Package leaflet: Information for the user

Rapamune 1 mg/mL oral solution
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 Rapamune is and what it is used for

Rapamune contains 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.

Rapamune 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.

Rapamune 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 Rapamune

Do not take Rapamune:

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

Warnings and precautions

Talk to your doctor or pharmacist before taking Rapamune

- 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 Rapamune that you receive and may result in your having additional blood tests.
- Rapamune, 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 Rapamune 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 Rapamune.

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 Rapamune in children and adolescents less than 18 years of age. The use of Rapamune is not recommended in this population.

Other medicines and Rapamune

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 Rapamune and, therefore, dose adjustment of Rapamune 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 Rapamune 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 Rapamune. Before vaccinations, please inform your doctor or pharmacist that you are receiving Rapamune.

The use of Rapamune 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 Rapamune 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.

Rapamune with food and drink

Rapamune should be taken consistently, either with or without food. If you prefer to take Rapamune with food, then you should always take it with food. If you prefer to take Rapamune 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 Rapamune remain more stable.

Rapamune should not be taken with grapefruit juice.

Pregnancy, breast-feeding and fertility

Rapamune should not be used during pregnancy unless clearly necessary. You must use an effective method of contraception during treatment with Rapamune 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 Rapamune passes into breast milk. Patients taking Rapamune should discontinue breast-feeding.

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

Driving and using machines

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

Rapamune contains ethanol (alcohol)

Rapamune contains up to 3.17 vol % ethanol (alcohol). An initial dose of 6 mg contains up to 150 mg of alcohol which is equivalent to 3.80 mL beer or 1.58 mL wine. This amount of alcohol may be harmful for those suffering from alcoholism as well as for pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy. Alcohol may modify or increase the effect of other medicines.

Maintenance doses of 4 mg or less contain small amounts of ethanol (100 mg or less) that are likely to be too low to be harmful.

3. How to take Rapamune

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 Rapamune you must take and how often to take it. Follow your doctor's instructions exactly, and never change the dose yourself.

Rapamune is for oral use only. Inform your doctor if you have difficulty taking the oral solution.

Rapamune 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 Rapamune each day, until otherwise directed by your doctor. Your dose will be adjusted depending on the level of Rapamune in your blood. Your doctor will need to perform blood tests to measure Rapamune concentrations.

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

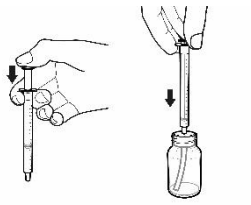
It is recommended that Rapamune be used first in combination with ciclosporin and corticosteroids. After 3 months, your doctor may discontinue either Rapamune or ciclosporin, as it is not recommended that these medicines be taken together beyond this period.

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

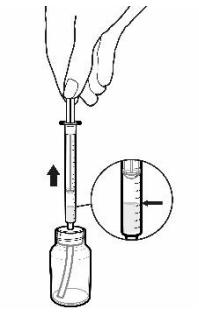
Instructions on how to dilute Rapamune

1. Remove the safety cap from the bottle by squeezing the tabs on the cap and twisting. Insert the syringe adapter into the bottle until it is flush with the top of the bottle. Do not attempt to remove the syringe adapter from the bottle once inserted.

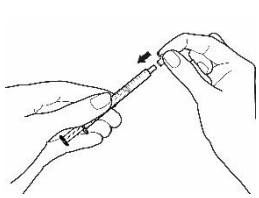
2. With the plunger fully depressed, insert one of the dosing syringes into the opening in the adapter.

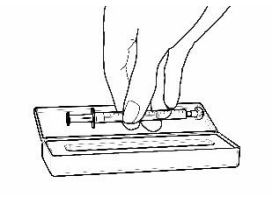


3. Withdraw the exact amount of Rapamune oral solution as prescribed by your doctor by gently pulling out the plunger of the dosing syringe until the level of the oral solution is even with the appropriate mark on the dosing syringe. The bottle should remain in an upright position when withdrawing the solution. If bubbles form in the oral solution in the dosing syringe during withdrawal, empty the Rapamune solution back into the bottle and repeat the withdrawal procedure. You may need to repeat step 3 more than once to deliver your dose.

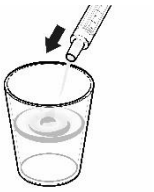


4. You may have been instructed to take your Rapamune oral solution at a particular time of day. If it is necessary to carry your medication with you, fill the dosing syringe to the appropriate mark and place a cap securely on it – the cap should snap into place. Then place the capped dosing syringe in the carrying case provided. Once in the syringe the medication may be kept at room temperature (not exceeding 25°C) or refrigerated and should be used within 24 hours.





5. Empty the contents of the dosing syringe into only a glass or plastic container holding at least 60 mL of water or orange juice. Stir well for one minute and drink immediately at once. Refill the glass with at least 120 mL of water or orange juice, stir well, and drink immediately. No other liquids, including grapefruit juice, should be used for dilution. The dosing syringe and cap are to be used once and then discarded.



When refrigerated the solution in the bottle may develop a slight haze. If this occurs, simply bring your Rapamune oral solution to room temperature and shake gently. The presence of this haze does not affect the quality of Rapamune.

If you take more Rapamune than you should

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

If you forget to take Rapamune

If you forget to take Rapamune, 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 Rapamune and ciclosporin approximately 4 hours apart. If you miss a dose of Rapamune completely, you should inform your doctor.

If you stop taking Rapamune

Do not stop taking Rapamune 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), Rapamune 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

Rapamune 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 Rapamune, 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 Rapamune

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 carton after “EXP”. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).

Keep Rapamune oral solution in its original bottle in order to protect from light.

Once the bottle has been opened, the contents should be kept refrigerated and used within 30 days. If necessary, you may store the bottle at room temperature up to 25°C for a short period of time, but no longer than 24 hours.

Once the dosing syringe has been filled with Rapamune oral solution, it should be kept at room temperature, but not above 25°C, for maximum 24 hours.

Once the contents of the dosing syringe have been diluted with water or orange juice, the preparation should be drunk immediately.

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 Rapamune contains

The active substance is sirolimus. Each mL of Rapamune oral solution contains 1 mg of sirolimus.

The other ingredients are:

Polysorbate 80 (E433) and phosal 50 PG (phosphatidylcholine, propylene glycol [E1520], mono-and diglycerides, ethanol, soya fatty acids, and ascorbyl palmitate).

This medicine contains approximately 350 mg propylene glycol (E1520) in each mL.

What Rapamune looks like and contents of the pack

Rapamune oral solution is a pale yellow to yellow solution supplied in a 60 mL bottle.

Each pack contains: one bottle (amber glass) containing 60 mL of Rapamune solution, one syringe adapter, 30 dosing syringes (amber plastic) and one syringe carry case.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
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Manufacturer:
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