PATIENT PACKAGE IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

This medicine is dispensed with a doctor's prescription only

TACROCEL 0.5 mg Capsules

Each capsule contains:
Tacrolimus 0.5 mg

TACROCEL 1 mg Capsules

Each capsule contains:
Tacrolimus 1 mg

TACROCEL 5 mg Capsules

Each capsule contains:
Tacrolimus 5 mg

For a list of the inactive ingredients in the medicine, see section 6 "Further information".

Read this entire leaflet carefully before using this 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 medicinal products.
Therapeutic group: Immunosuppressants.

2. BEFORE TAKING THE MEDICINE:

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

☒ Do not take the medicine if:
- You are sensitive (allergic) to the active ingredient tacrolimus or to any of the other ingredients contained in the medicine (see section 6 "Further information").
- You are sensitive to other medicines belonging to the macrolide group (e.g., erythromycin, clarithromycin, josamycin).
- You are breastfeeding.
- Do not use this medicine together with cyclosporine.

Take special care:
- This medicine contains lactose and might cause an allergy in people who are sensitive to lactose.
- During the course of treatment with this medicine, the following tests should be performed from time to time: blood; blood pressure; urine; liver, heart and kidney function; eye examinations and neurological tests.
- Avoid taking herbal remedies, such as a herbal remedy for depression that contains the herb hypericum perforatum or any other herbal product, as they may affect the effectiveness of the treatment and the required dose of Tacrocel. If in doubt, refer to the doctor prior to taking herbal products or remedies.
- Due to the high risk of developing malignant skin changes as a result of immunosuppressive therapy, you should wear appropriate clothing and use sunscreen with a high sun protection factor in order to limit your exposure to sunlight and UV light during treatment with Tarcocel.
- Do not drink wines or alcoholic beverages during the course of treatment with this medicine.

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

Inform the doctor before starting treatment if:
- You are sensitive to any type of food or medicine.
- You experience severe abdominal pain accompanied/not accompanied by other effects such as: chills, fever nausea or vomiting.
- Your E.C.G indicates an alteration of the electrical conduction of the heart called "prolonged QT interval".
- You suffer or have suffered in the past from:
  - Liver problems
  - Impaired function of the heart and/or blood vessels (hypertension)
  - Impaired function of the kidney/urinary system
  - Impaired function of the immune system
  - Diabetes
  - Any infection
- If you suffer from diarrhea for more than a 24-hour period, tell your doctor because it might be necessary to adjust the dosage of Tacrocel that you are taking.
- If you need to be vaccinated, consult your doctor.
- Patients treated with Tacrocel have been reported to have increased risk of developing lymphoproliferative disorders. Consult the doctor.

Drug interactions:
Before taking the medicine, tell the doctor or pharmacist if you are taking, or have recently taken other medicines including non-prescription medicines, herbal remedies, vitamins and nutritional supplements.
The level of Tacrocel in the blood can be affected by taking other medicines, and alternatively, the levels of other medicines can be affected by taking Tacrocel, which may require discontinuation, an increase or decrease in the dosage of Tacrocel.
Inform the doctor if you are taking or have recently taken medicines such as:
- Anticoagulants
- Contraceptive pills or danazol
- Potassium supplements, products containing potassium
- Potassium-sparing diuretics (e.g., amiloride, triamterene, or spironolactone)
- Antihypertensives and medicine for the heart (e.g., nifedipine, nicradipine, diltiazem, verapamil)
- Medicines for lowering lipids and cholesterol (e.g., statins)
- Anti-epileptics, e.g., phenytoin or phenobarbital
- Nefazodone (antidepressant)
- Methylprednisolone and prednisolone (corticosteroid)
- Oral antidiabetic medicines
- Medicines to treat ulcer and acid reflux (e.g., omeprazole, lansoprazole)
- Medicines to prevent nausea and vomiting (e.g., metoclopramide)
- Combined antacids: magnesium and aluminum hydroxide to treat heartburn
- Antibiotics, particularly rifampicin and macrolide antibiotics (e.g., erythromycin, clarithromycin, josamycin)
- Antifungals (e.g., ketoconazole, fluconazole, itraconazole, voriconazole, clotrimazole)
- Antiarrhythmics (e.g., amiodarone)
- Antivirals (e.g., ganciclovir, nelfinavir, saquinavir, acyclovir or ritonavir)
- HCV protease inhibitors (e.g., telaprevir, boceprevir) to treat hepatitis C.
- Herbal remedies containing the herb Hypericum perforatum (St. John's Wort) or Schisandra sphenanthera extracts (a plant used in traditional Chinese medicine)
- Vaccines
- The following medicines may have an undesired effect on the kidneys: aminoglycosides, co-trimoxazole, amphotericin B, vancomycin, gyrase inhibitors (antibiotics) or non-steroidal anti-inflammatory drugs (NSAIDs)
- **Do not use Tacrocel together with cyclosporine (for transplantations) (see above "do not take the medicine if")**

Taking the medicine with food
In general, the medicine should be taken on an empty stomach or at least one hour before or 2-3 hours after a meal, in two divided doses, usually in the morning and evening. Avoid eating grapefruit or drinking grapefruit juice when taking Tacrocel.

Pregnancy
Tell the doctor if you are considering getting pregnant, think you may be pregnant, or are pregnant.

Breastfeeding
Tacrocel is excreted into breastmilk, therefore do not breastfeed while using Tacrocel (see above "do not take the medicine if").

Driving and using machines
Use of this medicine may cause vision or nervous system disorders, feelings of dizziness or drowsiness, and therefore, caution should be exercised when driving a car, operating dangerous machinery and when engaging in any activity that require alertness. These effects are more frequent if alcohol is consumed while using the medicine.
Children should be cautioned about riding bicycles or playing games near the road and the like.

Important information about some of the ingredients of the medicine
The medicine contains lactose, which may cause an allergy in people sensitive to lactose, therefore you should tell your doctor about it before taking the medicine (for the quantity of lactose see section 6 "Further information").

3. HOW SHOULD YOU USE THIS MEDICINE?

Always use according to the doctor's instructions. Check with the doctor or pharmacist if you are not sure about the dosage and treatment regimen with the medicine. Take this medicine twice a day. If you notice a change in the appearance of the medicine or in the directions for use, report to the doctor or pharmacist as fast as possible to make sure you are taking the correct medicine.
The dosage and the treatment regimen will be determined by the doctor only.
The usual dosage is generally:
The starting dosage for prevention of rejection of a transplanted organ will be determined by the doctor in accordance with your body weight. Starting dosages immediately after transplantation usually range between 0.075-0.30 mg per kg body weight per day, in accordance with the transplanted organ.
The dosage appropriate for you depends on your general health and on the additional immunosuppressant medications you are taking. Perform routine blood tests, as per the doctor's instructions, to determine the correct dosage and to adjust it from time to time. The doctor will consider lowering the dosage of Tacrocel after your condition has stabilized. The doctor will instruct you in regards to the exact number of capsules and how often they should be taken.
- Tacrocel should be taken twice a day, usually in the morning and evening. Usually Tacrocel should be taken on an empty stomach or at least one hour before or 2-3 hours after a meal.
- Swallow the capsules whole with a glass of water immediately following its removal from the blister.
- Do not chew the capsule and do not open the capsule and disperse its content.
- Avoid eating grapefruits and consuming grapefruit juice when using Tacrocel.
- **Do not swallow the desiccant sachet inside the aluminum wrapper.**

Do not exceed the recommended dose.
If you have taken an overdose or if someone has accidentally swallowed the medicine, refer to a doctor or proceed to a hospital emergency room immediately and bring the package of the medicine with you.
If you forgot to take the medicine
If you forgot to take the medicine at the scheduled time, take the dose as soon as you remember, but never take two doses together. If there are less than 5 hours left to the time for the next dose, skip the forgotten dose and carry on taking the medicine at the next scheduled dose.
Be sure to adhere to the treatment recommended by the doctor.
If you stop taking the medicine
Stopping the treatment with Tacrocel may increase the risk of rejection of the transplanted organ. Do not stop treatment unless instructed by the doctor.
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 use of the medicine, refer to the doctor or pharmacist.

4. SIDE EFFECTS:

As with any medicine, 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 weakens your body's defense mechanisms to prevent rejection of your transplanted organ. Consequently, your body is not at its usual state where it has the ability to protect itself from infections. Therefore, when compared to your normal condition, you may be more susceptible to infectious diseases such as: infections of the skin, mouth, stomach, intestines, lungs and urinary tract.

Severe side effects may occur, including the effects listed below. If you notice or suspect any of the following side effects, refer to the doctor immediately:
- Opportunistic infections (of bacterial, fungal, viral or protozoal origin); prolonged diarrhea, fever and sore throat; cases of benign and malignant tumors due to transplant rejection therapies have been reported.
- Reduced blood platelets and thrombocytes (thrombotic thrombocytopenic purpura) - a condition manifested by fever and bruising under the skin that appear as red spots, with or without extreme and unusual tiredness, confusion, yellow skin or eyes (jaundice), and symptoms of kidney failure (reduced urination or urinary retention).
- Sharp drop in red blood cell count (red cell aplasia) and hemolytic anemia (abnormal breakdown of red blood cells, accompanied by tiredness). As the condition worsens, other effects may occur: fatigue, exhaustion, apathy, abnormal paleness of the skin, shortness of breath, dizziness, headaches, chest pains and cold sensation in the hands and legs.
- Sharp drop in white blood cell count, accompanied by mouth sores, fever and infections (agranulocytosis). Signs may not appear or, alternatively, you may feel sudden fever, chills and sore throat.
- Allergic and anaphylactic reactions, manifested by the following effects: sudden itchy rash (urticaria); swelling of the hands, legs, ankles, face, lips, mouth or throat (which may cause swallowing or breathing difficulties) with a faint feeling.
- Posterior Reversible Encephalopathy Syndrome (PRES) manifested by headaches, altered mental status, seizures and blurred vision.
- Torsades de Pointes cardiac flutter: which is a change in the rate of the heart beats that may be accompanied by effects such as chest pain (angina pectoris), fainting, vertigo or nausea, palpitations, and breathing difficulties.
- Gastrointestinal perforation – manifested by strong abdominal pains, which may be accompanied by other symptoms such as chills, fever, nausea or vomiting.
- Stevens-Johnson syndrome: widespread and unusual skin pain, facial swelling, a severe illness with blistering of the skin, mouth, eyes and genitals, intense irritation (urticaria), tongue swelling, red or purple skin rash that spreads, skin shedding.
- Toxic epidermal necrolysis syndrome: blisters and lumps on the skin or soft tissue, red and swollen skin which may detach in large parts of the body.
- Hemolytic uremic syndrome: manifested by the following symptoms: urinary reduction or retention (kidney failure), increased fatigue, yellow skin and eyes (jaundice) and abnormal bruising or bleeding and signs of infection.
- Impaired function of the transplanted organ.

Additional side effects
Very common side effects (may affect more than 1 in 10 patients)
- Increased blood sugar level, diabetes mellitus, increased level of potassium in the blood
- Insomnia
- 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 levels 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, confusion, disorientation, depression, mood changes, nightmares, hallucinations, mental disorders.
- Convulsions, disturbances in consciousness, tingling sensation 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 in the ears.
- Reduced blood flow in the heart, faster heartbeat.
- Bleeding, partial or complete blocking of blood vessels, reduced blood pressure.
- Shortness of breath, changes in the lung tissue, collection of fluid around the lungs, inflammation of the pharynx, cough, flu-like symptoms.
- Inflammations or ulcers causing abdominal pain, diarrhea, bleeding in the stomach, inflammations or sores in the mouth, collection of fluid in the abdomen, vomiting, abdominal pain, indigestion, constipation, flatulence, abdominal 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 or back, muscle cramps.
- Renal insufficiency, reduced urine production, impaired or painful urination.
- General weakness, fever, collection of fluid in your body, pain and discomfort, increased level of the enzyme alkaline phosphatase in your blood, weight gain, 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 level in the blood.
- Coma, bleeding in the brain, stroke, paralysis, brain function disorder, speech and language abnormalities, memory disorders.
- Opacity of the eye lenses.
- Impaired hearing
- Irregular heartbeat, cardiac arrest, reduced heart function, disorders of the heart muscle function, enlargement of the heart muscle, strong heartbeat, abnormal ECG, abnormal heart rate and pulse.
- Formation of a blood clot in a vein of the arm or leg, shock.
- Difficulties in breathing, respiratory tract disorders, asthma.
- Obstruction of the gut, increased level of the enzyme amylase, reflux of stomach content in your throat (GERD), delayed emptying of the stomach.
- Dermatitis, burning sensation on exposure to sunlight.
- Joint disorders.
- Inability to urinate, strong menstrual pains, abnormal menstrual bleeding.
- Failure of some organs, influenza-like illness, increased sensitivity to heat and cold, feeling of pressure on your chest, jittery or abnormal feeling, increase in the level of the enzyme lactate dehydrogenase in your blood, weight loss.

Rare side effects (may affect up to 1 in 1,000 patients)
- Minor skin bleedings due to blood clots
- Increased muscle stiffness
- Blindness
- Deafness
- Collection of fluid around the heart
- Acute breathlessness
- Cyst formation in the pancreas
- Problems with blood flow in the liver
- Increased hairiness;
- Thirst, falls, 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 echocardiogram (ECG)
- Liver failure, narrowing of the bile vessels
- Painful urination with blood in the urine
- Increase of fat tissue

If a side effect occurs, if one of the side effects worsens, or if you suffer from side effects not mentioned in this leaflet, consult the doctor.

Reporting side effects
Side effects can be reported to the Ministry of Health by clicking on the "Reporting side effects following drug treatment" link 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://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il
In addition, you can report to Perrigo via the following address:
www.perrigo-pharma.co.il

5. HOW SHOULD THE MEDICINE BE STORED?

- Avoid poisoning! This medicine and any other medicine must be kept in a safe place out of the reach 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 wrapping and blister tray. The expiry date refers to the last day of that month.
- Store in the original package, below 25°C.
- After first opening of the aluminum wrapping of the blister trays, the capsules can be used for 3 months, but not later than the expiry date.
- Each aluminum wrapping contains a desiccant sache. Do not swallow it.

6. FURTHER INFORMATION:

In addition to the active ingredient, the medicine also contains:
Lactose monohydrate, magnesium stearate, croscarmellose sodium, hypromellose, gelatin, titanium dioxide E171, sodium lauryl sulfate, sorbitan monolaurate , iron oxide yellow E172 (in Tacrocel 0.5 mg and Tacrocel 1 mg), iron oxide red E172 (in Tacrocel 1 mg and Tacrocel 5 mg), iron oxide black E172 (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 wrapping. Each blister tray contains 10 capsules. The capsule colors are: 0.5 mg – yellow and ivory, 1 mg – brown and ivory, 5 mg – pink and ivory.

Registration holder and address: Perrigo Israel Agencies Ltd., 29 Lehi St., Bnei Brak 51200.
Manufacturer: Lek Pharmaceuticals d.d., Ljubljana, Slovenia.

This leaflet was checked and approved by the Ministry of Health in January 2017, and was updated in accordance with the Ministry of Health instructions in May 2018.
Registration number of the medicine in the National Drug Registry of the Ministry of Health:
0.5 mg: 14854.33452
1 mg: 14855.33453
5 mg: 14856.33455

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