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

The medicine is dispensed with a doctor's prescription only

Acrolimus PR 0.5 mg Extended release capsules

Composition:
Each capsule contains:
Tacrolimus (as monohydrate) 0.5 mg

Acrolimus PR 1 mg Extended release capsules

Composition:
Each capsule contains:
Tacrolimus (as monohydrate) 1 mg

Acrolimus PR 3 mg Extended release capsules

Composition:
Each capsule contains:
Tacrolimus (as monohydrate) 3 mg

Acrolimus PR 5 mg Extended release capsules

Composition:
Each capsule contains:
Tacrolimus (as monohydrate) 5 mg

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

Read the entire leaflet carefully before using the medicine. This leaflet contains concise information about the medicine. If you have additional questions, refer to the doctor or the 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.

The medicine is not intended for children and adolescents under the age of 18.

1. WHAT IS THE MEDICINE INTENDED FOR?

Prevention of transplant rejection after kidney or liver transplant.

Treatment of transplant rejection, after kidney or liver transplant, when there is resistance to other immunosuppressive medicines.

Therapeutic class: Immunosuppressants.

2. BEFORE USING THE MEDICINE

Do not use this medicine if:
- You are sensitive (allergic) to tacrolimus or to any of the other ingredients this medicine contains (see section 6 – "Additional information").
- You are sensitive (allergic) to sirolimus or to macrolide antibiotics (such as erythromycin, clarithromycin, josamycin).

Special warnings regarding the use of the medicine

Some tacrolimus medicines for immediate release and for sustained release contain the same active ingredient, tacrolimus. Acrolimus PR capsules are sustained release capsules and are taken once a day, while immediate release capsules are taken twice a day. This is because Acrolimus PR capsules allow administration of tacrolimus by extended release (a slower release over a longer period of time). Acrolimus PR sustained release capsules are not interchangeable with immediate release tacrolimus.

You must notify the doctor or the pharmacist in the following cases:
- If you are taking any of the medicines listed in the subsection "Drug interactions".
- If you suffer or have suffered in the past from liver problems.
- If you suffer from diarrhea for longer than one day.
- If you suffer from severe abdominal pain, whether or not accompanied by other symptoms such as chills, fever, nausea or vomiting.
- If you have changes in the electrical activity of the heart, a condition called "QT prolongation".
- If you have damage or have had damage caused to the smallest blood vessels, known as thrombosis in small blood vessels (thrombotic microangiopathy) / thrombotic thrombocytopenic purpura / haemolytic uraemic syndrome. Inform 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, decreased urination, loss of vision and convulsions (see section 4 - "Side effects"). When tacrolimus is taken together with sirolimus or everolimus, the risk of developing these symptoms may increase.

Avoid taking any herbal preparation such as Hypericum – 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 Acrolimus PR that you need to receive. If in doubt, please refer to your doctor prior to taking any herbal products or remedies.

The doctor may need to change the dosage of Acrolimus PR.

Avoid exposure to the sun or to UV light (ultraviolet light) while taking Acrolimus PR, because immunosuppressive preparations may increase the risk of skin cancer. Wear appropriate clothing that provide protection from the sun and use a sunscreen with a high protection factor.

Treatment precautions:

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, wash the skin and eyes.

Children and adolescents

The medicine is not intended for children and adolescents under the age of 18.

Tests and follow-up

You should keep in regular contact with your doctor. Occasionally your doctor will need to carry out urine, blood, heart or eye tests, in order to determine the appropriate dosage of Acrolimus PR (see section 3 – "How should you use the medicine?").

Drug interactions

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

It is not recommended to take Acrolimus PR concomitantly with ciclosporin (another medicine intended for the prevention of transplanted organ rejection).

At every visit to a doctor who is not your transplant specialist, tell the doctor that you are taking tacrolimus. The doctor may need to consult your transplant specialist if you need to use another medicine that may increase or decrease tacrolimus blood levels.

The medicine's blood levels may be affected by other medicines that you are taking, and Acrolimus PR may affect the blood levels of other medicines that you are taking, which may lead to an interruption, an increase or a decrease in the dosage of Acrolimus PR. Some patients have experienced an increase of tacrolimus blood levels while taking other medicines. An increase in tacrolimus blood levels may cause serious side effects, such as kidney problems, problems in the nervous system and heart rhythm disturbances (see section 4 – "Side effects").

The effect on the medicine's blood levels may happen a very short time after starting the use of another medicine, therefore frequent monitoring of tacrolimus blood levels may be needed during the first days of starting another medicine and often during the treatment with the other medicine. There are other medicines that may cause a decrease in tacrolimus blood levels, which may increase the risk of rejection of the transplanted organ.

Inform the doctor or pharmacist if you are taking:
- Medicines for treatment of fungal infections such as ketoconazole, fluconazole, itraconazole, posaconazole, voriconazole, clotrimazole, isavuconazole, miconazole and caspofungin.
- Antibiotics for treatment of infections, especially from the macrolides group, such as telithromycin, erythromycin, clarithromycin, josamycin, azithromycin, rifampicin, rifabutin, isoniazid and flucloxacillin.
- Letermovir, used for prevention of illness caused by cytomegalovirus (CMV).
- HIV protease inhibitors (such as ritonavir, nelfinavir, saquinavir), the supporting medicine cobicistat, tablets for combination therapy, or non-nucleoside reverse transcriptase inhibitors (efavirenz, etravirine, nevirapine) used for the treatment of HIV infection.
- HCV protease inhibitors (such as telaprevir, boceprevir, the combination therapy ombitasvir/paritaprevir/ritonavir with or without dasabuvir, elbasvir/grazoprevir, and glecaprevir/pibrentasvir) used for the treatment of viral hepatitis type C.
- Nilotinib and imatinib, idelalisib, ceritinib, crizotinib, apalutamide, enzalutamide or mitotane (used for treatment of certain types of cancer).
- Mycophenolic acid, used for immunosuppression to prevent transplant rejection.
- Medicines to treat gastric ulcer and gastroesophageal reflux (such as omeprazole, lansoprazole or cimetidine).
- Medicines to treat nausea and vomiting (such as metoclopramide).
- Cisapride or magnesium-aluminum-hydroxide antacids used for the treatment of heartburn.
- Oral contraceptives or other hormonal treatments containing ethinylestradiol, hormonal treatments with danazol.
- Medicines used for treatment of high blood pressure or heart problems (such as nifedipine, nicardipine, diltiazem and verapamil).
- Medicines for treatment of heart rhythm problems (irregular heart rhythm) such as amiodarone.
- Medicines known as "statins" and used for treatment of high levels of cholesterol and triglycerides.
- Carbamazepine, phenytoin or phenobarbital which are used for treatment of epilepsy.
- Metamizole, used for treatment of fever and pain.
- Prednisolone and methylprednisolone which belong to the group of corticosteroids that are used for the treatment of inflammations or as immunosuppressants (e.g. to prevent transplant rejection).
- Nefazodone for treatment of depression.
- Herbal preparations that contain Hypericum – St. John's wort *(Hypericum perforatum)* or *Schisandra sphenanthera* extracts.
- Cannabidiol (used for treatment of seizures, among other things).

Tell your doctor if you are receiving treatment for hepatitis C (liver infection). The medical treatment for hepatitis C may change your liver function and may affect tacrolimus blood levels. Tacrolimus blood levels may decrease or increase depending on the medicines prescribed for treatment of hepatitis C. Your doctor may need to closely monitor your tacrolimus blood levels and make necessary adjustments to the dosage of Acrolimus PR after you start the treatment for hepatitis C.

Inform the doctor if you are taking or need to take ibuprofen (for treatment of fever, inflammation and pain), antibiotics (cotrimoxazole, vancomycin, aminoglycoside antibiotics such as gentamicin), amphotericin B (for treatment of fungal infections) or antiviral medicines (for treatment of viral infections, such as acyclovir, ganciclovir, cidofovir and foscarnet), because they may worsen problems in the kidneys or in the nervous system when taken together with Acrolimus PR.

Inform your 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, haemolytic uraemic syndrome may increase (see section 4 - "Side effects").

The doctor also needs to know if while taking Acrolimus PR you are concomitantly taking potassium supplements or specific diuretics for treatment of heart failure, high blood pressure and kidney diseases (such as amiloride, triamterene or spironolactone), or the antibiotics trimethoprim or cotrimoxazole which may increase potassium blood levels, nonsteroidal anti-inflammatory medicines (NSAIDs, such as ibuprofen) which are used for treatment of fever, inflammation and pain, anticoagulants (blood thinners) or oral medicines for treatment of diabetes.

If you are in need of any vaccines, tell your doctor before taking the vaccine.

Use of the medicine and food

You should avoid eating grapefruit or drinking grapefruit juice during treatment with Acrolimus PR, because it may affect the medicine blood levels.

Use of the medicine and alcohol consumption

Consuming alcohol while taking the medicine may increase the side effects of drowsiness, dizziness and blurry vision.

Pregnancy and breastfeeding

If you are pregnant, think you may be pregnant or are planning to become pregnant, consult the doctor before taking Acrolimus PR.

Tacrolimus passes into breastmilk, therefore do not breastfeed while taking Acrolimus PR.

Driving and operating machinery

Do not drive or use tools and machinery if you are feeling dizzy or drowsy or if you cannot see clearly after taking Acrolimus PR. The frequency of these effects increases if you also consume alcohol.

Important information about some of the ingredients of the medicine
- Acrolimus PR contains lactose. If you have been told by your doctor that you have an intolerance (sensitivity) to some sugars, consult with your doctor before taking this medicine.
- Acrolimus PR 5 mg capsules contain the coloring agent Ponceau 4R, which may cause allergic reactions.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the medicine according to the doctor's instructions.

Check with the doctor or pharmacist if you are uncertain about the dosage and how to use the medicine.

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

Take this medicine once a day.
- You should make sure that you receive the same tacrolimus preparation every time you get the medicine dispensed, unless the transplant specialist has agreed to change to another tacrolimus preparation. If the shape of the medicine is different than usual or if the instructions for use have changed, consult the doctor or pharmacist as soon as possible in order to make sure that you have received the correct medicine.
- The starting dose to prevent the rejection of the transplanted organ will be calculated by the doctor, according to your body weight. The starting dose after transplantation is usually 0.1-0.3 mg per kg body weight per day, depending on the transplanted organ. The dosage intended for the treatment of transplant rejection is the same.
- The dosage you receive depends on your general condition and on the type of additional immunosuppressive medications you are taking.
- You should take Acrolimus PR daily, as long as you need immunosuppressive treatment to prevent transplant rejection. You must be in constant contact with your doctor.

After starting treatment with Acrolimus PR, the doctor will perform frequent blood tests in order to determine the correct dosage. Afterwards, blood tests will be required periodically in order to determine the correct dosage and to adjust the dosage from time to time. Usually, the doctor will reduce the dosage of Acrolimus PR once your condition has stabilized.

Do not exceed the recommended dose.

Method of use
- You should take the medicine once a day, in the morning.
- Acrolimus PR should be taken on an empty stomach or 2-3 hours after a meal. You should wait at least one hour from taking the medicine until the next meal.
- Take the capsules immediately following removal from the blister.
- Do not chew or crush the capsules.
- The capsules should be swallowed whole with a glass of water.
- Do not swallow the desiccant included in the package.

If you accidentally took a higher dosage

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

If you forgot to take the medicine

If you have forgotten to take this medicine in the morning, take a dose as soon as you remember, on the same day. Never take two doses together on the following morning! Follow the treatment as recommended by the doctor.

Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the doctor. Do not stop taking the medicine without an instruction from the doctor.

If you stop taking the medicine

Stopping the medicine may increase the risk of transplant rejection. Do not stop taking the medicine without an instruction from the doctor.

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

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

4. SIDE EFFECTS

As with any medicine, using Acrolimus PR may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not experience any of them. Acrolimus PR suppresses the activity of the immune system, so you may develop infections more easily while taking Acrolimus PR.

Certain 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 any signs of infection, which include:
- Fever, cough, sore throat, weakness or general malaise.
- Memory loss, trouble thinking, difficulty walking or loss of vision – these may be due to a very rare, serious brain infection, which can be fatal (progressive multifocal leukoencephalopathy or PML).

Severe side effects may occur, including allergic reactions and anaphylaxis. Benign and malignant tumors have been reported after taking Acrolimus PR.

Refer to the doctor immediately if you experience or suspect you may be experiencing any of the following severe side effects:

Common severe side effects (may affect up to 1 in 10 people):
- Gastrointestinal perforation: manifested by strong abdominal pain which may or may not be accompanied by other symptoms, such as chills, fever, nausea or vomiting.
- Impaired function of the transplanted organ.
- Blurred vision.

Uncommon severe side effects (may affect up to 1 in 100 people):
- Thrombosis in small blood vessels (thrombotic microangiopathy, damage to the smallest blood vessels) including haemolytic uraemic syndrome, which is manifested by the following symptoms: low or no urine output (acute renal failure), extreme fatigue, yellowing of the skin or eyes (jaundice) and abnormal bruising or bleeding and signs of infection.

Rare severe side effects (may affect up to 1 in 1,000 people):
- Thrombotic thrombocytopenic purpura – a condition manifested by fever and bruises under the skin which may appear as small red dots, with or without extreme and unexplained tiredness, confusion, yellowing of the skin or eyes (jaundice), with symptoms of acute renal failure (low or no urine output), loss of vision and convulsions.
- A skin syndrome called toxic epidermal necrolysis: erosion and blisters on the skin or mucous membranes, red and swollen skin which may detach in large parts of the body.
- Blindness.

Very rare severe side effects (may affect up to 1 in 10,000 people):
- Stevens Johnson syndrome: unexplained and widespread skin pain, swelling in the face, a serious disease with blisters on the skin and in the mouth, eyes and genitals, hives (skin allergy), tongue swelling, red or purple skin rash that spreads through the skin, skin shedding.
- *Torsades de pointes* – type heart rate disturbances: changes in heart rate frequency which may or may not be accompanied by symptoms such as chest pain (angina pectoris), fainting, vertigo or nausea, a sensation of heart pounding (palpitations) and difficulty breathing.

Severe side effects with unknown frequency (side effects whose frequency cannot be estimated from the available data):
- Opportunistic infections (bacterial, fungal, viral or parasitic): prolonged diarrhea, fever and sore throat.
- Cases of benign and malignant tumors resulting from immunosuppression have been reported.
- There have been reports of cases of pure red cell aplasia (a very severe decline in red blood cell count), hemolytic anemia (a decline in red blood cell count as a result of abnormal breakdown accompanied by tiredness) and neutropenic fever (a decrease in the type of white blood cells that fight infections, accompanied by fever). The exact frequency of these side effects is unknown. You may not experience any symptoms at all, or depending on the severity of your condition, you may experience: tiredness, apathy, abnormal pallor of the skin, shortness of breath, dizziness, headache, chest pain and cold sensation in the hands and feet.
- Cases of agranulocytosis (a severe decline in white blood cell count, accompanied by mouth ulcers, fever and infections). You may not have any symptoms at all, or you may have a 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 swallowing or breathing) and you may feel on the verge of fainting.
- Posterior reversible encephalopathy syndrome (PRES): manifested by headaches, confusion, mood swings, convulsions and visual disorders. These may be signs of posterior reversible encephalopathy syndrome which has been reported in a number of patients treated with tacrolimus.
- Optic neuropathy (damage to the optic nerve): vision problems such as blurry vision, changes in color vision, difficulty seeing details or restriction in your visual field.

Additional side effects:

The following side effects may also occur after taking Acrolimus PR and may be severe:

Very common side effects (may affect more than 1 in 10 people):
- Increased blood sugar levels, diabetes, increased levels of potassium in the blood
- Sleeping difficulties
- Tremors, headaches
- Rise in blood pressure
- Abnormal liver function test results
- Diarrhea, nausea
- Kidney function problems

Common side effects (may affect up to 1 in 10 people):
- Decrease in all blood cell counts (platelets, red or white blood cells), increase in white blood cell count, changes in red blood cell count (seen in blood tests)
- Decrease in blood levels of magnesium, phosphate, potassium, calcium or sodium, fluid overload, increased level of uric acid or lipids in the blood, decreased appetite, increased acidity of the blood, other changes in blood salts (seen in blood tests)
- Symptoms of anxiety, confusion and disorientation, depression, mood swings, nightmares, hallucinations, 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 disturbances
- Ringing in the ears (tinnitus)
- Reduced blood flow in the heart's blood vessels, accelerated heartbeats
- Bleeding, partial or complete blocking of blood vessels, drop in blood pressure
- Shortness of breath, changes in lung tissue, collection of fluids around the lungs, 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, collection of fluids in the abdomen, vomiting, abdominal pain, digestive difficulties, constipation, flatulence, bloating, loose stools, stomach problems
- Damage to the bile ducts, yellowing of the skin due to liver problems, liver tissue damage and inflammation of the liver
- Itch, rash, hair loss, acne, excessive sweating
- Pain in the joints, limbs, back and feet, muscle cramps
- Decreased kidney function, reduced production of urine, impaired or painful urination
- General weakness, fever, collection of fluids in your body, pain and discomfort, increase in the levels of the enzyme alkaline phosphatase (ALKP) in the blood, weight gain, sensation of disturbance in body temperature

Uncommon side effects (may affect up to 1 in 100 people):
- Changes in blood clotting, reduction in all blood cell counts (seen in blood tests)
- Dehydration
- Reduction in blood protein or sugar, increase in blood phosphate
- Coma, cerebral bleeding, stroke, paralysis, brain function disorders, speech and language impairments, memory problems
- Clouding of the eye lens
- Impaired hearing
- Irregular heartbeat, cardiac arrest, reduced heart performance, impaired function of the heart muscle, enlargement of the heart muscle, stronger heartbeat, abnormal ECG, abnormal heart rate and pulse
- Blood clot in a limb vein, shock
- Breathing difficulties, respiratory tract impairment, asthma
- Intestinal obstruction, increased blood level of the enzyme amylase, gastroesophageal reflux, delayed emptying of the stomach
- Skin inflammations, burning sensation when exposed to the sun
- Joint impairment
- Inability to urinate, painful menstruation and abnormal menstrual bleeding
- Multi-system failure, a flu-like illness, increased sensitivity to heat and cold, feeling of tightness in your chest, increased blood level of the enzyme lactate dehydrogenase, stress or abnormal feeling, weight loss

Rare side effects (may affect up to 1 in 1,000 people):
- Small bleedings in your skin due to blood clots
- Increased muscle stiffness
- Deafness
- Fluid accumulation around the heart
- Severe shortness of breath
- Formation of cysts in the pancreas
- Problems with blood flow in the liver
- A serious disease with blisters on the skin and in the mouth, eyes and genitals; excessive hairiness
- Thirst, falling, feeling of tightness in your chest, decreased mobility, an ulcer

Very rare side effects (may affect up to 1 in 10,000 people):
- Muscle weakness
- Abnormal myocardial perfusion
- Liver failure
- Painful urination accompanied by blood in the urine
- Increase in fat tissue

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

Reporting side effects

Side effects may be reported to the Ministry of Health by clicking on the link "Report side effects due to medicinal treatment" found on the Ministry of Health website homepage (www.health.gov.il), which will direct you to the online form for reporting side effects, or by clicking on the following link: https://sideeffects.health.gov.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 to avoid poisoning.
- Do not induce vomiting without an explicit instruction from the doctor.
- Do not use the medicine after the expiry date (Exp. date) appearing on the package/ label. The expiry date refers to the last day of that month.
- **Store below 25°C, in the original package, to protect from light and moisture.**
- The medicine should be used within one year after first opening the aluminum wrapping, but no later than the expiry date.

Note: The aluminum wrapping contains desiccants. Do not swallow! The desiccants should be left inside the package!

6. ADDITIONAL INFORMATION

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

Lactose monohydrate, magnesium stearate, ethylcellulose, hypromellose, gelatin, titanium dioxide, yellow iron oxide, red iron oxide, shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide, potassium hydroxide.

Present only in 5 mg: ponceau 4R, black iron oxide.

What does the medicine look like and what are the contents of the package?

Acrolimus PR 0.5 mg: light yellow and light orange capsules imprinted with "TR" and "0.5mg".

Acrolimus PR 1 mg: white and light orange capsules imprinted with "TR" and "1mg".

Acrolimus PR 3 mg: light orange capsules imprinted with "TR" and "3mg".

Acrolimus PR 5 mg: greyish red and light orange capsules imprinted with "TR" and "5mg".

The packages contain 30, 50 or 100 capsules. Not all package sizes may be marketed.

Name and address of the manufacturer and marketing authorization holder

Teva Israel Ltd.,
124 Dvora HaNevi'a St., Tel Aviv 6944020.

The leaflet was revised in January 2023 in accordance with the Ministry of Health guidelines.

Registration numbers of the medicines in the National Drug Registry of the Ministry of Health

Acrolimus PR 0.5 mg:	170.08.37001
Acrolimus PR 1 mg:	170.09.37002
Acrolimus PR 3 mg:	170.10.37003
Acrolimus PR 5 mg:	170.11.37004

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