

Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986
This medicine is dispensed with a doctor's prescription only

| TACROCEL 0.5 mg Capsules | TACROCEL 1 mg Capsules | TACROCEL 5 mg Capsules |
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| Each capsule contains: Tacrolimus (as monohydrate) 0.5 mg | Each capsule contains: Tacrolimus (as monohydrate) 1 mg | Each capsule contains: Tacrolimus (as monohydrate) 5 mg |

For information about inactive ingredients and allergens in the medicine see section 2 "Important information about some of the ingredients of the medicine" and section 6 "Additional information".

Read this entire leaflet carefully before using the medicine. This leaflet contains concise information about the medicine. If you have any further questions, refer to the doctor or pharmacist.
This medicine has been prescribed for the treatment of your illness. Do not pass it on to others. It might harm them, even if you think that their medical condition is similar.

1. WHAT IS THE MEDICINE INTENDED FOR?

Prophylaxis of transplant rejection in liver, kidney or heart allograft recipients.
Treatment of allograft rejection resistant to treatment with other immunosuppressive drugs.
Tacrocel belongs to a group of medicines called immunosuppressants. Following an organ transplant (such as liver, kidney, heart), your body's immune system will try to reject the new organ. Tacrocel is used to control your body's immune response enabling your body to accept the transplanted organ.

Therapeutic group: Immunosuppressants.

2. BEFORE TAKING THE MEDICINE:

Do not replace with another tacrolimus medicine, unless the doctor from the transplant clinic you are treated in is aware of and approves it.

Do not use the medicine if:

- You are hypersensitive (allergic) to the active ingredient tacrolimus or to any of the other ingredients this medicine contains (see section 6 "Additional information").
- You are hypersensitive (allergic) to any antibiotic medicine of the macrolide group (such as erythromycin, clarithromycin, josamycin).

Special warnings regarding the use of the medicine: For your attention, it is important that you make sure you always receive the same medicine your transplantation specialist prescribed for you each time you receive the medicine at the pharmacy. If the medicine you received looks different from the one you usually receive or the directions for use have been changed, please refer to the pharmacist immediately to make sure you have received the correct medicine. Any substitution or change in dosing of a medicine containing tacrolimus (the active ingredient of the medicine) must be done under the knowledge and approval of the doctor at the transplant clinic you are being treated in. Please check the trade name of the medicine prescribed by your doctor versus the medicine you received from the pharmacist and make sure they are identical.

Before starting treatment with Tacrocel, tell the doctor if:

- you will need to take Tacrocel every day, as long as you need immunosuppression to prevent rejection of your transplanted organ. You should keep in regular contact with your doctor.
- while you are being treated with Tacrocel, your doctor may want to carry out a number of tests (including blood, urine, heart function, visual and

diagnostics and verapamil). This is a normal procedure and will help your doctor decide on the most appropriate dose of Tacrocel for you.

- you take herbal remedies. Avoid taking any herbal remedies, such as St. John's Wort (hypericum perforatum) or any other herbal products, as this may affect the effectiveness of the treatment and the required dose of Tacrocel that you need to receive. If in doubt, refer to your doctor prior to taking any herbal products or remedies.
 - you have liver problems or a disease which may affect your liver, tell your doctor as this may affect the dosage of Tacrocel that you receive.
 - you feel strong abdominal pain accompanied or not with other symptoms, such as chills, fever, nausea or vomiting.
 - you have diarrhea for more than one day, tell your doctor, because it might be necessary to adjust the dosage of Tacrocel that you take.
 - you have an alteration of the electrical activity of your heart called "QT prolongation".
 - limit your exposure to sunlight and UV light whilst taking Tacrocel by wearing appropriate protective clothing and using a sunscreen with a high sun protection factor. This is because of the potential risk of malignant skin changes with immunosuppressive therapy.
 - you need to have any vaccinations, inform your doctor beforehand. Your doctor will advise you on the best course of action.
 - patients treated with Tacrocel have been reported to have an increased risk of developing a lymphatic system dysfunction manifested by cell overproduction (lymphoproliferative disorders) (see section 4 – "side effects"). Consult the doctor about these disorders.
- Report to your doctor immediately if during treatment you suffer from: problems with your vision such as blurred vision, changes in color vision, difficulty in seeing details or if your field of vision becomes restricted.

Drug interactions:

If you are taking or have recently taken other medicines, including non-prescription medicines and nutritional supplements, inform the doctor or pharmacist.

- Tacrocel must not be taken with ciclosporin.

Tacrocel blood levels might be affected by other medicines you take, and alternatively blood levels of other medicines might be affected by Tacrocel. This may require interruption, an increase or a decrease in Tacrocel dose. In particular, you should tell your doctor if you are taking or have recently taken medicines with active ingredients such as:

- antifungal medicines and antibiotics, particularly antibiotics of the macrolide group, which are used to treat infections such as ketoconazole, fluconazole, itraconazole, voriconazole, clotrimazole, isavuconazole, erythromycin, clarithromycin, josamycin, and rifampicin.
- letermovir, used to prevent illness caused by CMV (human cytomegalovirus).
- HIV protease inhibitors (such as ritonavir, nelfinavir, saquinavir), the enhancer medicine cobicistat, and combined tablets, which are used to treat HIV (Human Immunodeficiency Virus) infection.
- HCV protease inhibitors (such as telaprevir, boceprevir, and the combination ombitasvir/paritaprevir/ritonavir with or without dasabuvir), which are used to treat hepatitis C infection.
- nilotinib and imatinib (used to treat certain cancer types).
- mycophenolic acid, which is used to suppress the immune system in order to prevent transplant rejection.
- medicines which are to treat stomach ulcer and acid reflux (such as omeprazole, lansoprazole or cimetidine).
- antiemetics, which are used to treat nausea and vomiting (such as metoclopramide).
- antacids containing magnesium-aluminum-hydroxide, which are used to treat heartburn.
- hormone treatments containing ethinylestradiol (such as oral contraceptive pills) or danazol.
- medicines which are used to treat hypertension or heart problems such as: nifedipine, nicardipine,

diltiazem and verapamil).

- anti-arrhythmic medicines (amiodarone) which are used to treat heart rate disturbances (arrhythmia).
- medicines called statins which are used to treat high levels of cholesterol and triglycerides.
- the anti-epileptic medicines phenytoin or phenobarbital.
- the corticosteroids prednisolone and methylprednisolone.
- the anti-depressant nefazodone.
- Herbal medicines containing St. John's Wort (hypericum perforatum) or extracts of Schisandra sphenanthera.

Tell your doctor if you are taking or need to take ibuprofen, amphotericin B, or antiviral medicines (such as aciclovir). These medicines may worsen kidney or nervous system problems when taken together with Tacrocel. Additionally, tell your doctor if you are taking potassium supplements or potassium-sparing diuretics (such as, amiloride, triamterene, or spironolactone), certain pain killers (non-steroidal anti-inflammatory drugs [NSAIDs], such as ibuprofen), anticoagulants, or oral antidiabetics, while you take Tacrocel.
If you need to have any vaccinations, inform your doctor beforehand.

Use of the medicine and food

The medicine should be taken in general on an empty stomach or at least one hour before or 2-3 hours after a meal. Grapefruit and grapefruit juice should be avoided while taking Tacrocel.

Pregnancy, breastfeeding and fertility

If you are pregnant or breastfeeding, think you may be pregnant or are planning to become pregnant, consult the doctor or pharmacist before taking this medicine.
Tacrocel is excreted into breast milk, therefore, you should not breastfeed while taking Tacrocel.

Driving and using machines

Do not drive or use any tools or machines if you feel dizzy or sleepy, or have problems seeing clearly after taking Tacrocel. These effects were more frequently observed when Tacrocel was taken in conjunction with alcohol use.

Important information about some of the ingredients of the medicine

The medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 23 mg sodium per capsule, that is to say essentially "sodium-free".

3. HOW SHOULD YOU USE THIS MEDICINE?

Always use the medicine according to the doctor's instructions. You should check with the doctor or pharmacist if you are not sure about the dosage and treatment regimen with the medicine. The dosage and the treatment regimen will be determined by the doctor only.

Make sure that you receive the same tacrolimus medicine every time you receive your medicine at the pharmacy, unless your specialist from the transplant clinic you are treated in has agreed to change to a different tacrolimus medicine.

The dosage and the treatment regimen will be determined by the doctor only. The usual recommended dose is:
This medicine should be taken twice a day. If the appearance of this medicine is not the same as usual, or if dosage instructions have changed, speak to your doctor or pharmacist as soon as possible to make sure that you take the right medicine.
The starting dose to prevent the rejection of your transplanted organ will be determined by your doctor and calculated according to your body weight. Initial doses just after transplantation will generally be in the range of 0.075 - 0.30 mg per kg body weight per day, depending on the transplanted organ.
Your suitable dose depends on your general condition and on which other immunosuppressive medication you are taking. Regular blood tests by your doctor will be required to define the correct dose and to adjust it from time to time. Your doctor will consider reducing your Tacrocel dose once your condition has stabilized.

Your doctor will tell you exactly how many capsules to take and how often.
Do not exceed the recommended dose.

Method of administration:

- Tacrocel should be taken twice daily, usually in the morning and evening. You should generally take Tacrocel on an empty stomach, or at least one hour before or 2-3 hours after a meal.
- The capsules should be swallowed whole with a glass of water immediately following removal from the blister.
- Do not chew the capsule and do not open the capsule and disperse its content.
- Avoid grapefruit and grapefruit juice while using Tacrocel.
- Do not swallow the desiccant sachet contained in the aluminum wrapper.**

If you have accidentally taken an overdose or if a child or someone has accidentally swallowed the medicine, refer immediately to a doctor or to a hospital emergency room and bring the package of the medicine with you.

If you forgot to take the medicine, do not take a double dose to make up for a forgotten dose. If you have forgotten to take your Tacrocel capsules, wait until it is time for the next dose, and continue to take the capsules as usual. Adhere to the treatment as recommended by the doctor.

If you stop taking the medicine

Stopping your treatment with Tacrocel may increase the risk of rejection of your transplanted organ. Do not stop your treatment unless your doctor tells you to do so.

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

If you have any further questions regarding the use of the medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS:

As with any medicine, the use of Tacrocel can cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them.
Tacrocel reduces your body's own defense mechanisms in order to prevent the rejection of your transplanted organ. Consequently, your body will not be as good as usual at fighting infections. Therefore, when you are taking Tacrocel you may catch more infections than usual such as: infections of the skin, mouth, stomach, intestines, lungs and urinary tract.
Serious side effects may occur, including the ones listed below.

Refer to the doctor immediately if you have or suspect you may have any of the following serious side effects:

- Opportunistic infections (bacterial, fungal, viral or protozoal): prolonged diarrhea, fever and sore throat.
- Benign and malignant tumors have been reported as a result of immunosuppression.
- Thrombotic Thrombocytopenic Purpura (or TTP) - a condition characterized by fever, bruising under the skin that may appear as red pinpoint dots, with or without unexplained extreme tiredness, confusion, yellowing of the skin or eyes (jaundice), with symptoms of acute renal failure (low or no urine output).
- Cases of pure red cell aplasia (a very severe reduction in red blood cell counts), hemolytic anemia (decreased number of red blood cells due to abnormal breakdown accompanied with tiredness) and febrile neutropenia (a decrease in the type of white blood cells which fight infection, accompanied with fever) have been reported. It is not known exactly how often these side effects occur. You may have no symptoms or depending on the severity of the condition, you may feel: fatigue, apathy, abnormal paleness of the skin (pallor), shortness of breath, dizziness, headache, chest pain and cold sensation in the hands and feet.
- Cases of agranulocytosis (a severely lowered

number of white blood cells accompanied with ulcers in the mouth, fever and infections). You may have no symptoms or you may feel sudden fever, chills and sore throat.

- Allergic and anaphylactic reactions manifested by the following symptoms: a sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing) and you may feel you are going to faint.
- Posterior Reversible Encephalopathy Syndrome (PRES) manifested by headache, altered mental status, seizures, and visual disturbances.
- Arrhythmias of Torsades de Pointes type: change in the heart rhythm that may or may not be accompanied with symptoms, such as chest pain (angina), fainting, vertigo or nausea, palpitations (feeling the heartbeat) and difficulty breathing.
- Gastrointestinal perforation - strong abdominal pains that may or may not be accompanied with additional symptoms, such as chills, fever, nausea or vomiting.
- Stevens-Johnson syndrome: unexplained widespread skin pain, facial swelling, serious illness with blistering of skin, mouth, eyes and genitals; hives, tongue swelling, red or purple skin rash that spreads, skin shedding.
- Toxic epidermal necrolysis: erosion and blistering of skin or mucous membranes, red and swollen skin that may detach in large parts of the body.
- Hemolytic uremic syndrome, manifested by the following symptoms: low or no urine output (acute renal failure), extreme tiredness, yellowing of the skin or eyes (jaundice) and abnormal bruising or bleeding and signs of infection.
- Insufficient function of your transplanted organ.

The side effects listed below may occur after taking Tacrocel:

Very common side effects (may affect more than 1 in 10 patients):

Increased blood sugar, diabetes mellitus, increased potassium in the blood, difficulty in sleeping, trembling, headache, increased blood pressure, diarrhea, nausea, kidney problems.

Common side effects (may affect up to 1 in 10 patients):

- Reduced magnesium, phosphate, potassium, calcium or sodium in the blood, fluid overload, increased uric acid or lipids in the blood, decreased appetite, increased acidity of the blood, other changes in the blood salts.
- Anxiety symptoms, confusion and disorientation, depression, mood changes, nightmares, hallucination, mental disorders.
- Convulsions, disturbances in consciousness, tingling and numbness (sometimes painful) in the hands and feet, dizziness, impaired writing ability, nervous system disorders.
- Blurred vision, increased sensitivity to light, eye disorders.
- Ringing sound in your ears.
- Reduced blood flow in the heart vessels, faster heartbeat.
- Bleeding, partial or complete blocking of blood vessels, reduced blood pressure.
- Shortness of breath, changes in the lung tissue, collection of liquid around the lung, inflammation of the pharynx, cough, flu-like symptoms.
- Inflammations or ulcers causing abdominal pain or diarrhea, bleeding in the stomach, inflammations or ulcers in the mouth, buildup of fluid in the abdomen, vomiting, abdominal pains, indigestion, constipation, flatulence, bloating, loose stools, stomach problems.
- Changes in liver enzymes and function, yellowing of the skin due to liver problems, liver tissue damage, inflammation of the liver.
- Itching, rash, hair loss, acne, increased sweating.
- Pain in joints, limbs, back and feet, muscle spasms.
- Renal failure, reduced production of urine, impaired or painful urination.
- General weakness, fever, collection of fluid in your body, pain and discomfort, increase of the enzyme alkaline phosphatase in your blood, weight gain, sensation of changes in body temperature.

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

- Changes in blood clotting, reduction in all blood cell counts.
- Dehydration, reduced protein or sugar in the blood, increased phosphate in the blood.
- Coma, bleeding in the brain, stroke, paralysis, brain disorder, speech and language abnormalities, memory problems.
- Blurring of the vision due to impairment of the eye lens.
- Impaired hearing.
- Irregular heartbeat, cardiac arrest, reduced heart performance, disorder of the heart muscle, enlargement of the heart muscle, stronger heartbeat, abnormal ECG, abnormal heart rate and pulse.
- Blood clot in a vein of a limb, shock.
- Difficulties in breathing, respiratory tract disorders, asthma.
- Obstruction of the gut, increased blood level of the enzyme amylase, reflux of stomach content in your esophagus, delayed emptying of the stomach.
- Dermatitis, burning sensation in the sunlight.
- Joint disorders.
- Inability to urinate, painful menstruation and abnormal menstrual bleeding.
- Failure of some organs, influenza-like illness, increased sensitivity to heat and cold, feeling of pressure in your chest, nervousness or abnormal feeling, increase of the enzyme lactate dehydrogenase in your blood, weight loss.

Rare side effects (may affect up to 1 in 1,000 patients):

Mild bleeds in your skin due to blood clots, increased muscle stiffness, blindness, deafness, collection of fluid around the heart, acute shortness of breath, cyst formation in your pancreas, problems with blood flow in the liver, excessive hairiness, thirst, tendency to fall, feeling of tightness in your chest, decreased mobility, ulcer.

Very rare side effects (may affect up to 1 in 10,000 patients):

Muscular weakness, abnormal results in echocardiogram, liver failure, narrowing of the bile vessel, painful urination with blood in the urine, increase of fat tissue.

Side effect of unknown frequency (frequency cannot be estimated from the available data):

Abnormality of the optic nerve (optic neuropathy)

If a side effect appears, if any of the side effects gets worse, or if you suffer from a side effect not mentioned in the leaflet, consult the doctor.

Reporting side effects

Side effects can be reported to the Ministry of Health by clicking on the link "Reporting Side Effects from Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link:

<https://sideeffects.health.gov.il>

Additionally, you can report to Perrigo via the following address:

www.perrigo-pharma.co.il

5. HOW TO STORE THE MEDICINE?

- Avoid poisoning! This medicine and any other medicine must be kept in a closed place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (exp. date) that appears on the package, aluminum sachet and blister. The expiry date refers to the last day of that month.
- Take the capsules immediately following removal from the blister.
- Store in the original package below 25°C.
- After opening the aluminum sachet covering the blisters, the capsules can be used for 3 months, but not later than the expiry date.
- Each aluminum wrapping contains a desiccant sachet. Do not swallow it or remove it from the aluminum wrapping.

6. ADDITIONAL INFORMATION:

In addition to the active ingredient, the medicine also contains:

Lactose monohydrate, gelatin, titanium dioxide, magnesium stearate, croscarmellose sodium, hypromellose, yellow iron oxide (in Tacrocel 0.5 mg and Tacrocel 1 mg), sodium lauryl sulfate, sorbitan monolaurate, red iron oxide (in Tacrocel 1 mg and Tacrocel 5 mg), black iron oxide (in Tacrocel 1 mg).

Each 0.5 mg Tacrocel capsule contains 48.489 mg lactose monohydrate and 0.021 mg sodium.

Each 1 mg Tacrocel capsule contains 47.378 mg lactose monohydrate and 0.040 mg sodium.

Each 5 mg Tacrocel capsule contains 236.890 mg lactose monohydrate and 0.193 mg sodium.

What the medicine looks like and the contents of the package:

The capsules are packed in blister trays within a sealed aluminum sachet.

Each blister tray contains 10 capsules.

The capsule colors are: 0.5 mg – white and ivory, 1 mg – white and light brown, 5 mg – white and pink

Registration holder and address: Perrigo Israel Agencies Ltd., 1 Rakefet St., Shoham

Manufacturer: Lek Pharmaceuticals d.d., Ljubljana, Slovenia.

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Registration number of the medicine in the National Drug Registry of the Ministry of Health:

Tacrocel 0.5 mg: 14854.33452

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Tacrocel 5 mg: 14856.33455

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