Package leaflet: Information for the user

Sirolimus 0.5 mg coated tablets
Sirolimus 1 mg coated tablets
Sirolimus 2 mg coated tablets
sirolimus

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Sirolimus is and what it is used for

Sirolimus coated tablets contain the active substance sirolimus, which belongs to a group of medicines called immunosuppressants. It helps to control your body's immune system after you have received a kidney transplant.

Sirolimus is used in adults to prevent your body from rejecting transplanted kidneys and is normally used with other immunosuppressant medicines called corticosteroids and initially (the first 2 to 3 months) with ciclosporin.

Sirolimus is also used for the treatment of patients with sporadic lymphangioleiomyomatosis (S-LAM) with moderate lung disease or declining lung function. S-LAM is a rare progressive lung disease that affects predominantly women of childbearing age. The most common symptom of S-LAM is shortness of breath.

2. What you need to know before you take Sirolimus

Do not take Sirolimus:

- if you are allergic to sirolimus or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist before taking Sirolimus

- If you have any liver problems or have had a disease which may have affected your liver, please tell your doctor as this may affect the dose of sirolimus that you receive and may result in your having additional blood tests.

- Sirolimus, like other immunosuppressive medicines, may decrease your body's ability to fight infection, and may increase the risk of developing cancer of the lymphoid tissues and skin.
- If you have a body mass index (BMI) greater than 30 kg/m^2, you may be at increased risk of abnormal wound healing.
- If you are considered to be at high risk for kidney rejection, such as if you had a previous transplant that was lost to rejection.

Your doctor will perform tests to monitor the levels of sirolimus in your blood. Your doctor will also perform tests to monitor your kidney function, your blood fat (cholesterol and/or triglycerides) levels and possibly your liver function, during treatment with Sirolimus.

Exposure to sunlight and UV light should be limited by covering your skin with clothing and using a sunscreen with a high protection factor because of the increased risk for skin cancer.

Children and adolescents

There is limited experience on the use of sirolimus in children and adolescents less than 18 years of age. The use of Sirolimus is not recommended in this population.

Other medicines and Sirolimus

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Some medicines can interfere with the action of sirolimus and, therefore, dose adjustments may be required. In particular, you should inform your doctor or pharmacist if you are taking any of the following:

- any other immunosuppressant medicines.
- antibiotics or antifungal medicines used to treat infection e.g. clarithromycin, erythromycin, telithromycin, troleandomycin, rifabutin, clotrimazole, fluconazole, itraconazole. It is not recommended that Sirolimus be taken with rifampicin, ketoconazole or voriconazole.
- any high blood pressure medicines or medicines for heart problems including nicardipine, verapamil and diltiazem.
- anti-epileptic medicines including carbamazepine, phenobarbital, phenytoin.
- medicines used to treat ulcers or other gastrointestinal disorders such as cisapride, cimetidine, metoclopramide.
- bromocriptine (used in the treatment of Parkinson's disease and various hormonal disorders), danazol (used in the treatment of gynaecological disorders), or protease inhibitors (e.g., for HIV and hepatitis C such as ritonavir, indinavir, boceprevir, and telaprevir).
- St. John's Wort (*Hypericum perforatum*).
- letermovir (an antiviral medicine to prevent getting ill from cytomegalovirus).
- cannabidiol (uses amongst others include treatment of seizures).

The use of live vaccines should be avoided with the use of Sirolimus. Before vaccinations, please inform your doctor or pharmacist that you are receiving Sirolimus.

The use of Sirolimus may lead to increased levels of cholesterol and triglycerides (blood fats) in your blood that may require treatment. Medicines known as "statins" and "fibrates" used to treat elevated cholesterol and triglycerides have been associated with an increased risk of muscle breakdown (rhabdomyolysis). Please inform your doctor if you are taking medicines to lower your blood fats.

The combined use of Sirolimus with angiotensin-converting enzyme (ACE) inhibitors (a type of medicine used to lower blood pressure) may result in allergic reactions. Please inform your doctor if you are taking any of these medicines.

Sirolimus with food and drink

Sirolimus should be taken consistently, either with or without food. If you prefer to take Sirolimus with food, then you should always take it with food. If you prefer to take Sirolimus without food, then you should always take it without food. Food can affect the amount of medicine that gets into your bloodstream, and taking your medicine in a consistent way means that the blood levels of Sirolimus remain more stable.

Sirolimus should not be taken with grapefruit juice.

Pregnancy, breast-feeding and fertility

Sirolimus should not be used during pregnancy unless clearly necessary. You must use an effective method of contraception during treatment with Sirolimus and for 12 weeks after treatment has stopped. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

It is not known whether sirolimus passes into breast milk. Patients taking Sirolimus should discontinue breast-feeding.

Decreased sperm count has been associated with the use of Sirolimus and usually returns to normal once treatment is stopped.

Driving and using machines

Although Sirolimus treatment is not expected to affect your ability to drive, if you have any concerns please consult your doctor.

Sirolimus contains lactose and sucrose

Sirolimus contains 86.4 mg of lactose and up to 215.8 mg of sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Sirolimus

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will decide exactly what dose of sirolimus you must take and how often to take it. Follow your doctor's instructions exactly, and never change the dose yourself.

Sirolimus is for oral use only. Do not crush, chew, or split the tablets. Inform your doctor if you have difficulty taking the tablet.

Multiples of 0.5 mg tablets should not be used as a substitute for 1 mg and 2 mg tablets, as the different strengths are not directly interchangeable.

Sirolimus should be taken consistently, either with or without food.

<u>Kidney Transplant</u>
Your doctor will give you an initial dose of 6 mg as soon as possible after the kidney transplant operation. Then you will need to take 2 mg of Sirolimus each day, until otherwise directed by your doctor. Your dose will be adjusted depending on the level of sirolimus in your blood. Your doctor will need to perform blood tests to measure sirolimus concentrations.

If you are also taking ciclosporin, then you must take the two medicines approximately 4 hours apart.

It is recommended that Sirolimus be used first in combination with ciclosporin and corticosteroids. After 3 months, your doctor may discontinue either Sirolimus or ciclosporin, as it is not recommended that these medicines be taken together beyond this period.

Sporadic Lymphangioleiomyomatosis (S-LAM)
Your doctor will give you 2 mg of Sirolimus each day, until otherwise directed by your doctor. Your dose will be adjusted depending on the level of Sirolimus in your blood. Your doctor will need to perform blood tests to measure sirolimus concentrations.

If you take more Sirolimus than you should

If you have taken more medicine than you were told to, contact a doctor or go to the nearest hospital emergency department as soon as possible. Always take the labelled blister with you, even if it is empty.

If you forget to take Sirolimus

If you forget to take Sirolimus, take it as soon as you remember, but not within 4 hours of the next dose of ciclosporin. After that, continue to take your medicines as usual. Do not take a double dose to make up for a forgotten dose, and always take Sirolimus and ciclosporin approximately 4 hours apart. If you miss a dose of Sirolimus completely, you should inform your doctor.

If you stop taking Sirolimus

Do not stop taking Sirolimus unless your doctor tells you to, as you risk losing your transplant.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions

You should **see your doctor immediately** if you experience symptoms, such as swollen face, tongue and/or back of the mouth (pharynx) and/or difficulties in breathing (angioedema), or a skin condition whereby the skin can peel off (exfoliative dermatitis). These may be symptoms of a serious allergic reaction.

Kidney damage with low blood cell counts (thrombocytopaenic purpura/haemolytic uraemic syndrome)

When taken with medicines called calcineurin inhibitors (ciclosporin or tacrolimus), Sirolimus may increase the risk of kidney damage with low blood platelets and low red blood cell counts, with or without rash (thrombocytopaenic purpura/haemolytic uraemic syndrome). If you experience symptoms such as bruising or rash, changes in your urine, or changes in behaviour or any others that are serious, unusual or prolonged, contact your doctor.

Infections

Sirolimus reduces your body's own defence mechanisms. Consequently your body will not be as good as normal at fighting infections. So if you are taking Sirolimus, you may therefore catch more infections than usual, such as infections of the skin, mouth, stomach and intestines, lungs and urinary tract (see list below). You should contact your doctor if you experience symptoms that are serious, unusual, or prolonged.

Side effect frequencies

Very common: may affect more than 1 in 10 people

- Fluid collection around the kidney
- Swelling of the body including hands and feet
- Pain
- Fever
- Headache
- Increased blood pressure
- Stomach pain, diarrhoea, constipation, nausea
- Low red blood cells, low blood platelets
- Increased fat in the blood (cholesterol and/or triglycerides), increased blood sugar, low blood potassium, low blood phosphorus, increased lactate dehydrogenase in the blood, increased creatinine in the blood
- Joint pain
- Acne
- Urinary tract infection
- Pneumonia and other bacterial, viral, and fungal infections
- A reduced number of infection-fighting cells in the blood (white blood cells)
- Diabetes
- Abnormal tests of liver function, elevated AST and/or ALT liver enzymes
- Rash
- Elevated protein in the urine
- Menstrual disorders (including absent, infrequent or heavy periods)
- Slow healing (this may include separation of the layers of a surgical wound or stitch line)
- Rapid heart rate
- There is a general tendency for fluid to collect in various tissues

Common: may affect up to 1 in 10 people

- Infections (including life-threatening infections)
- Blood clots in the legs
- Blood clots in the lung
- Mouth sores
- Fluid collection in the abdomen
- Kidney damage with low blood platelets and low red blood cell counts, with or without rash (haemolytic uraemic syndrome)
- Low levels of a type of white blood cells called neutrophils
- Deterioration of bone
- Inflammation that may lead to lung damage, fluid around the lung
- Nose bleeds
- Skin cancer
- Kidney infection
- Ovarian cysts
- Fluid collection in the sac around the heart, that in some cases may decrease the heart's ability to pump blood
- Inflammation of the pancreas
- Allergic reactions
- Shingles
- Cytomegalovirus infection

Uncommon: may affect up to 1 in 100 people

- Cancer of the lymph tissue (lymphoma/post-transplant lympho-proliferative disorder), combined lowering of red blood cells, white blood cells and blood platelets
- Bleeding from the lung
- Protein in the urine, occasionally severe and associated with side effects, such as swelling
- Scarring in the kidney that may reduce kidney function
- Too much fluid collecting in the tissues due to irregular lymph function
- Low blood platelets, with or without rash (thrombocytopaenic purpura)
- Serious allergic reactions that can cause peeling of the skin
- Tuberculosis
- Epstein-Barr virus infection
- Infectious diarrhoea with *Clostridium difficile*
- Serious liver damage

Rare: may affect up to 1 in 1,000 people

- Protein build-up in the air sacs of the lungs that may interfere with breathing
- Serious allergic reactions that can affect blood vessels (see above paragraph on allergic reactions)

Not known: frequency cannot be estimated from the available data

- Posterior reversible encephalopathy syndrome (PRES), a serious nervous system syndrome that has the following symptoms: headache, nausea, vomiting, confusion, seizures, and visual loss. Should any of these occur together, please contact your physician.

S-LAM patients experienced similar side effects to those of kidney transplant patients, with the addition of weight loss, which may affect up to 1 in 10 people.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Sirolimus

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the blister and carton after "EXP". The expiry date refers to the last day of that month.

Do not store above 25˚C.
Keep the blister in the outer carton in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Sirolimus contains

The active substance is sirolimus.
Each Sirolimus 0.5 mg coated tablet contains 0.5 mg of sirolimus.

Each Sirolimus 1 mg coated tablet contains 1 mg of sirolimus.
Each Sirolimus 2 mg coated tablet contains 2 mg of sirolimus.

The other ingredients are:
Tablet core: lactose monohydrate, macrogol, magnesium stearate, talc
Tablet coating: macrogol, glycerol monooleate, pharmaceutical glaze, calcium sulfate, microcrystalline cellulose, sucrose, titanium dioxide, poloxamer 188, α-tocopherol, povidone, carnauba wax, Printing ink (Shellac, Iron Oxide Red, Propylene Glycol [E1520], Concentrated Ammonia Solution, Simethicone). The 0.5 mg and 2 mg tablets also contain yellow iron oxide (E172) and brown iron oxide (E172).

What Sirolimus looks like and contents of the pack

Sirolimus 0.5 mg is supplied to you as tan-coloured, triangular-shaped, coated tablets marked "RAPAMUNE 0.5 mg" on one side.

Sirolimus 1 mg is supplied to you as white-coloured, triangular-shaped, coated tablets marked "RAPAMUNE 1 mg" on one side.

Sirolimus 2 mg is supplied to you as yellow to beige-coloured, triangular-shaped, coated tablets marked "RAPAMUNE 2 mg" on one side.

The tablets are supplied in blister packs of 30 and 100 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
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