PROGRAF®

Tacrolimus (0.5 mg, 1 mg, 5 mg)

What is in this leaflet

What *Prograf* is used for

Following your organ transplant (liver, kidney), Prograf is used to control your body's immune response enabling your body to accept the transplanted organ. You may also be given Prograf for an ongoing rejection of your transplanted liver or kidney when any previous treatment you were taking was unable to control this immune response after your transplantation, or for lupus nephritis where the effect of steroids is insufficient or administration of steroids is difficult because of their adverse reactions.

How *Prograf* works

Prograf contains an active ingredient called tacrolimus. It belongs to a group of medicines called immunosuppressants. Prograf reduces your body's own defence mechanism to stop you rejecting your transplanted organ.

Before you use *Prograf*

- *When you must not use it*
- If you are allergic (hypersensitive) to tacrolimus or any of the other ingredients of Prograf.
- If you are allergic (hypersensitive) to macrolide antibiotics (e.g. *erythromycin, clarithromycin, josamycin).*

Pregnancy and lactation

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. One study assessed pregnancy outcomes in women treated with tacrolimus and those treated with other immunosuppressants. While there was insufficient evidence in this study to draw conclusions, higher rates of miscarriage were reported among liver and kidney transplant patients treated with tacrolimus, as well as higher rates among kidney transplant patients of persistent hypertension associated with protein loss in the urine that develops during pregnancy or the postpartum period (a condition called pre-eclampsia). No increased risk of major birth defects associated with Prograf use was found. Prograf is excreted into breast milk. Therefore, you should not breast-feed whilst receiving Prograf.

Prograf contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking Prograf.

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

The printing ink used on Prograf capsules 0.5 mg and 1 mg contains soya lecithin.
If you are allergic to peanut or soya, talk to your doctor to determine whether you should use this medicine.

- *Before you start to use it*

Talk to your doctor or pharmacist before taking Prograf:

- If you have liver problems or have had a disease which may have affected your liver, please tell your doctor as this may affect the dose of Prograf that you receive.
- If you have strong abdominal pain accompanied or not with other symptoms, such as chills, fever, nausea or vomiting.
- If you have an alteration of the electrical activity of your heart called QT prolongation.
- If you have diarrhoea for more than one day, please tell your doctor, because it might be necessary to adapt the dose of Prograf that you receive.

Precaution for handling:

Direct contact with any part of your body like your skin or eyes, or breathing in of injection solutions, powder or granules contained in tacrolimus products should be avoided during preparation. If such contact occurs, wash the skin and eyes.

- *Taking other medicines*

Tell your doctor if you are taking any other medicines, including any that you buy without a prescription from a pharmacy, supermarket or health food shop.

Prograf must not be taken with ciclosporin.

If you need to attend 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 should use another medicine that could increase or decrease your tacrolimus blood level.

Other medicines you take can affect Prograf blood levels, and Prograf can affect blood levels of other medicines, which may require interruption, an increase or a decrease in Prograf dose.

As increased tacrolimus blood levels could lead to serious side effects (see **Side effects**), frequent continued monitoring of your Prograf blood level may be needed within the first few days of starting another medicine and during treatment with the other medicine. Some other medicines may cause tacrolimus blood levels to decrease, which could increase the risk of rejecting the transplanted organ.

Tell your doctor if you are taking or have recently taken medicines with active substances like:

- antifungal medicines and antibiotics, used to treat infections e.g. ketoconazole, fluconazole, itraconazole, posaconazole, voriconazole, clotrimazole, isavuconazole, miconazole, caspofungin, telithromycin, erythromycin, clarithromycin, josamycin, azithromycin, rifampicin, rifabutin, and isoniazid
- HCV protease inhibitors (e.g. telaprevir, boceprevir), used to treat hepatitis C infection

- antiemetics, used to treat nausea and vomiting (e.g. metoclopramide)
- magnesium-aluminium-hydroxide (antacid), used to treat heartburn
- HIV protease inhibitors (e.g. ritonavir, nelfinavir, saquinavir), the booster medicine cobicistat, and combination tablets, or HIV non-nucleoside reverse transcriptase inhibitors (efavirenz, etravirine, nevirapine), used to treat HIV infection
- HCV protease inhibitors (e.g. telaprevir, boceprevir, the combination ombitasvir/paritaprevir/ritonavir with or without dasabuvir, elbasvir/grazoprevir, and glecaprevir/pibrentasvir), used to treat hepatitis C infection
- nilotinib and imatinib, idelalisib, ceritinib, crizotinib, apalutamide, enzalutamide, or mitotane (used to treat certain cancers)
- mycophenolic acid, used to suppress the immune system to prevent transplant rejection
- medicines for stomach ulcer and acid reflux (e.g. omeprazole, lansoprazole or cimetidine)
- antiemetics, used to treat nausea and vomiting (e.g. metoclopramide)
- magnesium-aluminium-hydroxide (antacid), used to treat heartburn
- hormone treatments with ethinylestradiol (e.g. the oral contraceptive pill) or danazol
- medicines for high blood pressure or heart problems such as nifedipine, nicardipine, diltiazem and verapamil
- anti-arrhythmic medicines (amiodarone) used to control arrhythmia (uneven beating of the heart)
- medicines known as "statins" used to treat elevated cholesterol and triglycerides
- the anti-epileptic medicines carbamazepine, phenytoin or phenobarbital
- metamizole, used to treat pain and fever
- the corticosteroids (e.g. prednisolone and methylprednisolone)
- the anti-depressant nefazodone
- herbal preparations containing St. John's wort (*Hypericum perforatum*) or extracts of *Schisandra sphenanthera*
- cannabidiol (uses amongst others include treatment of seizures).

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

Tell your doctor if you are taking or need to take ibuprofen, amphotericin B, antibiotics (cotrimoxazole, vancomycin, or so-called aminoglycoside antibiotics such as gentamicin), or antivirals (e.g. acyclovir, ganciclovir, cidofovir, or foscarnet). These may worsen kidney or nervous system problems when taken together with Prograf.

Your doctor also needs to know if you are taking potassium supplements or potassium-sparing diuretics (e.g. amiloride, triamterene, or spironolactone), certain pain killers (so-called NSAIDs, e.g. ibuprofen), anticoagulants, or oral medication for diabetic treatment, while you take Prograf.

Food and drink
Grapefruit and grapefruit juice should be avoided while using Prograf.

How to use *Prograf*
-*How much to use*
Follow all directions given to you by your doctor and pharmacist carefully. They may differ from the information contained in this leaflet. If you do not understand the instructions on the label, ask your doctor or pharmacist for help. Make sure that you receive the same tacrolimus medicine every time you collect your prescription, unless your transplant specialist has agreed to change to a different tacrolimus medicine.

Initial oral doses just after transplantation will generally be in the range of 0.1 – 0.3 mg per kg body weight per day, depending on the transplanted organ.

For lupus nephritis, a dose of 3mg is orally administered, once daily after supper.

Your 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 the dose from time to time. Your doctor will usually reduce your Prograf dose once your condition has stabilised. Your doctor will tell you exactly how many capsules to take and how often. Prograf capsule is taken orally twice daily, usually in the morning and evening. You should generally take Prograf on an empty stomach or at least 1 hour before or 2 to 3 hours after the meal. The capsules should be swallowed whole with a glass of water.

-*When to use it*
Use as directed by your doctor or pharmacist.

-*How long to use it*
Take *Prograf* for time period set by your doctor.

- *If you forget to use it*
Consult your doctor or pharmacist on what you should do if you forget to use it.
Take the missed dose as soon as you remember. If it is almost time for your next dose, wait until then to take the medicine and skip the missed dose. Do not take a double dose to make up for the missed dose.

-*If you use too much (overdose)*
Contact your doctor immediately or go to the Emergency Department of your nearest hospital, if you think you or anyone else may have taken too much of this medicine. Do this even if there are no signs of discomfort or poisoning. You may need urgent medical attention.

Taking too many tablets may cause tremor, headache, nausea and vomiting, infections, hives, lethargy, increase in blood levels of urea and creatinine (urea and creatinine are waste products of the body), and increase in alanine

aminotransferase levels which is related to liver damage.

While you are using it

-*Things you must do*

- Tell all the doctors, dentists and pharmacists treating you that you are taking Prograf.
- Tell your doctor immediately if you become pregnant while taking this medication.
- Attend all the appointments given to you as your doctor may carry out a number of tests from time to time. This is important and will help your doctor to decide on the most appropriate dose of Prograf for you.
- Limit your exposure to sunlight and UV light whilst taking Prograf 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.
- If you need to have any vaccinations, please inform your doctor beforehand. Your doctor will advise you on the best course of action.
- Patients treated with Prograf have been reported to have an increased risk of developing lymphoproliferative disorders and other malignancies, including skin cancers and Kaposi's sarcoma. Ask your doctor for specific advice on these disorders.
- If you have or have had damage to the smallest blood vessels, known as thrombotic microangiopathy/thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome. Tell your 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. When tacrolimus is taken together with sirolimus or everolimus, the risk of developing these symptoms may increase.

-*Things you must not do*

- Do not stop taking the medicine unless advised by your doctor. Stopping your treatment with Prograf may increase the risk of rejection of your transplanted organ.
- Do not take any new medicines without consulting your doctor.
- Do not give Prograf to anyone else, even if they have the same symptoms or condition as you.

-*Things to be careful of*

Driving and using machines

Do not drive or use machines if you feel dizzy or sleepy, or have problems seeing clearly after taking Prograf.

The effects are more frequent if you also drink alcohol.

Side effects

Like all medicines, Prograf can cause side effects, although not everybody gets them.
Visit your doctor or pharmacist immediately if you experience any side effects after taking this medicine.

Since Prograf reduces your body's defense mechanism to stop you rejecting your transplanted organ, you may be more prone to infections while taking Prograf.

Some infections could be serious or fatal and may include infections caused by bacteria, viruses, fungi, parasites, or other infections.

Tell your 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 people):

- Gastrointestinal perforation: strong abdominal pain accompanied or not with other symptoms, such as chills, fever, nausea or vomiting;
  Insufficient function of your transplanted organ;
- Blurred vision.

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

- Thrombotic microangiopathy (damage to the smallest blood vessels) including haemolytic uraemic syndrome, a condition with 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.

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

- Thrombotic Thrombocytopenic Purpura: a condition involving damage to the smallest blood vessels and characterised by fever and 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 can detach in large parts of the body;
- Blindness.

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

- 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*: change in the heart frequency that can be accompanied or not of symptoms, such as chest pain (angina), faint, vertigo or nausea, palpitations (feeling the heartbeat) and difficulty breathing.

Serious side effects – frequency not known:

- Opportunistic infections (bacterial, fungal, viral and protozoal): prolonged diarrhea, fever and sore throat; Benign and malignant tumours including malignant skin cancers and a rare type of cancer that may include skin lesions known as Kaposi's sarcoma. Symptoms include skin changes such as new or changing discoloration, lesions or lumps; Pure red cell aplasia (a very severe reduction in red blood cell counts), haemolytic anaemia (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 by fever). 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 coldness in hands and feet; Agranulocytosis (a severely lowered number of white blood cells accompanied with ulcers in the mouth, fever and infection(s)). You may have no symptoms or you may feel sudden fever, rigors and sore throat; Allergic and anaphylactic reactions with the following symptoms: a sudden itchy rash (hives), swelling of hands, feet, ankle, 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): headache, confusion, mood changes, fits, and disturbances of your vision. These could be signs of a disorder known as PRES, which has been reported in some patients treated with tacrolimus; Optic neuropathy (abnormality of the optic nerve): problems with your vision such as blurred vision, changes in colour vision, difficulty in seeing detail or restriction of your field of vision.

Very common side effects (may affect more than 1 in 10 people):
- Increased blood sugar, diabetes mellitus, increased potassium in the blood; Difficulty in sleeping; Trembling, headache; Liver function tests abnormal; Increased blood pressure; Diarrhoea, nausea; Kidney problems.

Common side effects (may affect up to 1 in 10 people):
- Reduction in blood cell counts (platelets, red or white blood cells), increase in white blood cell counts, changes in red blood cell counts (seen in blood tests); 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, nightmare, hallucination, mental disorders; Fits, 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; 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 in 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 diarrhoea, bleedings in the stomach, inflammations or ulcers in the mouth, collection of fluid in the belly, vomiting, abdominal pains, indigestion, constipation, flatulence, bloating, loose stools, stomach problems; Yellowing of the skin due to liver problems, liver tissue damage and inflammation of the liver; Itching, rash, hair loss, acne, increased sweating; Pain in joints, limbs or back, muscle cramps; Insufficient function of the kidneys, 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, feeling of temperature disturbed; Insufficient function of your transplanted organ.

Uncommon side effects (may affect up to 1 in 100 people):
- 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; Opacity of the lens; Impaired hearing; Irregular heartbeat, stop of heartbeat, reduced performance of your heart, disorder of the heart muscle, enlargement of the heart muscle, stronger heartbeat, abnormal ECG, heart rate and pulse abnormal; 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 throat, 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 on your chest, jittery 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 people):
- Small bleedings in your skin due to blood clots; Increased muscle stiffness; Deafness; Collection of fluid around the heart; Acute breathlessness; Cyst formation in your pancreas; Problems with blood flow in the liver; Increased hairiness; Thirst, fall, feeling of tightness in your chest, decreased mobility, ulcer.

Very rare side effects (may affect up to 1 in 10,000 people):
- Muscular weakness; Echocardiogram abnormal; Liver failure, narrowing of the bile vessel; Painful urination with blood in the urine; Increase of fat tissue.

You may report any side effects or adverse drug reactions directly to the National Centre for Adverse Drug Reaction Monitoring by visiting the website npra.gov.my
[Consumers → Reporting Side Effects to Medicines (ConSERF) or Vaccines (AEFI)]

Storage and Disposal of *Prograf*

Storage

Keep out of the reach and sight of children.
Prograf Capsules 0.5 mg, 1 mg and 5 mg:
Store below 30°C in a dry place.

After opening of the aluminium

wrapper, the capsules are stable for 3 months.

Disposal
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Product Description
What it looks like
Prograf Capsules 0.5 mg, 1 mg and 5 mg. Ten capsules per blister sheet.

- *Ingredients*

Active ingredient
Prograf Capsule 0.5 mg contains 0.5 mg of tacrolimus
Prograf Capsule 1 mg contains 1 mg of tacrolimus
Prograf Capsule 5 mg contains 5 mg of tacrolimus

Inactive ingredients
Prograf 0.5 mg hard capsules:
- Capsule content: Hypromellose, croscarmellose sodium, lactose monohydrate, magnesium stearate.
- Capsule shell: Titanium dioxide (E 171), yellow iron oxide (E 172), gelatine.
- Printing ink of capsule shell: Shellac, lecithin (soya), hydroxypropyl cellulose, simeticone, red iron oxide (E 172).

Prograf 1 mg hard capsules:
- Capsule content: Hypromellose, croscarmellose sodium, lactose monohydrate, magnesium stearate.
- Capsule shell: Titanium dioxide (E 171), gelatine.
- Printing ink of capsule shell: Shellac, lecithin (soya), hydroxypropyl cellulose, simeticone, red iron oxide (E 172).

Prograf 5 mg hard capsules:
- Capsule content: Hypromellose, croscarmellose sodium, lactose monohydrate, magnesium stearate.
- Capsule shell: Titanium dioxide (E 171), red iron oxide (E 172), gelatine.
- Printing ink of capsule shell: Shellac, lecithin (soya), simeticone, titanium dioxide (E 171).

- *MAL number:*
- Prograf Capsule 0.5 mg MAL20031738AZ
- Prograf Capsule 1 mg MAL19990220AZ
- Prograf Capsule 5 mg MAL19990221AZ

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