Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed with a doctor's prescription only

Rapamune® 1 mg tablets

Coated tablets

Each tablet contains: sirolimus 1 mg

Inactive ingredients and allergens: See section 2 under 'Important information about some of this medicine's ingredients' and section 6 'Further information'.

Read the entire leaflet carefully before using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar to yours.

1. WHAT IS THIS MEDICINE INTENDED FOR?

Rapamune® is intended to suppress the immune system. This medicine is intended for prevention of transplant rejection in patients receiving a kidney transplant.

Therapeutic group: selective immunosuppressant.

2. BEFORE USING THIS MEDICINE

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredient or to any of the other ingredients in this medicine (see section 6).

Special warnings regarding use of the medicine

Before treatment with Rapamune®, tell your doctor if:

- you are pregnant – see the section 'Pregnancy, breastfeeding, and fertility'.
- you have impaired liver function or have had a disease which may have affected your liver. Your dose may need to change and you may need additional blood tests.
- you have problems with your immune system. Rapamune®, like other immunosuppressive medicines, may decrease your body's immune resistance, and may increase your risk of developing cancer of the lymphoid tissues and skin.
- you have a body mass index (BMI) greater than 30 (weight[kg]/height^2 [m^2]). You may be at increased risk of abnormal wound knitting and scabbing.
- you are at high risk for transplant rejection (such as if you had a previous transplant that was lost to rejection).

Rapamune® and exposure to light and sun

Exposure to sunlight and UV light can increase your risk of developing skin cancer; therefore, avoid exposure to the sun and be sure to have proper protection (long clothing, hat, high SPF sunscreen, etc.).

Children and adolescents
There is no information regarding the safety and effectiveness of using this medicine in children and adolescents less than 18 years old.

Tests and follow-up
During your course of treatment, you will be referred for blood tests to monitor the levels of this medicine in your blood, and for periodic tests to monitor your kidney function and your blood fat (cholesterol and/or triglycerides) levels. Your doctor may also order a test for liver function.

Drug interactions
If you are taking or have recently taken other medicines, including non-prescription medicines and dietary supplements, tell your doctor or pharmacist. Particularly if you are taking:
- other immunosuppressant medicines.
- medicines for reducing high blood pressure or medicines for heart problems such as nicardipine, verapamil and diltiazem.
- medicines used to treat ulcers or other digestive system problems such as cisapride, cimetidine, metoclopramide.
- antibiotics or antifungal medicines such as clotrimazole, fluconazole, itraconazole, clarithromycin, erythromycin, telithromycin, troleandomycin, rifabutin. It is not recommended that Rapamune® be taken with rifampicin, ketoconazole or voriconazole.
- anti-epileptic medicines such as carbamazepine, phenobarbital, phenytoin.
- danazol (used in the treatment of gynaecological disorders).
- bromocriptine (used in the treatment of Parkinson's disease and various hormonal disorders).
- protease inhibitors used to treat HIV and hepatitis C such as ritonavir, indinavir, boceprevir, and telaprevir.
- products containing St. John's Wort (*Hypericum perforatum*).
- letermovir (an antiviral medicine to prevent the disease caused by cytomegalovirus (CMV)).
- If you are planning to get vaccinated, tell your doctor or pharmacist that you are receiving Rapamune®. The use of live vaccines should be avoided during treatment with this medicine.
- medicines used to reduce cholesterol and triglycerides in your blood such as statins and fibrates: The use of Rapamune® may lead to increased levels of cholesterol and triglycerides (fats) in your blood. This increase may require treatment. Statin and fibrate medicines used to treat elevated levels of cholesterol and triglycerides, have been associated with an increased risk of muscle breakdown (rhabdomyolysis). Tell your doctor if you are taking such medicines.
- ACE inhibitors, a type of medicine for reducing blood pressure. The combined use of ACE inhibitors with Rapamune® may cause allergic reactions. Tell your doctor if you are taking such a medicine.

Using this medicine and food
If you take this medicine after food, then you should make sure to always take it after food. If you take this medicine without food, then you should make sure to always take it without food.
It is important to follow this direction because food can affect the level of medicine in your bloodstream, so taking your medicine in a consistent way (either with or without food) helps blood levels of this medicine remain more stable.

Do not take this medicine with grapefruit juice.

Pregnancy, breastfeeding, and fertility
Pregnancy
Do not use the medicine during pregnancy unless your doctor has decided the treatment is clearly necessary.
Women of childbearing age must use an effective method of contraception during treatment and for 12 weeks after treatment with Rapamune® tablets has stopped.
If you are pregnant or breastfeeding, think you are pregnant or are planning to become pregnant, consult your doctor before taking this medicine.
Breastfeeding
It is not known whether Rapamune® passes into breast milk. Women taking Rapamune® should discontinue breastfeeding.
Fertility
Decreased sperm count has been associated with the use of Rapamune® and usually returns to normal once treatment is stopped.

Driving and using machines
Rapamune® use is not expected to affect your ability to drive. if you are uncertain, consult your doctor.

Important information about some of this medicine's ingredients
Rapamune® tablets contains lactose (86.4 mg) and sucrose (215.8 mg). If you have an intolerance to some sugars, tell your doctor before taking this medicine.

3. HOW TO USE THIS MEDICINE?
Always use this medicine according to your doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the medicine.
The dosage and treatment regimen will be determined by your doctor only.
Your first dose will be given immediately after the transplant operation.
During your course of treatment, your doctor will order blood tests to measure Rapamune® concentrations in your blood, and will adjust your dose depending on the results.

Do not exceed the recommended dose.

Rapamune® tablets are for oral, daily use. Swallow the medicine with water. Consult your doctor if you have difficulty taking the tablet.
Take this medicine consistently, either with or without food. See additional information in the section 'Using this medicine and food'.
Do not chew, split, or crush the tablets because there is no information about the medicine's bioavailability (amount of medicine that gets into your bloodstream).
If you are taking ciclosporin in addition to Rapamune®, then you must take the two medicines approximately 4 hours apart.

If you have accidentally taken a higher dosage
If you have taken an overdose, or if a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

If you forget to take the medicine
If you forget to take this medicine at the scheduled time, take it as soon as you remember, but make sure to have at least 4 hours between taking Rapamune® and the next dose of ciclosporin. After that, continue to take your medicines as usual, taking your next dose at the usual time, and consult your doctor. Do not take a double dose to make up for a forgotten dose,
Remember to always take Rapamune® and ciclosporin 4 hours apart.
If you miss a dose of this medicine completely, you should inform your doctor.

Adhere to the treatment as recommended by your doctor.
Even if your health improves, do not stop taking this medicine without consulting your doctor.

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

Do not take medicines in the dark! Check the label and dose <u>each time</u> you take medicine. Wear glasses if you need them.

If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. SIDE EFFECTS
As with any medicine, use of Rapamune® may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

Allergic reactions
Contact your doctor immediately if you notice the following symptoms, which may be signs of a serious allergic reaction:
swollen face, tongue and/or back of the mouth (pharynx) and/or difficulties in breathing (angioedema), or a skin condition in which the skin can peel off (exfoliative dermatitis).

Kidney damage with low platelet count and low red blood cell counts with or without rash
Contact your doctor immediately if you experience symptoms such as bruising or rash, changes in your urine, or changes in behaviour, or any other effect that is serious/unusual/prolonged. This is because Rapamune® can increase the risk of kidney damage associated with low platelet and low red blood cell counts with or without rash (thrombocytopaenic purpura/haemolytic uraemic syndrome).

Tendency to get infections
Rapamune® suppresses your body's immune system to prevent transplant rejection. As a result, your immune resistance is reduced and you may therefore be more sensitive to infections such as skin, mouth, stomach and digestive system, lungs, and urinary tract infections. **Contact your doctor if** you experience serious, unusual, or prolonged symptoms.

Additional side effects

Very common side effects (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 LDH (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 results of liver function tests, elevated liver enzymes such as AST and/or ALT
- rash
- protein in the urine
- menstrual disorders (including absent, infrequent or heavy periods)
- slow healing of wounds (this may include separation of the layers of a surgical wound or stitch line)
- rapid heart rate
- a general tendency for fluid to collect in various tissues.

Common side effects (affect up to 1 in 10 people):
- infections (including life-threatening infections)
- blood clots in the legs
- blood clots in the lungs
- mouth sores
- fluid collection in the abdomen (ascites)
- kidney damage with low blood platelet and low red blood cell counts, with or without rash (haemolytic uraemic syndrome)
- low neutrophil count (of a type of white blood cells)
- deterioration of bone (osteonecrosis)
- inflammation that may lead to lung damage, fluid around the lungs
- 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 (CMV)

Uncommon side effects (affect up to 1 in 100 people):

- cancer of the lymph tissue (lymphoma/post-transplant lympho-proliferative disorder), combined low count of red blood cells, white blood cells, and platelets
- bleeding from the lung
- protein in the urine, occasionally severe and associated with side effects, such as swelling (nephrotic syndrome)
- 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 (EBV) infection
- infectious diarrhoea with *Clostridium difficile*
- serious liver damage

Rare side effects (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)

Side effects of unknown frequency (the frequency of these effects has not been established yet):
- 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 symptoms occur together, contact your doctor.

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects or by using the link: https://sideeffects.health.gov.il .

5. HOW TO STORE THE MEDICINE?

- Prevent poisoning! This and any other medicine should be kept in a closed place, out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by a doctor.
- Do not use the medicine after the expiry date (exp. date) which is stated on the package. The expiry date refers to the last day of that month.
- Store below 25˚C.
- Keep the blister tray in the outer carton in order to protect from light.

6. FURTHER INFORMATION

In addition to the active ingredient, this medicine also contains:
sucrose, lactose monohydrate, polyethylene glycol (macrogol) 8000 powdered, calcium sulfate anhydrous, microcrystalline cellulose, pharmaceutical glaze (shellac), talc, titanium dioxide, magnesium stearate, povidone, poloxamer 188, polyethylene glycol (macrogol) type 20,000, ink-red Opacode S-1-15095, glyceryl monooleate, carnauba wax, vitamin E (*dl*-α-tocopherol).

Each tablet contains 86.4 mg lactose and 215.8 mg sucrose.

What the medicine looks like and contents of the pack:
white-coloured, triangular-shaped, coated tablets imprinted with “RAPAMUNE 1 mg” on one side.
The tablets are supplied in blister trays, in packs of either 30 or 100 tablets.

Not all pack sizes may be marketed.

Registration holder’s name and address: Pfizer Pharmaceuticals Israel Ltd.,
9 Shenkar St., Herzliya Pituach 46725.

Registration number of the medicine in the Ministry of Health’s National Drug Registry: 131-73-30909

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