PATIENT LEAFLET IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986

The medicine is dispensed with a doctor's prescription only

TACROCEL 0.5 mg Capsules

Each capsule contains:

Tacrolimus (as monohydrate) 0.5 mg

TACROCEL 1 mg Capsules

Each capsule contains:

Tacrolimus (as monohydrate) 1 mg

TACROCEL 5 mg Capsules

Each capsule contains:

Tacrolimus (as monohydrate) 5 mg

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

Read the leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed to treat you. Do not pass it on to others. It may harm them, even if it seems to you 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.

Tacrocel belongs to a group of medicines called immunosuppressants. Following an organ transplant (such as: liver, kidney and 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 USING THE MEDICINE:

Do not replace with another tacrolimus preparation, 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 sensitive (allergic) to the active ingredient tacrolimus or to any of the additional ingredients contained in the medicine (see section 6 "Further information").
- You are sensitive (allergic) to any antibiotic belonging to the macrolide antibiotic group (such as: erythromycin, clarithromycin, josamycin).

Special warnings regarding use of the medicine:

For your attention, it is important that you make sure you always receive the same medicine the 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 instructions for use have 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 with the knowledge and approval of the doctor at the transplant clinic you are being treated in. Please check the trade name of the preparation prescribed by the doctor versus the medicine you received from the pharmacist and make sure they are identical.

Before 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.
- Avoid taking any herbal medicines, such as St. John's Wort (*Hypericum perforatum*) or any other herbal product, 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 product or remedy.
- You suffer from 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 suffer from 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 interval 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 changes in the skin associated 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 tacrolimus 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.
- You have or have had damage to the smallest blood vessels, known as thrombotic microangiopathy/thrombotic thrombocytopenic purpura/ haemolytic uraemic syndrome. Tell the doctor if you develop fever, bruising under the skin (which may appear as red dots), unexplained tiredness, confusion, yellowing of the skin or eyes, reduced urine output, vision loss and seizures (see section 4 "Side effects"). When tacrolimus is taken together with sirolimus or everolimus, the risk of developing these symptoms may increase.

Treatment precautions:

During preparation, avoid direct contact with any part of your body, such as: the skin or eyes, or inhalation of the injection solution, powder or granules included in tacrolimus preparations. If such contact occurs, rinse the skin and eyes.

Tests and follow-up:

Throughout the course of treatment with Tacrocel, your doctor may, from time to time, refer you for several tests (including blood, urine, heart function, vision and neurological tests). This is a normal procedure and will help your doctor determine the Tacrocel dosage most appropriate for you.

Drug interactions:

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

- Tacrocel must not be taken with ciclosporin.

At any visit to a doctor other than your transplant specialist, tell the doctor that you are taking tacrolimus. Your doctor may need to consult your transplant specialist if you need to use another medicine that may increase or decrease your tacrolimus blood level.

Tacrocel blood levels may be affected by other medicines you take, and alternatively, blood levels of other medicines may be affected by Tacrocel. This may require interruption, an increase or a decrease in Tacrocel dosage. Some patients have experienced an increase in tacrolimus blood levels while taking other medicines. An increase in tacrolimus blood levels may lead to serious side effects, such as: kidney problems, nervous system problems, and heart rhythm disturbances (see section 4 "Side effects").

An effect on the Tacrocel blood levels may occur very soon after starting the use of another medicine; therefore, frequent monitoring of your Tacrocel blood level may be needed within the first few days of starting another medicine and frequently while treatment with the other medicine continues. Some other medicines may cause tacrolimus blood levels to decrease, which may increase the risk of rejecting the transplanted organ.

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, posaconazole, voriconazole, clotrimazole, isavuconazole, miconazole, caspofungin, telithromycin, erythromycin, clarithromycin, josamycin, azithromycin, rifampicin, rifabutin, isoniazid and flucloxacillin.
- 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, or non-nucleoside reverse transcriptase inhibitors (efavirenz, etravirine, nevirapine) 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, elbasvir/grazoprevir, and glecaprevir/pibrentasvir) which are used to treat hepatitis C infection.
- Nilotinib and imatinib, idelalisib, ceritinib, crizotinib, apalutamide, enzalutamide or mitotane (used to treat certain types of cancer).
- 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).
- Medicines 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 carbamazepine, phenytoin or phenobarbital.
- Metamizole, used to treat pain and fever.
- The corticosteroids prednisolone and methylprednisolone.
- The anti-depressant nefazodone.
- Herbal preparations containing St. John's Wort (*Hypericum perforatum*) or extracts of the herb *Schisandra sphenanthera*.
- Cannabidiol (uses include, among others, treatment of seizures).

Tell your doctor if you are receiving treatment for hepatitis C. The drug treatment for hepatitis C may change your liver functions and may affect blood levels of tacrolimus. Tacrolimus blood levels may fall or increase depending on the medicines prescribed for hepatitis C treatment. Your doctor may need to closely monitor tacrolimus blood levels and make necessary adjustments of Tacrocel dosage after you start treatment for hepatitis C.

Tell the doctor if you are taking or need to take ibuprofen, amphotericin B, antibiotics (cotrimoxazole, vancomycin, aminoglycoside antibiotics, such as gentamicin) or antiviral medicines (such as: aciclovir, ganciclovir, cidofovir and foscarnet). These medicines may worsen kidney or nervous system problems when taken together with Tacrocel.

Tell the doctor if you are taking sirolimus or everolimus. When tacrolimus is taken together with sirolimus or everolimus, the risk of developing thrombotic microangiopathy, thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome may increase (see section 4 "Side effects").

Additionally, tell your doctor if you are taking potassium supplements or potassium-sparing diuretics (such as: amiloride, triamterene or spironolactone), or the antibiotics trimethoprim or cotrimoxazole, which may increase levels of potassium in the blood, non-steroidal anti-inflammatory drugs (NSAIDs, such as: ibuprofen), used to treat fever, inflammation and pain, 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 generally be taken 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 and breastfeeding:

If you are pregnant or breastfeeding, think you are pregnant or are planning a pregnancy, consult the doctor or pharmacist before taking this medicine.

Tacrocel is secreted into breast milk, therefore, you should not breastfeed while taking Tacrocel.

Driving and operating machinery:

Do not drive or use any tools or machinery 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 certain sugars, refer to your doctor before taking this medicine. This medicine contains less than 23 mg sodium per capsule, that is to say it is essentially "sodium-free".

3. HOW SHOULD YOU USE THIS MEDICINE?

Always use the preparation according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the preparation.

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

The dosage and the treatment regimen will be determined by the doctor only. The usual dosage is generally:

This medicine should be taken twice a day. If the appearance of the 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 dosage to prevent the rejection of the transplanted organ will be determined by the doctor and calculated according to your body weight. Initial dosage 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 dosage depends on your general health condition and on which other immunosuppressive preparations you are taking. Regular blood tests by the doctor will be required to define the correct dosage and to adjust it from time to time. The doctor will consider reducing the Tacrocel dosage once your condition has stabilized. The 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 eating grapefruits and consuming grapefruit juice while using Tacrocel.
- **Do not swallow the desiccant sachet contained in the aluminum wrapper.**

If you have accidentally taken a higher dosage or if a child 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 this medicine at the designated time, do not take a double dose to make up for a forgotten dose. If you have forgotten to take Tacrocel capsules, wait until it is time for the next dose, and continue to take the capsules as usual. Adhere to the treatment regimen as recommended by the doctor.

If you stop taking the medicine, stopping treatment with Tacrocel may increase the risk of rejection of the 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 use of the medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS:

As with any medicine, use of Tacrocel may 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 mechanism (immune system), which impairs the body's ability to fight infections. Therefore, you may be more prone to infections while you are taking Tacrocel. Some infections may be serious or fatal and may include infections caused by bacteria, viruses, fungi, parasites or other infections.

Tell the doctor immediately if you notice signs indicative of an infection, including:

- Fever, cough, sore throat, weakness or malaise.
- Memory loss, trouble thinking, difficulty walking or loss of vision – these may be due to a very rare brain infection, which may be fatal – Progressive multifocal leukoencephalopathy (or PML).

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:

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

- Gastrointestinal perforation: manifests by strong abdominal pains which may be accompanied or not by other effects, such as: chills, fever, nausea or vomiting.
- Dysfunction of the transplanted organ.
- Blurred vision.

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

- Thrombotic microangiopathy (damage to the smallest blood vessels), including haemolytic uraemic syndrome, a condition which manifests by the following effects:

  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.

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

- Thrombotic thrombocytopenic purpura:

  A condition involving damage to the smallest blood vessels and characterised 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), vision loss and seizures.
- Toxic epidermal necrolysis: erosion and blistering of skin or mucous membranes, red swollen skin that may detach in large parts of the body.
- Blindness.

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

- 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.
- Torsades de pointes heart rhythm disturbances: change in the heart rate frequency that may be accompanied or not by effects, such as: chest pain (angina), fainting, vertigo or nausea, palpitations (feeling the heart pounding) and difficulty breathing.

Serious side effect of unknown frequency (effects whose frequency cannot be estimated from the available data):

- Opportunistic infections (bacterial, fungal, viral or protozoal infection): prolonged diarrhea, fever and sore throat.
- Benign and malignant tumors have been reported as a result of immunosuppression.
- Cases of pure red cell aplasia (a very severe reduction in red blood cell count), 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 swallowing or breathing difficulties) and you may feel you are going to faint.
- Posterior reversible encephalopathy syndrome (PRES): headaches, confusion, mood changes, seizures, and visual disturbances. These could be signs of posterior reversible encephalopathy syndrome, which has been reported in some patients treated with tacrolimus.
- Optic neuropathy (damage to the optic nerve): vision problems such as: blurred vision, changes in color vision, difficulty in seeing details or restriction of your field of vision.

The side effects listed below may occur after taking Tacrocel and may be serious:

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

- Increased blood sugar level, diabetes, increased potassium level in the blood.
- Sleeping difficulties.
- Trembling, headache.
- Increased blood pressure.
- Abnormal liver function test results.
- Diarrhea, nausea.
- Kidney problems.

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

- Reduction in blood cell counts (platelets, red or white blood cells), increase in white blood cell count, changes in red blood cell counts (seen in blood tests).
- Reduced level of magnesium, phosphate, potassium, calcium or sodium in the blood, fluid overload, increased level of uric acid or lipids in the blood, decreased appetite, increased acidity of the blood, other changes in the blood salts.
- Anxiety symptoms, confusion, 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.
- Increased sensitivity to light, eye disorders.
- Tinnitus (ringing sound in the 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 the body, pain and discomfort, increased level of the enzyme alkaline phosphatase in the 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 levels in the blood, increased phosphate level 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 function, disorder of the heart muscle, enlargement of the heart muscle (hypertrophic cardiomyopathy), strong heartbeat, abnormal ECG, abnormal heart rate and pulse.
- Blood clot in a vein of a limb, shock.
- Difficulties in breathing, respiratory tract disorders, asthma.
- Bowel obstruction, increased blood level of the enzyme amylase, reflux of stomach content to the throat, delayed emptying of the stomach.
- Dermatitis, burning sensation when exposed to the sun.
- 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 the chest, nervousness or abnormal feeling, increase of the enzyme lactate dehydrogenase in the blood, weight loss.

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

- Mild bleeding of the skin due to blood clots.
- Increased muscle stiffness.
- Deafness.
- Collection of fluid around the heart.
- Acute shortness of breath.
- Cyst formation in the pancreas.
- Problems with blood flow in the liver.
- Excessive hairiness.
- Thirst, tendency to fall, feeling of tightness in the 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 duct.
- Painful urination with blood in the urine.
- Increase in fat tissue.

If a side effect occurs, if one of the side effects worsens, 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 "Report Side Effects of 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 Padagis via the following address:
padagis.co.il

5. HOW TO STORE THE MEDICINE?

- Avoid poisoning! This medicine and any other medicine should be kept in a safe 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 wrapping and blister. The expiry date refers to the last day of that month.
- Store below 25°C.
- After opening the aluminum wrapping 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. FURTHER INFORMATION:

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

Tacrocel 0.5 mg capsules

Lactose monohydrate, gelatin, titanium dioxide, magnesium stearate, croscarmellose sodium, hypromellose, yellow iron oxide, sodium lauryl sulfate, sorbitan monolaurate.

Tacrocel 1 mg capsules

Lactose monohydrate, gelatin, titanium dioxide, croscarmellose sodium, hypromellose, magnesium stearate, yellow iron oxide, sodium lauryl sulfate, sorbitan monolaurate, red iron oxide, black iron oxide.

Tacrocel 5 mg capsules

Lactose monohydrate, gelatin, croscarmellose sodium, hypromellose, magnesium stearate, titanium dioxide, red iron oxide, sodium lauryl sulfate, sorbitan monolaurate.

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 trays (blisters) within a sealed aluminum wrapping. Each blister tray contains 10 capsules.

Package content: Tacrocel 0.5 mg – 50 capsules, Tacrocel 1 mg – 100 capsules, Tacrocel 5 mg – 50 capsules.

Not all package sizes may be marketed.

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

Registration holder: Padagis Israel Agencies Ltd., 1 Rakefet St., Shoham.

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

Revised in March 2023 according to MOH guidelines.

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

Tacrocel 0.5 mg: 14854.33452
Tacrocel 1 mg: 14855.33453
Tacrocel 5 mg: 14856.33455