced live litter size, occurred at 0.5 mg/kg (2.5-fold the clinical dose of 2 mg/kg on a body surface area basis). At 0.1 mg/kg (0.5-fold the clinical dose of 2 mg), there were no adverse effects on offspring. Sirolimus did not cause maternal toxicity or affect developmental parameters in the surviving offspring (morphological development, motor activity, learning, or fertility assessment) at 0.5 mg/kg, the highest dose tested.

8.2 Lactation

Risk Summary

It is not known whether sirolimus is present in human milk. There are no data on its effects on the breastfed infant or milk production. The pharmacokinetic and safety profiles of sirolimus in infants are not known. Sirolimus is present in the milk of lactating rats. There is potential fo ous adverse effects from sirolimus in breastfed infants based on mechanism of action [see Clinical Pharmacology (12.1)]. The developmental an health benefits of breastfeeding should be considered along with the mother's clinical need for sirolimus and any potential adverse effects on the breastfed child from sirolimus

# 8.3 Females and Males of Reproductive Potentia

Females should not be pregnant or become pregnant while receiving sirolimus. Advise females of reproductive potential that animal studies have been shown sirolimus to be harmful to the developing fetus. Females of reproductive potential are recommended to use highly effective contraceptive method. Effective contraception must be initiated before sirolimus therapy, during sirolimus therapy, and for 12 weeks after sirolimus therapy has been stopped [see Warnings and Precautions (5.15), Use in Specific Populations (8.1)].

Based on clinical findings and findings in animals, male and female fertility may be compromised by the treatment with sirolimus [see Adverse Reactions (6.7), Nonclinical Toxicology (13.1)]. Ovarian cysts and menstrual disorders (including amenorrhea and menorrhagia) have been reported in females with the use of sirolimus. Azoospermia has been reported in males with the use of sirolimus and has been reversible upon discontinuation of sirolimus in most cases.

8.4 Pediatric Use

#### Renal Transplant The safety and efficacy of sirolimus in pediatric patients < 13 years have not been established.

The safety and efficacy of sirolimus oral solution and sirolimus tablets have been established for prophylaxis of organ rejection in renal transplantation in children  $\geq$  13 years judged to be at low- to moderate-immunologic risk. Use of sirolimus oral solution and sirolimus tablets in this subpopulation of children  $\geq$  13 years is supported by evidence from adequate and well-controlled trials of sirolimus oral solution in adults with additional pharmacokinetic data in pediatric renal transplantation patients [see Clinical Pharmacology (12.3)]. Safety and efficacy information from a controlled clinical trial in pediatric and adolescent (< 18 years of age) renal transplant patients judged to be

at high-immunologic risk, defined as a history of one or more acute rejection episodes and/or the presence of chronic allograft nephropathy, do not support the chronic use of sirolimus oral solution in combination with calcineurin inhibitors and corticosteroids, due to the higher incidence of lipid abnormalities and deterioration of renal function associated with these immunosuppressive regimens compared to calcineurin inhibitors, without increased benefit with respect to acute rejection, graft survival, or patient survival [see Clinical Studies (14.6]].

#### Lymphangioleiomyomatosis The safety and efficacy of sirolimus oral solution in pediatric patients < 18 years have not been established

#### 8.5 Geriatric Use

- Clinical studies of sirolimus oral solution did not include sufficient numbers of patients > 65 years to determine whether they respond differently from younger patients. Data pertaining to sirolimus trough concentrations suggest that dose adjustments based upon age in geriatric renal patient are not necessary.
- Differences in responses the elderly and younger patients have not been identified. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, or cardiac function, and of oncomitant disease or other drug therap
- 8.6 Patients with Hepatic Impairme
- The maintenance dose of sirolimus should be reduced in patients with hepatic impairment [see Dosage and Administration (2.7), Clinical Pharmacology (12.3)].
- 8 7 Patients with Renal Impairment
- Dosage adjustment is not required in patients with renal impairment [see Dosage and Administration (2.8), Clinical Pharmacology (12.3)].
- 10 OVERDOSAGE Reports of overdose with sirolimus have been received; however, experience has been limited. In general, the adverse effects of overdose are

consistent with those listed in the adverse reactions section [see Adverse Reactions (6/]. General supportive measures should be followed in all cases of overdose. Based on the low aqueous solubility and high erythrocyte and plasma protein binding of sirolimus, it is anticipated that sirolimus is not dialyzable to any significant extent. In mice and rats, the acute oral LD<sub>so</sub> was greater than 800 mg/kg.

# 11 DESCRIPTION

Sirolimus is an mTOR inhibitor immunosuppressive agent. Sirolimus is a macrocyclic lactone produced by Streptomyces hygroscopicus. The Chemical is an information minimospherastic agent: Original is a metodyna technic processing origination of the information of a metodynamic origination of the information of the in othylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c] [1,4] oxaazacyclo hentriacontine-1,5,11,28,29 (4H,6H,31H)-pentone. Its molecular formula is C<sub>61</sub>H<sub>28</sub>NO<sub>13</sub> and its molecular weight is 914.2. The structural formula of sirolimus is illustrated as



 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<sup>®</sup> 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.



Revised: 05/2024

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

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

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

patients, and renal transplant patients.

C<sub>max</sub> (ng/mL)

AUC (ng•h/mL)

CL/F (mL/h/kg)

c: Average C\_, over 6 months.

and Precautions (5.17)]

C<sub>min</sub> (ng/mL)<sup>c</sup>

t<sub>mar</sub> (hr)

12.1 Mechanism of Action

The pharmacokinetic parameters of sirolimus in low- to moderate-immunologic risk adult renal transplant patients following multiple dosing with

TABLE 4: MEAN  $\pm$  SD STEADY STATE SIROLIMUS PHARMACOKINETIC PARAMETERS IN LOW-TO MODERATE-IMMUNOLOGIC

RISK ADULT RENAL TRANSPLANT PATIENTS FOLLOWING SIROLIMUS 2 MG DAILY<sup>2,2</sup>

 $14.4 \pm 5.3$ 

 $2.1 \pm 0.8$ 

194 ± 78

7.1 ± 3.5

 $173 \pm 50$ 

Dose (daily dose)

Tahlet

 $15.0 \pm 4.9$ 

 $3.5 \pm 2.4$ 

 $230 \pm 67$ 

7.6 ± 3.1

 $139 \pm 63$ 

sirolimus 2 mg daily, in combination with cyclosporine and corticosteroids, is summarized in Table 4.

a: In presence of cyclosporine administered 4 hours before sirolimus dosing.

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

arathioprine 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 Strolimus 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 G1 to the S phase of the cell cycle

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

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

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 Q. INCIDENCE (0/) OF FEFERACY FAILURE AT CAND 24 MONTHS FOR CTUDY 45

TABLE 8: INCIDENCE (%) OF EFFICACY FAILURE AT 6 AND 24 MONTHS FOR STODY 1	

Mammalian target of rapamycin (mTOR) inhibitors such as sirolimus have been shown <i>in vitro</i> 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	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)
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.	Efficacy failure at 6 months <sup>e</sup> Components of efficacy failure	18.7	16.8	32.3
In rodent models of autoimmune disease, sirolimus suppresses immune-mediated events associated with systemic lupus erythematosus, collagen-	Biopsy-proven acute rejection	16.5	11.3	29.2
induced arthritis, autoimmune type I diabetes, autoimmune myocarditis, experimental allergic encephalomyelitis, graft-versus-host disease, and	Graft loss	1.1	2.9	2.5
autoimmune uveoretinitis.	Death	0.7	1.8	0
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	Lost to follow-up	0.4	0.7	0.6
release of lymphangiogenic growth factors. Sirolimus inhibits the activated mTOR pathway and thus the proliferation of LAM cells.	Efficacy failure at 24 months	32.8	25.9	36.0
12.2 Pharmacodynamics	Components of efficacy failure			
Orally-administered sirolimus, at doses of 2 mg/day and 5 mg/day, significantly reduced the incidence of organ rejection in low- to moderate-	Biopsy-proven acute rejection	23.6	17.5	32.3
immunologic risk renal transplant patients at 6 months following transplantation compared with either azathioprine or placebo [see Clinical Studies	Graft loss	3.9	4.7	3.1
(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	Death	4.2	3.3	0
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/).	Lost to follow-up	1.1	0.4	0.6
12.3 Pharmacokinetics Sirolimus pharmacokinetics activity have been determined following oral administration in healthy subjects, pediatric patients, hepatically impaired patients and enal transmission and inter-	a: Patients received cyclosporine and b: Includes patients who prematurely c: Primary endpoint.			

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 <sup>6</sup>	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 Components of efficacy failure	44.1	41.6	54.6
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

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 TADLE 10. CDAET AND DATIENT CUDVIVAL (8/) FOD CTUDV 1 (12 AND 24 MONTUC) AND CTUDV 2 (12 AND 26 MONTUC

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: I 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 601 outcident waves concluded

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

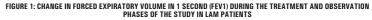
6U / patients were enrolled. The study failed to demonstrate superiority of conversion to a sirolimus-based regimen compared to continuation of a CNI-based regimen in baseline-dijusted GFR, as estimated by Cockcroft-Gault, at 12 months (62 mL/min in the sirolimus conversion group and 63 mL/min in the 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 (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 or events or compared to the CNI continuation group.

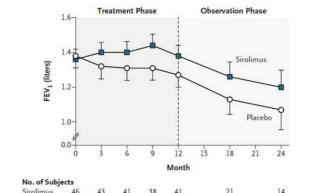
Prenic 2017 01 (21-27) versus 41/12 (1-3.7) in the showing group compare to the tactominus group. The incidence of biopsy-confirmed acute rejection was higher for patients in the shoribinus group 11/131 (8.4%) compared to the tacrolimus group 2/123 (1.6%) through 2 years post-transplant. The rate of 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  $\geq$  126 mg/dL or a non fasting glucose  $\geq$  200 mg/dL, was higher in the isolihuus group 15/2 (13.3%) compared to the tacrolimus group 4/72 (5.6%). A greater incidence o proteinuria, was seen in the sirolimus group 19/131 (14.5%) versus 2/123 (1.6%) in the tacrolimus group.

#### 14.6 Pediatric Renal Transplant Patients

ated in a 36-month, open-label, randomized, controlled clinical trial at 14 North American centers in pediatric (aged 3 to < 18Strollmus was evaluated in a  $3\hat{c}$ -month, open-label, randomized, controlled clinical trial at 14 North American centers in pediatric laged 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, griaf to a calcineurin-inhibitor-based regimeno. The cumulative incidence of efficacy failure up to 36 months was 45.3% in the sirolimus group compared to 4.0% in the control group, and did not demonstrate superiority. There was one death in each group. The use of sirolimus in combination with a susceided with an increased risk of deteroints of the functions [*see Warnings and Precautions*]*(5.0*/l). This turd does not support the addition of sirolimus to a locineurin-inhibitor-based serum triglycerides and cholesterol), and urinary tract infections [*see Warnings and Precautions*]*(5.0*/l). This turd does not support the addition of sirolimus to calcineurin inhibitors of sirolimus to real transplant patients. calcineurin-inhibitor-based imi nosuppressive therapy in this subpopulation of pediatric renal to

14.7 Lymphangioleiomyomatosis 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 (does-adjusted to maintain hold trught 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 15 second (FEVI). During the treatment period, FEVI stop was: 12 ± 2 mL per month in the placebo group and 1 ± 2 mL per month in the sirolimus group (treatment difference = 13 mL (85% CL: 7, 18). The absolute between sergoup difference in the mean change in FEVI 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 decline in lung function resumed in the sirolimus group and paralleled that in the decline in lung function resumed in the sirolimus group and paralleled that in the decline in lung function resumed in the sirolimus group and paralleled that in the decline in lung function resumed in the sirolimus group and paralleled that in the decline in lung function resumed in the sirolimus group and paralleled that in the flacebo area. placebo group (see Figure 1).





43 41 38 41 40 42 39 34 Placebo 43

15 REFERENCES Clinical Therapeutics, Volume 22, Supplement B, April 2000 [see Dosage and Administration (2.5/].

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 gp/mL/imonth) compared to placebo (-2.42 ± 17.2 pg/mL/imonth) with a treatment difference of -85 pg/mL/imonth (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 renolment.

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 veys, 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.

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

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).

to the egg interfore using rotary of interorters). A syringe (more color) and egg 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

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

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 decompart.

**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]].

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)].

male and female patients that sirolimus may impair fertility [see Warnings and Precautions (5.16), Adverse Reactions (6.7), Use in Specific

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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.

perature and shake gently until the haze disappears. The presence of this haze does not affect the quality of the p

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

Patients should be given complete dosage instructions [see FDA-Anoroved Medication Guide]

17.1 Dosage

17.4 Infertility

CAMBER

By: Annora Pharma Pvt 1td

, Sangareddy - 502313, Telangana, Indi

Manufactured for: Camber Pharmaceuticals Piscataway, NJ 08854

Revised: 05/2024

Populations (8.1, 8.3), Nonclinical Toxicology (13.1).

uticals In

# **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.

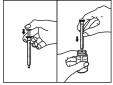
# Figure 2: Inserting adapter



# 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).

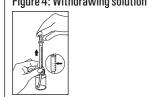
# Figure 3: Inserting syringe



# 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



If your doctor tells you to carry your medicine with you:

14% after the piects, the n 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 transplar patients, are dose-proportional between 3 and 12 mg/m<sup>2</sup>

healthy subjects and renal transplant patients, respectively. The systemic availability of sirolimus is low, and was estimated to be appro-

Whole blood trough sirolimus concentrations, as measured by LC/MS/MS in renal transplant patients, were significantly correlated with AUC, ... Upon repeated, twice-daily administration without an initial loading dose in a multiple-dose study, the average trough concentration of sirolimu

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

Following administration of sirolimus oral solution, the mean times to peak concentration (t<sub>mu</sub>) of sirolimus are approximately 1 hour and 2 hours in

maintenance dose will provide near steady-state concentrations within 1 day in most patients [see Dosage and Administration (2.3, 2.5), Warning

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 2: to 35%, compared with fasting. The effect of food on the mean sirolimus C\_ma was inconsistent depending on the sirolimus dosage form evaluated.

The mean (± SD) blood-to-plasma ratio of sirolimus was 36 ± 18 in stable renal allograft patients, indicating that sirolimus is extensively partiti 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%),  $\alpha_{i}$  -acid glycoprotein, and lipoprotein

Sirolimus is a substrate for both CYP3A4 and P.gp. Sirolimus is extensively metabolized in the intestinal wall and liver and undergoes countertransport 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 (77). 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.

After a single dose of [<sup>14</sup>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<sub>u</sub>) 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

			Year 1		Year 3
Patient Population (Study number)	Treatment	Mean (ng/mL)	$10^{\rm th}$ to $90^{\rm th}$ percentiles (ng/mL)	Mean (ng/mL)	$10^{\rm th}$ to $90^{\rm th}$ percentiles ng/mL)
Low-to-moderate risk	Sirolimus (2 mg/day) + CsA	7.2	3.6 to 11	-	-
(Studies 1 & 2)	Sirolimus (5 mg/day) + CsA	14	8 to 22	-	-
Low-to-moderate	Sirolimus + CsA	8.6	5 to 13°	9.1	5.4 to 14
risk (Study 3)	Sirolimus alone	19	14 to 22°	16	11 to 22
	Sirolimus + CsA	15.7	5.4 to 27.3°	-	-
High risk (Study 4)		11.8	6.2 to 16.9°		
(otady i)		11.5	6.3 to 17.3 <sup>d</sup>		

d: Week 26 to Week 52; observed CsA  $\overline{C_{\rm min}}$  was 136 (54. to 218) ng/mL The withdrawal of cyclosporine and concurrent increases in sirolimus trough concentrations to steady-state required approximately 6 week Following cyclosporine withdrawal, larger sirolimus doses were required due to the absence of the inhibition of sirolimus metabolism and transpo by cyclosporine and to achieve higher target sirolimus trough concentrations during concentration-controlled administration [see Dosage and

# Administration (2.1), Drug Interactions (7.1)].

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<sub>max</sub>. As the severity of hepatic impairment increased, there were steady increases in mean sirolimus t<sub>1,24</sub> 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<sup>2</sup>). 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<sup>2</sup>). At the time of sirolimus blood sampling for pharmacokinetic evaluation, the majority (80%) of these pediatric patients d the sirolimus dose at 16 hours after the once-daily cyclosporine dose. See Table 6 below.

TABLE 6: SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN $\pm$ SD) IN PEDIATRIC RENAL TRANSPLANT PATIENTS	
(MULTIPLE-DOSE CONCENTRATION CONTROL) <sup>28</sup>	

Age	n	Body weight	C <sub>max,ss</sub>	t <sub>max,ss</sub>	C <sub>min.ss</sub>	AUC <sub>⊺,ss</sub>	CL/F <sup>c</sup>	CL/F <sup>c</sup>	T
(y)		(kg)	(ng/mL)	(h)	(ng/mL)	(ng∙h/mL)	(mL/h/kg)	(L/h/m <sup>2</sup> )	P
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<sup>®</sup> Soft Gelatin Capsules).

herna voir ceraun capanes). b: A s 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<sup>2</sup>).

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

#### TABLE 7: SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN $\pm$ SD) IN PEDIATRIC PATIENTS WITH END-STAGE KIDNEY SEASE MAINTAINED ON HEMODIALYSIS OR PERITONEAL DIALYSIS (1 3 9 15 mg/m<sup>2</sup> SINGLE DOS

Age Group (y)	n	t <sub>max</sub> (h)	t <sub>1/2</sub> (h)	CL/F/WT(mL/h/kg
5 to 11	9	1.1 ± 0.5	71 ± 40	$580 \pm 450$
12 to 18	11	0.79 ± 0.17	55 ± 18	450 ± 232

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<sub>10</sub> than did female subjects (72.3 hours versus 61.3 hours). Dose adjustments based on gender are not recomm 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<sup>®</sup> Oral Solution) and/or cyclosporine capsules [MODIFIED] (e.g., Neoral<sup>®</sup> 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 transplantat

# Drug-Drug Interactions

Jimus 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 or adjustice of the second sec

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\_a, 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<sub>max</sub> 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 gral solution either simultaneously or 4 hours

			.,	
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

b: Includes patients who prematurely discontinued treatment

a: Patients received cyclosporine and corticosteroids.

The reduction in the incidence of first biopsy-confirmed acute rejection episodes in patients treated with sirolimus compared with the control groups ncluded 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<sup>ab</sup>

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)
	porine and corticosteroids.	ment		
b: Includes patients who pr Mean glomerular filtration 36 months for Study 2. M cyclosporine and the respe	rates (GFR) post-transplant v lean GFR was lower in patie ective azathioprine or placebo	vere calculated by using the Nai nts treated with cyclosporine a control.	nd sirolimus oral solution con	npared with those treated
b: Includes patients who pr Mean glomerular filtration 36 months for Study 2. M cyclosporine and the respe	rematurely discontinued treat rates (GFR) post-transplant v lean GFR was lower in patie cctive azathioprine or placebo DVERALL CALCULATED GL	vere calculated by using the Na nts treated with cyclosporine a control. OMERULAR FILTRATION RA	nd sirolimus oral solution con TES (Mean ± SEM, cc/min)	npared with those treated
b: Includes patients who pr Mean glomerular filtration 36 months for Study 2. M cyclosporine and the respe	rematurely discontinued treat rates (GFR) post-transplant v lean GFR was lower in patie cctive azathioprine or placebo DVERALL CALCULATED GL	vere calculated by using the Nai nts treated with cyclosporine a control.	nd sirolimus oral solution con TES (Mean ± SEM, cc/min)	npared with those treated
b: Includes patients who pr Mean glomerular filtration 36 months for Study 2. M cyclosporine and the respe	rematurely discontinued treat rates (GFR) post-transplant v lean GFR was lower in patie cctive azathioprine or placebo DVERALL CALCULATED GL	vere calculated by using the Na nts treated with cyclosporine a control. OMERULAR FILTRATION RA	nd sirolimus oral solution con TES (Mean ± SEM, cc/min)	npared with those treated

	Study I				
	Month 12	57.4 ± 1.3 (n = 269)	54.6 ± 1.3 (n = 248)	64.1 ± 1.6 (n = 149)	
g	Month 24	58.4 ± 1.5 (n = 221)	52.6 ± 1.5 (n = 222)	62.4 ± 1.9 (n = 132)	
	Study 2				
	Month 12	52.4 ± 1.5 (n = 211)	51.5 ± 1.5 (n = 199)		58.0 ± 2.1 (n = 117)
	Month 36	48.1 ± 1.8 (n = 183)	46.1 ± 2.0 (n = 177)		53.4 ± 2.7 (n = 102)
	a: Includes nationts u	he promoturally discontinued treat	mont		

b: Patients who had a graft loss were included in the analysis with GFR set to 0.0.

Within each treatment group in Studies 1 and 2, mean GFR at one-year post-transplant was lower in patients who experienced at least one episode of biopsy-proven acute rejection, compared with those who did not.

Renal function should be monitored, and appropriate adjustment of the immunosuppressive regimen should be considered in patients with elevated or ncreasing serum creatinine levels [see Warnings and Precautions (5.8/].

#### Sirolimus Tablets

The safety and efficacy of sirolimus oral solution and sirolimus tablets for the prevention of organ rejection following renal transplantation were ated to be clinically equivalent in a randomized, multicenter, controlled trial [see Clinical Pharmacology (12.3)

# 14.2 Cyclosporine Withdrawal Study in Renal Transplant Patients

The safety and efficacy of sirolimus as a maintenance regimen were assessed following cyclosporine withdrawal at 3 to 4 months after renal transplantation. Study 3 was a randomized, multicenter, controlled trial conducted at 57 centers in Australia, Canada, and Europe. Five hundred twenty-five (525) patients were enrolled. All patients in this study received the tablet formulation. This study compared patients who were administered sirolimus, cyclosporine, and corticosteroids continuously with patients who received this same standardized therapy for the first 3 nths after transplantation (pre-randomization period) followed by the withdrawal of cyclosporine. During cyclosporine withdrawal, the sirolimus dosages were adjusted to achieve targeted sirolimus whole blood trough concentration ranges (16 to 24 ng/mL until month 12, then 12 to 20 ng/mL thereafter, expressed as chromatographic assay values). At 3 months, 430 patients were equally randomized to either continue sirolimus with cyclosporine therapy or to receive sirolimus as a maintenance regimen following cyclosporine withdrawal.

Eligibility for randomization included no Banff Grade 3 acute rejection or vascular rejection episode in the 4 weeks before random assignment, serum creatinine ≤ 4.5 mg/dL, and adequate renal function to support cyclosporine withdrawal (in the opinion of the investigator). The primary efficacy endpoint was graft survival at 12 months after transplantation. Secondary efficacy endpoints were the rate of biopsy-confirmed acute rejection, patient survival, incidence of efficacy failure (defined as the first occurrence of either biopsy-proven acute rejection, graft loss, or death), and treatment failure (defined as the first occurrence of either discontinuation, acute rejection, graft loss, or death).

The following table summarizes the resulting graft and patient survival at 12, 24, and 36 months for this trial. At 12, 24, and 36 months, graft and patient survival were similar for both groups

	TABLE 13: GRAFT AND PATIENT SURVIVAL (%): ST	UDY 3°
Parameter	Sirolimus with Cyclosporine Therapy (n = 215)	Sirolimus Following Cyclosporine Withdrawal (n = 215)
Graft Survival		
Month 12 <sup>b</sup>	95.3 <sup>°</sup>	97.2
Month 24	91.6	94.0
Month 36 <sup>d</sup>	87.0	91.6
Patient Survival		
Month 12	97.2	98.1
Month 24	94.4	95.8
Month 36 <sup>d</sup>	91.6	94.0

a: Includes patients who prematurely discontinued treatment. b: Primary efficacy endpoint.

c: Survival including loss to follow-up as an event d: Initial planned duration of the study.

The following table summarizes the results of first biopsy-proven acute rejection at 12 and 36 months. There was a significant difference in first biopsy-proven rejection rates between the two groups after randomization and through 12 months. Most of the post-randomization acute rejections occurred in the first 3 months following randomization

TABLE 14: INCIDENCE OF FIRST BIOPSY-PROVEN ACUTE REJECTION (%) BY TREATMENT GROUP AT 36 MONTHS: STUDY 3<sup>13</sup>

	Sirolimus	Sirolimus	
Period	with Cyclosporine Therapy (n = 215)	Following Cyclosporine Withdrawal (n = 215)	
Pre-randomization <sup>6</sup>	9.3	10.2	
Post-randomization through 12 months <sup>c</sup>	4.2	9.8	
Post-randomization from 12 to 36 months	1.4	0.5	
Post-randomization through 36 months	5.6	10.2	
Total at 36 months	14.9	20.5	

a: Includes patients who prematurely discontinued trea b: All patients received corticosteroids.

c: Randomization occurred at 3 months ± 2 weeks.

- 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 davs.
- 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: Camber Pharmaceuticals, Inc. Piscataway, NJ 08854

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

Revised: 05/2024

after a 300 mg dose of Neoral Soft Gelatin Capsules (cyclosporine cap FIED]). For simultaneous administration, the mean C<sub>max</sub> and AUC of sirolimus, following simultaneous administration were increased by 116% and 230%, respectively, relative to administration of sirolimus alone. anomics, nonvering annunaneous administration were increased by 110% and 230%, respectively, rearries to administration or anomica addie. However, when given A hours after Neoral Soft Gelatic Capsules (pcolosprine capsules (MODIFIED)) administration, sirolimus Cae, 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 Capsule: (cyclosporine capsules [MODIFIED]) administration, sirolimus C\_\_ and AUC were comparable to those with administration of sirolimus administration administration of sirolimus administration of sirolimus administration administrati of sirolimus alone.

Mean cyclosporine C\_, and AUC were not significantly affected when sirolimus oral solution was given simultaneously or when administered 4 hours The mean of puop many and not were not significantly a nected when submits on a solution was given and not significant of solution solution as given a solution of solution of solutions given 4 hours after Neoral<sup>®</sup> in renal post-transplant patients over 6 months, cyclosporine oral-dose clearance was reduced, and lower doses of Neoral<sup>®</sup> 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/m²/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

porine 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-op: 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<sub>mut</sub>, t<sub>mut</sub> 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 d cetyldiltiazem 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<sub>m</sub> and AUC were increased 4.4. and 4.2. fold respectively and t<sub>m</sub> was increased by 0.4 hr. Erythromycin C<sub>m</sub> and AUC were increased 1.6- and 1.7-fold, respectively, and t<sub>m</sub> 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  $C_{uur}$ ,  $t_{uur}$ , and AUC of 4.3-fold, 38%, and 10.9-fold, respectively. However, the terminal  $t_u$  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\_, 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: Isee Drug Interactions (7.4). The simultaneous oral administration of 2 mg daily of sirolimus oral solution and 180 mg o 12h of verapamil at steady state to 25 health volunteers significantly affected the bioavailability of sindinus and verapamil. Sirolimus C<sub>m</sub> and AUC were increased 2.3 and 2.2-fold, respectively, without substantial change in t<sub>m</sub>. The C<sub>m</sub> and AUC of the pharmacologically active S(-) enantiomer of verapamil

ere both increased 1.5-fold and  $t_{\scriptscriptstyle max}$  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-

ninistered without dose adjustments Acyclovir

- Atorvastatir
  Digoxin
- GlyburideNifedipine
- Norgestrel/ethinyl estradiol (Lo/Ovral®)
- Prednisolone
- Sulfamethoxazole/trimethoprim (Bactrim<sup>®</sup>) Other Drug-Drug Interactions

Co-administration of similinus 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 or 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
   TABLE 17: RENAL FUNCTION IN STABLE RENAL TRANSPLANT PATIENTS IN PATIENTS WITH BASELINE GFR > 40 mL/min THE 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 Interaction
- Grapefruit juice reduces CYP3A4-mediated drug metabolism. Grapefruit juice must not be taken with or used for dilution of sirolimus [see Dosage an 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 notential 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 daity clinical dose (adjusted for body surface area), there was a statistically significant increase in malignant lymphoma at all dose levels com with controls. In a second mouse study at dosages that were approximately 3 to 16 times the clinical dose (adjusted for body surface a hepatocellular adenoma and carcinoma in males were considered sirolimus-related. In the 104-week rat study at dosages equal to or lower than . 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

chical does of 2 mg, on a body surface area basis). Atrophy of testes, epididymides, prostate, seminiferous tubules, and reduced sper observed. The NOAEL for male rat fertility was 0.5 mg/kg (2.5-fold the clinical does 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 or adjustication (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

TABLE 15: CALCULATED GLOMERULAR FILTRATION RATES (mL/min) BY NANKIVELL EQUATION AT 12, 24, AND 36 MONTHS POST-TRANSPLANT: STUDY 3"""

porine withdrawal group, compared with patients who continued cyclosporine (15.3% versus 3.0%). Patients receiving renal allografts with

Patients receiving renal allografts with  $\geq$  4 HLA mismatches experienced significantly higher rates of acute rejection following randomization to the

≤3 HLA mismatches demonstrated similar rates of acute rejection between treatment groups (6.8% versus 7.7%) following randomization

	Sirolimus with	Sirolimus Following
Parameter	Cyclosporine Therapy	Cyclosporine Withdrawal
Month 12		
Mean ± SEM	53.2 ± 1.5 (n = 208)	59.3 ± 1.5 (n = 203)
Month 24		
Mean ± SEM	48.4 ± 1.7 (n = 203)	58.4 ± 1.6 (n = 201)
Month 36		
Mean ± SEM	47.0 ± 1.8 (n = 196)	58.5 ± 1.9 (n = 199)

c: All patients received co

The mean GFR at 12, 24, and 36 months, calculated by the Nankivell equation, was significantly higher for patients receiving sirolimus as a

The following table summarizes the mean calculated GFR in Study 3 (cyclosporine withdrawal study)

maintenance regimen following cyclosporine withdrawal than for those in the sirolimus with cyclosporine therapy group. Patients who had an acute ejection prior to randomization had a significantly higher GFR following cyclosporine withdrawal compared to those in the siofimus with cyclosporine group. There was no significant difference in GFR between groups for patients who experienced acute rejection post-randomization. Although the initial protocol was designed for 36 months, there was a subsequent amendment to extend this study. The results for the cyclosporing withdrawal group at months 48 and 60 were consistent with the results at month 36. Fifty-two percent (112/215) of the patients in the sirolimus e withdrawal group remained on therapy to month 60 and showed sustained GFR

#### 14.3 High-Immunologic Risk Renal Transplant Patients

Sirolimus was studied in a one-year, clinical trial in high risk patients (Study 4) who were defined as Black transplant recipients and/or repeat renal transplant recipients who loss previous allograft for immunologic reasons and/or patients with high panel-recipients and uses [PRA; peak PRA level > 80%]. Patients received concentration-controlled sirolimus and cyclosporine (MODIFIED), and corticosteroids per local practice. The sirolimus dose was adjusted to achieve target whole blood trough sirolimus concentrations of 10 to 15 ng/mL (chromatographic method) throughout the 12month study period. The cyclosporine dose was adjusted to achieve target whole blood trough concentrations of 200 to 300 ng/mL through week 2, 150 to 200 ng/mL from week 2 to week 26, and 100 to 150 ng/mL from week 26 to week 52 [see *Clinical Pharmacology (12.3)*] for the observed to too name the second PRA. Efficacy was assessed with the following endpoints, measured at 12 months: efficacy failure (defined as the first occurrence of biopsy-confirmed acute rejection, graft loss, or death), first occurrence of graft loss or death, and renal function as measured by the calculated GFR using the Nankivell formula. The table below summarizes the result of these endpoints.

#### TABLE 16: EFFICACY FAILURE, GRAFT LOSS OR DEATH AND CALCULATED GLOMERULAR FUNCTION RATES (mL/min) BY

Parameter	Sirolimus with Cyclosporine, Corticosteroids (n = 224)	
Efficacy Failure (%)	23.2	
Graft Loss or Death (%)	9.8	
Renal Function (mean ± SEM) <sup>1,6</sup>	$52.6 \pm 1.6 (n = 222)$	

a: Calculated glomerular filtration rate by Nankivell equation. b: Patients who had graft loss were included in this analysis with GFR set to 0.

Patient survival at 12 months was 94.6%. The incidence of bionsy-confirmed acute rejection was 17.4% and the majority of the episodes of acute

14.4 Conversion from Calcineurin Inhibitors to Sirolimus in Maintenance Renal Transplant Patients

Conversion from calcineurin inhibitors (CNI) to sirolimus was assessed in maintenance renal transplant patients 6 months to 10 years post-transplant (Study 5). This study was a randomized, multicenter, controlled trial conducted at 111 centers globally, including US and Europe, and was intended to show that renal function was improved by conversion from CNI to sirolimus. Eight hundred thirty (830) patients were enrolled and stratified by baseline calculated glomerular filtration rate (GFR, 20 to 40 mL/min versus greater than 40 mL/min). In this trial there was no benefit associated with conversion with regard to improvement in renal function and a greater incidence of proteinuria in the sirolimus conversion arm. In addition, enrollment of patients with baseline calculated GFR less than 40 mL/min was discontinued due to a higher rate of serious adverse events,

including pneumonia, acute rejection, graft loss and death [see Adverse Reactions (6.4)]. This study compared renal transplant patients (6 to 120 months after transplantation) who were converted from calcineurin inhibitors to sirolimus, with patients who continued to receive calcineurin inhibitors. Concomitant immunosuppressive medications included mycophenolate mofetil (MMF) archippenie AZA), and corticosteroids. Sirolimus was initiated with a single loading dose of 12 to 20 mg, after which dosing was adjusted to achieve a target sirolimus whole blood trough concentration of 8 to 20 ng/mL (chromatographic method). The efficacy endpoint was calculated GFR at 12 months post-randomization. Additional endpoints included biopsy-confirmed acute rejection, graft loss, and death. Findings in the patient stratum with baseline calculated GFR greater than 40 mL/min (sirolimus conversion, n = 497; CNI continuation, n = 246) are summarized below. There was no clinically or statistically significant improvement in Nankivell GFR compared to baselin

	Parameter	meter Sirolimus conversion N = 496		Difference (95% CI)	
	GFR mL/min (Nankivell) at 1 year	59.0	57.7	1.3 (-1.1, 3.7)	
and	GFR mL/min (Nankivell) at 2 year	53.7	52.1	1.6 (-1.4, 4.6)	

during the first 6 months after sirolimus conversion. The rates of pneumonia were significantly higher for the sirolimus conversion group.

s at baseline, significantly higher mean as shown in the table below [se inhibitors, a higher percentage o was seen in both patients who had a atients in the sirolimus conve 2 [9.5%] versus 9/239 [3.8%]), even uria was significantly higher in the tein to creatinine ratio >1 (13/29 versus 1/14), excluding patients with baseline nephrotic range proteinuria.

TABLE 18: MEAN AND MEDIAN VALUES FOR URINARY PROTEIN TO CREATININE RATIO (mg/mg) BETWEEN TREATMENT GROUPS AT BASELINE, 1 AND 2 YEARS IN THE STRATUM WITH BASELINE CALCULATED GFR > 40 mL/min

Study period	udy period Sirolimus Conversion		CNI C	ontinuation			
	N	Mean $\pm$ SD	Median	N	Mean ± SD	Median	p-value
Baseline	410	0.35 ± 0.76	0.13	207	0.28 ± 0.61	0.11	0.381
1 year	423	0.88 ± 1.61	0.31	203	0.37 ± 0.88	0.14	< 0.001
2 years	373	0.86 ± 1.48	0.32	190	0.47 ± 0.98	0.13	< 0.001

The above information should be taken into account when considering conversion from calcineurin inhibitors to sirolimus in stable renal transplant patients due to the lack of evidence showing that renal function improves following conversion, and the finding of a greater increment in urinary rotein excretion, and an increased incidence of treatment-emergent nephrotic range proteinuria following conversion to sirolimus. This was particularly true among patients with existing abnormal urinary protein excretion prior to conversion.

n an open-label, randomized, comparative, multicenter study where kidney transplant patients were either converted from tacrolimus to sirolimus 3 to 5 months post-transplant (sirolimus group) or remained on tacrolimus, there was no significant difference in renal function at 2 years post transplant. Overall, 44/131 (33.6%) discontinued treatment in the sirolimus group versus 12/123 (9.8%) in the tacrolimus group. More patient reported adverse events 130/131 (99.2%) versus 112/123 (91.1%) and more patients reported discontinuations from the treatment due to adverse

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	and median levels of urinary protein excretion were seen in the sirolimus conversion arm at 1 year and at 2 years,
	Warnings and Precautions (5.9)]. In addition, when compared to patients who continued to receive calcineurin in
	patients had urinary protein to creatinine ratios > 1 at 1 and 2 years after sirolimus conversion. This difference wa
e 2 mg	urinary protein to creatinine ratio $\leq$ 1 and those who had a protein to creatinine ratio $>$ 1 at baseline. More pa
npared	group developed nephrotic range proteinuria, as defined by a urinary protein to creatinine ratio > 3.5 (46/482 [9
area),	when the patients with baseline nephrotic range proteinuria were excluded. The rate of nephrotic range proteinur
ian the	sirolimus conversion group compared to the calcineurin inhibitor continuation group with baseline urinary protei

# The rates of acute rejection, graft loss, and death were similar at 1 and 2 years. Treatment-emergent adverse events occurred more frequently