Package leaflet: Information for the user

Prograf ® 0.5 mg hard capsules

tacrolimus

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Prograf is and what it is used for
2. What you need to know before you take Prograf
3. How to take Prograf
4. Possible side effects
5. How to store Prograf
6. Contents of the pack and other information

1. What Prograf is and what it is used for

Prograf belongs to a group of medicines called immunosuppressants. Following your organ transplant (e.g. liver, kidney, heart), your body's immune system will try to reject the new organ. Prograf is used to control your body's immune response enabling your body to accept the transplanted organ.
Prograf is often used in combination with other medicines that also suppress the immune system.

You may also be given Prograf for an ongoing rejection of your transplanted liver, kidney, heart or other organ or if any previous treatment you were taking was unable to control this immune response after your transplantation.

2. What you need to know before you take Prograf

Do not take Prograf
- If you are allergic (hypersensitive) to tacrolimus or any of the other ingredients of Prograf (listed in section 6).
- If you are allergic (hypersensitive) to any antibiotic belonging to the subgroup of macrolide antibiotics (e.g. erythromycin, clarithromycin, josamycin).

Warnings and precautions
Talk to your doctor or pharmacist before taking Prograf
- You will need to take Prograf every day as long as you need immunosuppression to prevent rejection of your transplanted organ. You should keep in regular contact with your doctor.
- Whilst you are taking Prograf your doctor may want to carry out a number of tests (including blood, urine, heart function, visual and neurological tests) from time to time. This is quite normal and will help your doctor to decide on the most appropriate dose of Prograf for you.
- Please avoid taking any herbal remedies, e.g. St. John's wort (*Hypericum perforatum*) or any other herbal products as this may affect the effectiveness and the dose of Prograf that you need to receive. If in doubt please consult your doctor prior to taking any herbal products or remedies.
- 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 feel strong abdominal pain accompanied or not with other symptoms, such as chills, fever, nausea or vomiting.
- 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.
- If you have an alteration of the electrical activity of your heart called "QT prolongation".
- 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 (see section 4). 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 (see section 4). When tacrolimus is taken together with sirolimus or everolimus, the risk of developing these symptoms may increase.

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.

Other medicines and Prograf
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription and herbal remedies.

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.

Prograf blood levels can be affected by other medicines you take, and blood levels of other medicines can be affected by taking Prograf which may require interruption, an increase or a decrease in Prograf dose.

Some patients have experienced increases in tacrolimus blood levels while taking other medicines.
This could lead to serious side effects, such as kidney problems, nervous system problems, and heart rhythm disturbances (see section 4).
An effect on the Prograf blood levels may occur very soon after starting the use of another medicine, therefore frequent continued monitoring of your Prograf 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 could 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 substances like:
- antifungal medicines and antibiotics, particularly so-called macrolide antibiotics, used to treat infections e.g. 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 (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 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.

Tell 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, and haemolytic uraemic syndrome may increase (see section 4).

Your doctor also needs to know if you are taking potassium supplements or potassium-sparing diuretics (e.g., amiloride, triamterene, or spironolactone), or the antibiotics trimethoprim or cotrimoxazole that may increase levels of potassium in your blood, certain pain killers (so-called NSAIDs, e.g. ibuprofen), anticoagulants, or oral medication for diabetic treatment, while you receive Prograf.

If you need to have any vaccinations, please inform your doctor beforehand.

Prograf with food and drink
You should generally take Prograf on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal. Grapefruit and grapefruit juice should be avoided while taking Prograf.

Pregnancy and breast-feeding
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 4 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.

Driving and using machines
Do not drive or use any tools or machines if you feel dizzy or sleepy, or have problems seeing clearly after taking Prograf. These effects are more frequently observed if Prograf is taken in conjunction with alcohol use.

Prograf contains lactose, sodium and lecithin (soya)
Prograf contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

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 contains soya lecithin. If you are allergic to peanut or soya, talk to your doctor to determine whether you should use this medicine.

3. How to take Prograf

Always take Prograf exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

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.
This medicine should be taken twice a day. If the appearance of this medicine is not the same as usual, or if dosage instructions have changed, speak to your doctor or pharmacist as soon as possible to make sure that you have the right medicine.

The starting dose to prevent the rejection of your transplanted organ will be determined by your doctor calculated according to your body weight. Initial doses just after transplantation will generally be in the range of 0.075 – 0.30 mg per kg body weight per day depending on the transplanted organ.

Your 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 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. Avoid grapefruit and grapefruit juice while taking Prograf. Do not swallow the desiccant contained in the foil wrapper.

If you take more Prograf than you should
If you have accidentally taken too much Prograf see your doctor or contact your nearest hospital emergency department immediately.

If you forget to take Prograf
Do not take a double dose to make up for forgotten individual doses.
If you have forgotten to take your Prograf capsules, wait until it is time for the next dose, and then continue as before.

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

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Prograf can cause side effects, although not everybody gets them.
Prograf reduces your body's own defense mechanism to stop you rejecting your transplanted organ. Consequently, your body will not be as good as usual at fighting infections. So if you are taking Prograf you may therefore catch more infections than usual such as infections of the skin, mouth, stomach and intestines, lungs and urinary tract.
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 get signs of an infection including:
- Fever, cough, sore throat, feeling weak or generally unwell
- 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 the ones listed below.

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 (frequency cannot be estimated from the available data):
- Opportunistic infections (bacterial, fungal, viral and protozoal): prolonged diarrhea, fever and sore throat.
- Benign and malignant tumours have been reported following treatment as a result of immunosuppression 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.
- Cases of 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) 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 coldness in hands and feet.
- Cases of 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 posterior reversible encephalopathy syndrome, 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.

The side effects listed below may also occur after receiving Prograf and could be serious:

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
- Increased blood pressure
- Liver function tests abnormal
- 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
- Changes in liver enzymes and function, 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, back and feet, muscle spasms
- 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

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

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, website: www.hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Prograf

Keep this medicine out of the sight and reach of children.
Hard capsules should be taken immediately following removal from the blister.
Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month. Use all the capsules within 1 year of opening the aluminium wrapping.
This medicinal product does not require any special temperature storage conditions.
Store in the original package in order to protect from moisture.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Prograf contains
Prograf 0.5 mg hard capsules
- The active substance is tacrolimus. Each capsule contains 0.5 mg of tacrolimus as tacrolimus monohydrate.
- The other ingredients are:
  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).

What Prograf looks like and contents of the pack
Prograf 0.5 mg hard capsules
Opaque light yellow capsules imprinted in red with "0.5 mg" and "[f] 607", containing white powder.
Prograf 0.5 mg hard capsules are supplied as blister strips containing 10 capsules within a protective foil wrapper, including a desiccant protecting the capsules from moisture. The desiccant should not be swallowed. Pack of 30 hard capsules in blister strips.

Manufacturer
Astellas Ireland Co. Ltd., Killorglin, County Kerry, V93FC86, Ireland

Product procured from within the EU, repackaged and distributed by the Parallel Product Authorisation holder:
PCO Manufacturing Ltd., Unit 10, Ashbourne Business Park, Rath, Ashbourne, Co. Meath, Ireland.

Prograf is a registered trademark of Astellas Pharma Inc.

Parallel Product Authorisation Number PPA0465/435/001

This medicinal product is authorised in the Member States of the EEA under the following names:
Prograf:
Austria, Cyprus, Czech Republic, Denmark, Germany, Greece, Spain, Finland, France, Hungary, Iceland, Ireland, Italy, Malta, Norway, Poland, Portugal, Slovakia, Slovenia, Sweden.

Prograft:
Belgium, Luxembourg, The Netherlands.

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