Package leaflet: Information for the user

Prograf 5 mg/ml concentrate for solution for infusion
Tacrolimus

Read all of this leaflet carefully before you start using 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, pharmacist or nurse.
- 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, pharmacist or nurse. 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

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 use Prograf

Do not use Prograf
- If you are allergic (hypersensitive) to tacrolimus or to any antibiotic belonging to the subgroup of macrolide antibiotics (e.g. erythromycin, clarithromycin, josamycin).
- If you are allergic (hypersensitive) to any of the other ingredients of Prograf (listed in section 6) - in particular polyoxyethylene hydrogenated castor oil or similar substances.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Prograf
- Whilst you are receiving 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.

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 used 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 using 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, 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*.

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), 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
Grapefruit and grapefruit juice should be avoided while using 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.
Prograf is excreted into breast milk. Therefore you should not breast-feed whilst receiving Prograf.

Prograf contains polyoxyethylene hydrogenated castor oil and ethanol
- Prograf contains polyoxyethylene hydrogenated castor oil that may, in a small number of patients, lead to a severe allergic reaction. If you have previously had such a problem, please inform your doctor.
- Prograf contains 81 vol % ethanol (alcohol), i.e. up to 638 mg per dose, equivalent to 16 ml beer, 7 ml wine per dose. The small amount of alcohol in this medicine will not have any noticeable effects.

3. How to take Prograf

The starting dose to prevent the rejection of your transplanted organ will be determined by your doctor calculated according to your body weight. Initial intravenous doses just after transplantation will generally be in the range of

0.01 – 0.10 mg per kg body weight per day

depending on the transplanted organ.

Prograf should be used for intravenous infusion only after it is diluted. You will receive Prograf as a continuous 24-hour infusion and never as a short injection.

Prograf may cause mild irritation if it is not infused directly into a vein.

Treatment with Prograf should not continue for more than 7 days. Your doctor will then prescribe Prograf capsules for you instead.

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.

If you receive more Prograf than you should
If you have received too much Prograf, your doctor will amend your next dose.

If you stop using 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):
- 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 (jaudince) 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 (or TTP) a condition 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).
- 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.
- 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 the national reporting system (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

Greece
National Agency for Medicines
Mesogeion 284
GR-15562 Cholargos, Athens
Tel: +30 21 32040380/337
Fax: +30 21 06549585
Website: http://www.eof.gr

Cyprus
Pharmaceutical Services
Ministry of Health
CY-1475 Nicosia
Tel: +357 22608607
Fax: + 357 22608669
Website: www.moh.gov.cy/phs

5. How to store Prograf

Keep out of the sight and reach of children.

Do not use Prograf after the expiry date which is stated on the carton and ampoule after EXP. The expiry date refers to the last day of that month.

Store ampoule in the original package in order to protect from light.
Do not store above 25 °C.

6. Contents of the pack and other information

What Prograf contains
- The active substance is tacrolimus. 1 ml of concentrate for solution for infusion contains 5 mg of tacrolimus.
- The other ingredients are polyoxyethylene hydrogenated castor oil and dehydrated alcohol.

What Prograf looks like and contents of the pack
The concentrate is a clear colourless solution supplied in transparent glass ampoules. Each ampoule contains 1 ml of concentrate for solution for infusion, which must be diluted before use.
Each carton contains 10 ampoules.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder:
Astellas Pharma Co. Ltd.
5 Waterside
Citywest Business Campus
Naas Road, Dublin 24
Ireland

Manufacturer:
Astellas Ireland Co. Ltd.
Killorglin

County Kerry, V93FC86
Ireland

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.

This leaflet was last revised in 02/2022.

The following information is intended for medical or healthcare professionals only:

Prograf 5 mg/ml concentrate for solution for infusion must not be injected undiluted.

Prograf 5 mg/ml concentrate for solution for infusion should be diluted in 5 % w/v glucose solution or physiological saline solution in polyethylene, polypropylene or glass bottles, but not in PVC containers. Only transparent and colourless solutions should be used.

The concentration of a solution for infusion should be within the range 0.004 - 0.100 mg/ml. The total volume of infusion during a 24-hour period should be in the range 20 – 500 ml.

The diluted solution should not be given as a bolus.

The solution for infusion should be used within 24 hours.

Unused concentrate for infusion in an opened ampoule or unused reconstituted solution should be disposed of immediately to avoid contamination.