PROFESSIONAL INFORMATION

SCHEDULING STATUS:

South Africa: S4

Namibia: NS2

Botswana: Schedule 2

PROPRIETARY NAME AND DOSAGE FORM

Prograf 0,5 mg (Capsules)

Prograf 1 mg (Capsules)

Prograf 5 mg (Capsules)

Prograf Concentrate for Infusion 5 mg/ml (Concentrate for intravenous infusion)

COMPOSITION

Prograf 0,5 mg (Capsules); Prograf 1 mg (Capsules); Prograf 5 mg (Capsules):

Active Ingredient: Each capsule contains 0,5 mg; 1 mg and 5 mg tacrolimus, respectively.

Excipients:

Capsule contents: hypromellose, croscarmellose sodium, lactose monohydrate, magnesium stearate.

Prograf 0,5 mg:

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).

Contains sugar: Lactose

Prograf 1 mg:

Capsule shell: titanium dioxide (E 171), gelatine

Printing ink of capsule shell: shellac, lecithin (soya), hydroxypropyl cellulose, simeticone, red iron oxide (E 172).

Contains sugar: Lactose

Prograf 5 mg:

Capsule shell: titanium dioxide (E 171), red iron oxide (E 172), gelatine

Printing ink of capsule shell: shellac, titanium dioxide (E 171), propylene glycol

Contains sugar: Lactose

Prograf Concentrate for Infusion 5 mg/ml

Active Ingredient: Concentrate for intravenous infusion containing tacrolimus 5 mg per 1 ml.

Excipients: polyoxyethylene hydrogenated castor oil

Contains ethanol, dehydrated 75,68 % v/v.

PHARMACOLOGICAL CLASSIFICATION

A.34 Other (Immuno-suppressive macrolide lactone)

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Tacrolimus is an immunosuppressive agent with activity in both *in vitro* and *in vivo* experiments.

Tacrolimus inhibits the formation of cytotoxic lymphocytes that are mainly responsible for graft rejection. Tacrolimus suppresses T-cell activation and T-helper-cell dependent B-cell proliferation, as well as the formation of lymphokines such as interleukin-2, -3 and γ-interferon and the expression of the interleukin-2 receptor. On the molecular level, the effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP), which is also responsible for the intracellular accumulation of the compound.

Pharmacokinetic properties

General characteristics:

Absorption

In the rat, the major site of absorption was identified as the upper gastrointestinal tract.

Absorption of tacrolimus is incomplete and highly variable following oral administration. After oral administration, tacrolimus is variably absorbed. Some patients achieve peak plasma concentrations within 0,5 hours to 3 hours,while in other patients it appears to be continuously absorbed over a prolonged period yielding a relatively flat absorption profile. The poor dissolution of tacrolimus in gastric fluids resulting from low aqueous solubility and alterations in gastric motility may be partially responsible for this observation.

In kidney allograft patients, single oral doses of 0,10; 0,15 and 0,2 mg/kg resulted in peak blood concentrations of 19,2; 24,2; and 47,9 ng/ml, respectively. The times to reach peak concentration varied from 0,7 to 6 hours.

The mean bioavailability of tacrolimus capsules was estimated to be 21,8 % in liver transplant patients, 20,1 % in kidney transplant patients, 14,4 to 17,4 % in healthy subjects and 25 % in paediatric liver transplant patients.

In heart allograft recipients tacrolimus is absorbed with a mean time to peak concentration (t_{max}) of approximately 1,5 hours. The oral bioavailability of tacrolimus averages 20 %, however there is a high degree of patient variability in heart transplant patients.

The oral bioavailability of tacrolimus was reduced when it was administered after a meal of moderate fat content. There was a decrease in AUC (plasma 27 %, whole blood 35 %), C_{max} (plasma 50 %, whole blood 57 %), and an increase in t_{max} (both plasma and whole blood 173 %). Both rate and extent of absorption were reduced when tacrolimus was given with food.

Bile does not influence the absorption of tacrolimus, and therefore commencement of tacrolimus therapy with an oral dose and early conversion of liver transplant patients to oral therapy is possible.

Distribution and elimination

Distribution of tacrolimus is extensive. It is highly bound to red blood cells and to plasma proteins. Following intravenous infusion of tacrolimus, peak plasma concentrations are reached at the end of the infusion. Concentration declines rapidly after the end of infusion indicating rapid distribution of the medicine outside the plasma compartment. Once

distribution equilibrium is reached, tacrolimus concentrations decline at a slower rate, corresponding to the disposition of the medicine.

The pharmacokinetics of tacrolimus after intravenous infusion to transplant patients may be described by a two-compartment model. In kidney transplant patients, the increase in AUC and C_{max} after single oral dose post-transplant was proportional to the increase in oral dose. In liver transplant patients, the mean trough level concentrations of tacrolimus remained relatively stable up to 6 months post-transplant.

Based on plasma level data in transplant patients, the apparent volume of distribution averaged 1342 l, suggesting extensive distribution of tacrolimus in the body. In liver transplant patients, the volume of distribution averaged 64,4 l based on whole blood concentrations (0,85 l /kg when normalised to body weight) and 1094,5 l based on the plasma concentrations (150,1 l /h or 2,0 l /h/kg when normalised to body weight).

Measurement of minimum blood or plasma levels, which were correlated with AUC, provided an accurate reflection of total tacrolimus exposure.

Tacrolimus is highly bound to plasma proteins (> 98,8 %) in rat, dog, monkey and man. The whole blood/plasma ratio appears to be approximately 20:1 (volunteer studies). Tacrolimus binds strongly to erythrocytes. This effect is dependent on temperature, lower temperatures resulting in lower plasma concentrations.

After oral administration (0,15 mg/kg twice daily) to liver transplant patients, steady-state concentrations of tacrolimus were achieved within 3 days in most patients.

The half-life of tacrolimus is long and variable, and clearance low.

The average total body clearance amounts to approximately 30 ml/min/g (7 - 103 ml/min/kg). In liver transplant patients, the total body clearance observed was 4,5 l /h (whole blood concentration) and 150,1 l /h or 2,0 l /h/kg when normalised to body weight (plasma concentrations).

The plasma half-life of tacrolimus ranges between 3,5 and 40,5 h in renal transplant patients, other references stating up to 50 h.

In liver transplant patients, the elimination half-life based on the whole blood concentration averaged 11,7 h (range 6,1 – 20,9 h) and based on the plasma concentration 6,5 h (range 2,7 – 13,3 h).

The renal clearance is less than 1 ml/ min. The metabolites of tacrolimus are primarily excreted via the bile.

The mean clearance after oral intake and volume of distribution averaged 0,21 ± 0,08 l /hr/kg and 2,4 ± 0,8 l /kg while $t_{1/2}$ averaged 8,7 ± 3,5 hrs in heart transplant patients.

Metabolism and biotransformation

Tacrolimus is metabolised in the liver, primarily by the cytochrome P450-3A4 family. Tacromilus is also considerably metabolised in the intestinal wall. There are several metabolites identified. Only one of these has been shown *in vitro* to have immunosuppressive activity similar to that of tacrolimus. The other metabolites have only weak or no immunosuppressive activity. Only one of the inactive metabolites is present at low concentrations in the systemic circulation. Therefore, metabolites do not meaningfully contribute to the pharmacological activity of tacrolimus.

Excretion

Following intravenous and oral administration of ^{14}C-labelled tacrolimus, most of the radioactivity was eliminated in the faeces. Approximately 2 % of the radioactivity was eliminated in the urine. Less than 1 % of unchanged tacrolimus was detected in the urine and faeces, indicating that tacrolimus is almost completely metabolised prior to elimination: bile being the principal route of elimination.

Characteristics in patients

Relationship between plasma/blood concentrations and therapeutic activity

Individual dose adjustment controlled by monitoring of tacrolimus levels in whole blood may be helpful to achieve optimal therapy.

Several immunoassays are available for determining tacrolimus concentrations in whole blood, including a fully automatic micro particle enzyme immunoassay (MEIA).

Variations with respect to confounding factors, age, polymorphism, metabolism and concomitant pathological situations (renal failure, hepatic insufficiency)

Based on limited clinical experience, the kinetic properties of tacrolimus are not altered in elderly patients.

Children require a higher dose of tacrolimus, approximately 1½ to 2 times higher than that recommended for adults, possibly owing to a higher metabolic turnover.

Patients with liver dysfunction

Patients with liver dysfunction tended to have higher tacrolimus concentrations (and correspondingly longer half-lives and smaller clearance values) compared with patients with normal liver function.

As tacrolimus is extensively metabolised by the liver, patients with impaired liver function should be carefully monitored, and dose adjustment may be necessary (see Dosage and Directions for Use).

Patients with kidney dysfunction

Since tacrolimus is nearly completely metabolised, highly lipid-soluble, and has a molecular weight of 822 g/mole, it is not expected to be dialysable. Also, less than 1 % of an administered intravenous dose is excreted in the urine. Therefore, changes to the dosing regimen from the pharmacokinetic point of view are not necessary in patients with renal failure or in patients undergoing dialysis. However, dosage adjustment may be necessary in patients with evidence of medicine-induced impairment of kidney function.

INDICATIONS

Primary immunosuppression in liver and kidney allograft recipients and liver, kidney or heart allograft rejection resistant to conventional immunosuppressive regimens.

CONTRAINDICATIONS

- Known hypersensitivity to tacrolimus, the active ingredient in Prograf, or other macrolides.
- Pregnancy and lactation (see Human Reproduction).

Prograf 0,5 mg (Capsules), Prograf 1 mg (Capsules) and Prograf 5 mg (Capsules) in addition:

- Known hypersensitivity to other ingredients of the capsules.

Prograf Concentrate for Infusion 5 mg/ml in addition:

- Known hypersensitivity to polyoxyethylated castor oil (HCO-60) or structurally related compounds.
- As Prograf may alter the metabolism of oral contraceptives, other forms of contraception should be used.
- Concomitant administration of live attenuated vaccines.
- Concomitant administration with ciclosporin.
- Concomitant use with grapefruit juice.

WARNINGS and SPECIAL PRECAUTIONS

Prolonged-release formulations of tacrolimus are not inter-changeable with immediate-release formulations of tacrolimus without careful monitoring and supervision by a transplant specialist.

Prograf therapy requires careful monitoring in units equipped and staffed with adequate laboratory and supportive medical resources. Prograf should only be prescribed and changes in immunosuppressive therapy, should only be initiated by medical practitioners experienced in immunosuppressive therapy and the management of transplant patients. The medical practitioner responsible for maintenance therapy should have complete information requisite for the follow-up of the patient. Dose and/or blood level adjustment,

should only be undertaken by the transplant centre responsible for the transplant patient. Patients should be thoroughly controlled. In particular, during the first months post-transplant, close monitoring of the patient is required.

Prograf is not recommended for use in children below 18 years due to limited data on safety and/or efficacy.

When substances with a potential for interaction (see Interactions) - particularly strong inhibitors of CYP3A4 (such as ritonavir, telaprevir, boceprevir, ketoconazole, voriconazole, itraconazole, telithromycin or clarithromycin) or inducers of CYP3A4 (such as rifampicin, rifabutin and anti-epileptic medicine) – are being combined with Prograf, tacrolimus blood levels should be monitored to adjust the Prograf dose as appropriate in order to maintain similar tacrolimus exposure.

Herbal preparations containing St. John's Wort (*Hypericum perforatum*) or other herbal preparations should be avoided when taking Prograf due to the risk of interactions that lead to decrease in blood concentrations of tacrolimus and reduced clinical effect of tacrolimus.

The combined administration of ciclosporin and tacrolimus should be avoided and care should be taken when administering tacrolimus to patients who have previously received ciclosporin (see Interactions).

High potassium intake or potassium-sparing diuretics should be avoided (see Interactions).

Certain combinations of tacrolimus with drugs known to have nephrotoxic or neurotoxic effects may increase the risk of these effects (see Interactions).

Nephrological adverse events can occur throughout the entire treatment period and, in the case of kidney transplant recipients, should be distinguished from symptoms of kidney graft rejection.

Immunosuppressants may affect the response to vaccination and vaccination during treatment with tacrolimus may be less effective. The use of live attenuated vaccines should be avoided.

Since levels of tacrolimus in blood may significantly change during diarrhoea episodes, extra monitoring of Prograf concentrations is recommended during episodes of diarrhoea.

Cardiac disorders

Cardiac hypertrophy or hypertrophy of the interventricular septum, reported as cardiomyopathies, has been observed, with Prograf blood trough concentrations much higher than the recommended maximum levels. Other factors observed to increase the risk of these clinical conditions included pre-existing heart disease, corticosteroid usage, hypertension, renal or hepatic dysfunction, infections, fluid overload, and oedema. Accordingly, high-risk patients receiving immunosuppression should be monitored, using such procedures as echocardiography or ECG pre- and post-transplant (e.g. initially at three months and then at 9-12 months). If abnormalities develop, dose reduction of Prograf therapy, or change of treatment to another immunosuppressive medicine should be considered. Prograf may prolong the QT interval and may cause *Torsades de Pointes*.

Lymphoproliferative disorders and malignancies

Patients treated with Prograf have been reported to develop Epstein-Barr Virus (EBV)-associated lymphoproliferative disorders. A combination of immunosuppressives such as antilymphocytic antibodies given concomitantly increases the risk of EBV-associated lymphoproliferative disorders. EBV-Viral Capsid Antigen (VCA)-negative patients have been reported to have an increased risk of developing lymphoproliferative disorders. Therefore, in

this patient group, EBV-VCA serology should be ascertained before starting treatment with PROGRAF. During treatment, careful monitoring with EBV-PCR is recommended. Positive EBV-PCR may persist for months and is per se not indicative of lymphoproliferative disease or lymphoma.
In view of potential risk of malignancies, patients who spend extended periods in the sun, or are otherwise exposed to UV light, should apply a high protection sun-cream.

Patients treated with Prograf, are at increased risk of opportunistic infections (bacterial, mycobacterial, fungal, viral and protozoal). Among these conditions are BK virus (a member of the Polyomavirus family) associated nephropathy and John Cunningham (JC) virus associated progressive multifocal leukoencephalopathy (PML).
These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that medical practitioners should consider in patients with deteriorating renal function or neurological symptoms.

Tuberculosis must be excluded prior to Prograf treatment.

Patients treated with Prograf have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking Prograf present with symptoms indicating PRES such as headache, altered mental status, seizures, and visual disturbances, a radiological procedure (e.g. MRI) should be performed. If PRES is diagnosed, adequate blood pressure control and immediate discontinuation of Prograf is advised. Most patients completely recover after appropriate measures are taken.

Pure Red Cell Aplasia
Cases of pure red cell aplasia (PRCA) have been reported in patients treated with Prograf. All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease or concomitant medications associated with PRCA.

Special populations

Dose reduction may be necessary in patients with severe liver impairment (see Dosage).

Excipients

Prograf Concentrate for Infusion 5 mg/ml contains polyoxyethylated castor oil, which has been reported to cause anaphylaxis and/or anaphylactoid reactions. Anaphylactoid reactions include flushing of the face and upper thorax, acute respiratory distress with dyspnoea and wheezing, blood pressure changes and tachycardia. Caution is therefore necessary in patients who have previously received, by intravenous injection or infusion, preparations containing polyoxyethylated castor oil (such as HCO-60) and in patients with an allergenic predisposition. Animal studies have shown that the risk of anaphylaxis may be reduced by slow infusion of polyoxyethylated castor oil containing medicines, such as Prograf, or by the prior administration of an antihistamine. Patients should be closely observed during the first 30 minutes of infusion for possible anaphylactoid reaction.
The ethanol content (638 mg per ml) of Prograf 5 mg/ml concentrate for solution for infusion should be taken into account.

If administered accidentally arterially or perivasally, Prograf Concentrate for Infusion 5 mg/ml may cause irritation. Aesthenia and malaise, fever, oedema in various organ systems, have all been reported. In isolated cases, allergic reactions can occur (see above).

As Prograf capsules contain lactose, special care should be taken in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

The printing ink used to mark Prograf capsules 0.5 mg and 1mg contains soya lecithin. In patients who are hypersensitive to peanut or soya, the risk and severity of hypersensitivity should be weighed against the benefit of using Prograf.

Effects on ability to drive and use machines

Prograf is associated with visual and neurological disturbances. Patients treated with Prograf who are affected by such disorders should not drive a car or operate dangerous machines. This effect may be enhanced when Prograf is given together with alcohol.

INTERACTIONS

Systemically available tacrolimus is metabolised by hepatic CYP3A4. There is also evidence of gastrointestinal metabolism by CYP3A4 in the intestinal wall. Concomitant use of substances known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels.

It is strongly recommended to closely monitor tacrolimus blood levels, as well as renal function and other side effects, whenever medicines which have the potential to alter CYP3A4 metabolism or otherwise influence tacrolimus blood levels are used concomitantly, and to interrupt or adjust the Prograf dose as appropriate in order to maintain similar tacrolimus exposure (see sections Dosage and Warnings and Special Precautions).

In vivo observations

Limited clinical data on medicine interactions are available. However, Prograf has been administered together with a great variety of other medicines in clinical trials.

CYP3A4 inhibitors potentially leading to increased tacrolimus blood levels

Clinically the following substances have been shown to increase tacrolimus blood levels:

Strong interactions have been observed with antifungal agents such as ketoconazole, fluconazole, itraconazole and voriconazole, the macrolide antibiotic erythromycin, HIV protease inhibitors (e.g. ritonavir, nelfinavir, saquinavir) or HCV protease inhibitors (e.g. telaprevir, boceprevir). Concomitant use of these substances may require decreased tacrolimus doses in nearly all patients. Pharmacokinetics studies have indicated that the increase in blood levels is mainly a result of increase in oral bioavailability of tacrolimus owing to the inhibition of gastrointestinal metabolism. Effect on hepatic clearance is less pronounced.

Weaker interactions have been observed with clotrimazole, clarithromycin, josamycin, nifedipine, nicardipine, diltiazem, verapamil, amiodarone, danazol, ethinylestradiol, omeprazole, nefazodone.

In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, miconazole, midazolam, nilvadipine, norethindrone, quinidine, tamoxifen, (triacetyl) oleandomycin.

Grapefruit juice has been reported to increase the blood level of tacrolimus and should therefore be avoided.

Lansoprazole and ciclosporin may potentially inhibit CYP3A4-mediated metabolism of tacrolimus and thereby increase tacrolimus whole blood concentrations.

Other interactions potentially leading to increased tacrolimus blood levels

Tacrolimus is extensively bound to plasma proteins. Possible interactions with other active substances known to have high affinity for plasma proteins should be considered (e.g., NSAIDs, oral anticoagulants, or oral antidiabetics).

Other potential interactions that may increase systemic exposure of tacrolimus include prokinetic agents (such as metoclopramide), cimetidine and magnesium-aluminium-hydroxide.

CYP3A4 inducers potentially leading to decreased tacrolimus blood levels

Clinically the following substances have been shown to decrease tacrolimus blood levels: Strong interactions have been observed with rifampicin, phenytoin, St. John's Wort (*Hypericum perforatum*) which may require increased tacrolimus doses in almost all patients. Clinically significant interactions have also been observed with phenobarbital. Maintenance doses of corticosteroids have been shown to reduce tacrolimus blood levels.

High dose prednisolone or methylprednisolone administered for the treatment of acute rejection have the potential to increase or decrease tacrolimus blood levels.
Carbamazepine, metamizole and isoniazid have the potential to decrease tacrolimus concentrations.

Effect of tacrolimus on the metabolism of other medicinal products

Tacrolimus is a known CYP3A4 inhibitor; thus concomitant use of tacrolimus with medicinal products known to be metabolised by CYP3A4 may affect the metabolism of such medicinal products.

The half-life of ciclosporin is prolonged when tacrolimus is given concomitantly. In addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration of ciclosporin and tacrolimus is contraindicated and care should be taken when administering tacrolimus to patients who have previously received ciclosporin (see Dosage and Warnings and Special Precautions).

Tacrolimus has been shown to increase the blood level of phenytoin.

As tacrolimus may reduce the clearance of steroid-based contraceptives leading to increased hormone exposure, particular care should be exercised when deciding upon contraceptive measures.

Limited knowledge of interactions between tacrolimus and statins is available. Clinical data suggest that the pharmacokinetics of statins are largely unaltered by the co-administration of tacrolimus.

Animal data have shown that tacrolimus could potentially decrease the clearance and increase the half-life of pentobarbital and antipyrine.

Other interactions leading to clinically detrimental effects
Concurrent use of tacrolimus with medicinal products known to have nephrotoxic or neurotoxic effects may increase these effects (e.g., aminoglycosides, gyrase inhibitors, vancomycin, cotrimoxazole, NSAIDs, ganciclovir or aciclovir).
Enhanced nephrotoxicity has been observed following the administration of amphotericin B and ibuprofen in conjunction with tacrolimus.

As tacrolimus treatment may be associated with hyperkalaemia, or may increase pre-existing hyperkalaemia, high potassium intake, or potassium-sparing diuretics (e.g. amiloride, triamterene, or spironolactone) should be avoided (see Warnings and Special Precautions).

Immunosuppressants may affect the response to vaccination and vaccination during treatment with tacrolimus may be less effective. The use of live attenuated vaccines should be avoided (see Contraindications).

HUMAN REPRODUCTION

Pregnancy

Prograf is contraindicated in pregnancy. In animal studies (rats and rabbits), Prograf has been shown to be teratogenic at doses that also demonstrated maternal toxicity. Preclinical and human data show that Prograf is able to cross the placenta. The possibility of pregnancy should therefore be excluded before initiating Prograf therapy.

Lactation

Preclinical data in rats suggest that Prograf is excreted into breast milk. Human data on effects of Prograf during the lactation period are limited. As detrimental effects on the newborn cannot be excluded, women should not breastfeed whilst receiving Prograf.

Fertility

A negative effect of Prograf on male fertility in the form of reduced sperm counts and motility was observed in rats.

DOSAGE AND DIRECTIONS FOR USE

Inadvertent, unintentional or unsupervised switching between immediate- and prolonged-release formulations of tacrolimus such as Prograf is unsafe. This can lead to graft rejection or increased incidence of side effects, including under- or overimmunosuppression, due to clinically relevant differences in systemic exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist. Following conversion to any alternative formulation, therapeutic medicine monitoring must be performed and dose adjustments made to ensure that systemic exposure to tacrolimus is maintained.

Absorption of orally administered tacrolimus in the immediate post-operative period in heart transplant patients is problematic and creates difficulties in designing a suitable dosing regimen. Therefore initiation of Prograf therapy via the intravenous route and conversion to oral dosing, when possible, or initiating Prograf orally following antibody induction therapy are the two preferable options for use of Prograf in heart transplant patients.

General statement

The dosage recommendations given below for oral and intravenous administration are intended to act as a guideline. Prograf doses should be adjusted according to individual patient requirements.

Patients receiving Prograf injection should be under continuous observation for at least the first 30 minutes following the start of the infusion and at frequent intervals thereafter. If signs or symptoms of anaphylaxis occur, the infusion should be stopped. Resuscitation facilities must be available at the bedside. Intravenous therapy should not be continued for more than 7 days.

If the clinical condition of the patient allows oral dosing, administration of oral Prograf should start as soon as practicable. In some liver transplantation patients, therapy has commenced orally by administering the capsule contents suspended in water via an intranasal gastric tube.

Prograf is normally administered together with other immunosuppressive medicines. In isolated cases, successful maintenance therapy with Prograf alone has also been described. Prograf should not be given together with ciclosporin (see Contraindications). If allograft rejection or adverse events occur, alteration in the immunosuppressive regimen should be considered.

Mode of intake

Prograf 0,5 mg/Prograf 1 mg/Prograf 5 mg

It is recommended that the oral daily dose should be taken in two divided doses. The capsules should be swallowed with fluid, preferably water. Based on pharmacokinetic considerations, the capsules should be taken on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal to achieve maximal absorption (see Interactions and Pharmacokinetic properties).

The capsules should be taken out of the blister only immediately before intake. After opening the aluminium wrapper, the capsules from the blisters must be used within 12

months. Patients should be cautioned not to swallow the desiccant contained within the aluminium wrapper.

Prograf Concentrate for Infusion 5 mg/ml

Note: Prograf Concentrate for Infusion 5 mg/ml must not be injected undiluted.

The concentrate for infusion should be diluted in 5 % glucose solution in polyethylene or glass bottles or in 0,9 % saline solution in polyethylene bottles. The concentration of a solution for final infusion produced in this way should be in the range of 0,004 to 0,1 mg/ml. The total volume of infusion during 24 hours should be in the range of 20 to 250 ml. The solution should not be given as a bolus.

Incompatibilities:

Prograf Concentrate for Infusion 5 mg/ml is incompatible with PVC plastics.

Mixed infusions between a solution prepared with Prograf Concentrate for Infusion 5 mg/ml and other medicines should be avoided. In particular, mixed infusions with medicines exhibiting a marked alkaline reaction in solution (e.g. acyclovir, ganciclovir) must not be administered as tacrolimus can disintegrate in this condition.

Duration and onset of intake

For onset of treatment see above.

Prograf 0,5 mg/Prograf 1 mg/Prograf 5 mg (Capsules)

To suppress graft rejection, the capsules normally have to be taken continuously. Therefore, no limitation of duration can be given.

Prograf Concentrate for Infusion 5 mg/ml

If clinically practicable, duration of treatment with the concentrate for infusion should not exceed 7 days.

Maintenance therapy in liver and kidney transplant recipients (adults and children) - General considerations

Continuous immunosuppression with Prograf is recommended to maintain graft survival. If progression of disease occurs (e.g. signs of acute rejection), alteration of the immunosuppressive regimen should be considered. Increase in the amount of corticosteroids, introduction of short courses of monoclonal antibodies and increase in the dose of Prograf have all been used to manage rejection episodes.
If signs of toxicity are noted, the dose of Prograf should be reduced. Patients should be instructed not to decrease the dose without the consent of the treating medical practitioner. During the course of the post-transplant improvement of the patient, it is likely that the pharmacokinetics of Prograf may be altered, requiring adjustment of the Prograf dose.

Primary immunosuppression - adult patients

Liver transplantation

Initial intravenous administration

Initially, an intravenous dose in a range 0,01 to 0,05 mg/kg/24 h should be administered as a continuous infusion over a 24-hour period. Intravenous Prograf has been administered in a range from 0,01 to 0,10 mg/kg/24 h. Administration should start approximately 6 hours after the completion of surgery. Patients should be converted from intravenous to oral medication as soon as the individual circumstances permit.

Oral administration

Initially, an oral dose in a range from 0,10 to 0,20 mg/kg/day should be administered in two divided doses. Initial oral doses have been administered in a range from 0,02 to 0,30 mg/kg/day.

Kidney transplantation

Initial administration

Initially, an oral dose in a range from 0,15 to 0,40 mg/kg/day should be administered in two divided doses. If the clinical condition of the patient does not allow for oral dosing, then an initial intravenous dose of 0,05 to 0,10 mg/kg/24 h should be administered as a continuous

infusion within the first 24 hours after the completion of surgery. Patients should be converted from intravenous to oral medication as soon as the individual circumstances permit.

Primary immunosuppression dose levels – paediatric patients

Paediatric patients generally require doses 1½ to 2 times higher than the recommended adult doses to achieve the same blood levels. Experience with initial oral administration in paediatric patients is limited.

Liver and kidney transplantation

An initial dose of 0,30 mg/kg/day for liver and kidney transplantation should be administered in two divided doses. If the dose cannot be given orally, an initial intravenous dose of 0,05 mg/kg/day for liver transplantation or 0,10 mg/kg/day for kidney transplantation should be administered as a continuous 24-hour infusion.

Maintenance therapy with Prograf in liver or kidney transplant recipients

It is necessary to continue immunosuppression with oral Prograf to maintain graft survival. Dosage recommendations should be based on individual patient experience (see introductory remarks above). There is a trend towards the use of lower doses of Prograf during maintenance therapy. Dosing should be primarily based on clinical assessments of rejection and tolerability.

Rescue therapy with Prograf

In patients experiencing rejection episodes that are unresponsive to conventional immunosuppressive therapy, Prograf treatment should begin with the initial dose recommended for primary immunosuppression in that particular allograft.

The combined administration of ciclosporin and Prograf is not recommended as Prograf may increase the half-life of ciclosporin and exacerbate any toxic effects (see Contraindications). Therefore, care should be taken when converting patients from ciclosporin- to Prograf-based

therapy. It is recommended that ciclosporin blood levels are monitored prior to the administration of Prograf. The most appropriate time to initiate Prograf therapy should be based upon information on ciclosporin blood levels and the clinical condition of the patient. Dosing may be delayed in the presence of elevated ciclosporin levels e.g. in patients experiencing renal failure. Monitoring of ciclosporin blood levels should be continued following conversion as the clearance of ciclosporin may be affected.

Heart allograft rejection

An initial oral dose of 0,30 mg/kg/day should be administered in two divided doses (e.g. morning and evening). If the clinical condition of the patient prevents oral administration, an intravenous dose of 0,05 mg/kg/day should be administered as a continuous 24-hour infusion.

DOSAGE ADJUSTMENTS IN SPECIFIC PATIENT POPULATIONS

- **Patients with liver impairment**

A dose reduction may be necessary in patients with pre- and/or post-operative impairment, e.g. early graft dysfunction.

- **Patients with kidney impairment**

No adjustment in dose is regarded as necessary on pharmacokinetic principles. However, careful monitoring of renal function, including serial creatinine estimations, calculations of creatinine clearance and monitoring of urine output, is recommended.

- **Race**

In comparison to Caucasians, Black patients may require higher Prograf doses to achieve similar trough levels.

- **Elderly patients**

There is no evidence presently available to suggest that doses should be altered in elderly patients.

- **Paediatric patients**

The safety and efficacy of Prograf in children under 18 years of age have not yet been established. Limited data are available but no recommendation on a dosage can be made.

- **Conversion from ciclosporin to Prograf**

Care should be taken when converting patients from ciclosporin-based to tacrolimus-based therapy. Prograf therapy should be initiated after considering ciclosporin blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated ciclosporin blood levels. In practice, Prograf therapy has been initiated 12 to 24 hours after discontinuation of ciclosporin. Monitoring of ciclosporin blood levels should be continued following conversion as the clearance of ciclosporin might be affected.

Various assays have been used to measure blood or plasma levels of Prograf. Monitoring of tacrolimus blood concentrations in conjunction with other laboratory and clinical parameters is considered an essential aid to patient management for the evaluation of rejection, toxicity, dose adjustments and compliance. Factors influencing frequency of monitoring include but are not limited to hepatic or renal dysfunction, the addition or discontinuation of potentially interacting medicines and the post transplant time interval. Blood concentration monitoring is not a replacement for renal and liver function monitoring and tissue biopsies.

Whole blood specimens should be collected into tubes containing ethylene diamine tetra acetic acid (EDTA) anticoagulant. Heparin anticoagulation is not recommended because of the tendency to form clots on storage. Samples that are not analysed immediately should be stored at room temperature or in a refrigerator and assayed within 7 days; if samples are to be kept longer they should be deep frozen at -20 ºC for up to 12 months.
Prograf whole blood trough levels should be monitored periodically during maintenance therapy. The frequency of blood level monitoring should be based on clinical needs, but in general, because of its long half-life, it is unnecessary to measure blood levels on a daily basis. Medicine level monitoring (TDM) is recommended during the early post-

transplantation period, following dose adjustment, after switching from another immunosuppressive regimen, and following co-administration of medicines which are likely to lead to interactions.

Clinical experience suggests that the majority of patients can be successfully managed if the blood concentrations of Prograf are maintained below 25 ng/ml. It is necessary to consider the clinical condition of the patient when interpreting whole blood level concentrations. If the blood levels are below the limit of quantification of the assay and the patient's clinical condition is satisfactory, then the dose should not be adjusted.

SIDE EFFECTS

The adverse events are listed below in descending order by frequency of occurrence:
Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100);
rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

Infections and infestations

Patients receiving Prograf are frequently at increased risk for infections (viral, bacterial, mycobacterial, fungal, protozoal). The course of pre-existing infections may be aggravated. Both generalised and localised infections can occur.

Cases of BK virus (a member of the Polyomavirus family) associated nephropathy, as well as cases of John Cunningham (JC) virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including Prograf.

Neoplasms: benign, malignant and unspecified (incl. cysts and polyps)

Patients receiving immunosuppressive therapy are at increased risk of developing malignancies. Benign as well as malignant neoplasms including Epstein-Barr Virus (EBV)-associated lymphoproliferative disorders and skin malignancies have been reported in association with Prograf treatment.

Blood and lymphatic system disorders

common: anaemia, leukopenia, thrombocytopenia, leukocytosis, abnormal red blood cell analyses

uncommon: coagulopathies, abnormal coagulation and bleeding analyses, pancytopenia, neutropenia

rare: thrombotic thrombocytopenic purpura, hypoprothrombinaemia

not known: pure red cell aplasia, agranulocytosis, haemolytic anaemia

Immune system disorders

Allergic and anaphylactoid reactions have been observed in patients receiving Prograf (see Warnings and Special Precautions).

Endocrine disorders

rare: hirsutism

Metabolism and nutrition disorders

very common: hyperglycaemic conditions, diabetes mellitus, hyperkalaemia

common: hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, decreased appetite, anorexia, metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte abnormalities

uncommon: dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia

Psychiatric disorders

very common: insomnia

common: anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders

uncommon: psychotic disorder

Nervous system disorders

very common: tremor, headache

common: seizures, disturbances in consciousness, paraesthesias and dysaesthesias, peripheral neuropathies, dizziness, impaired writing, nervous system disorders

uncommon: coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia

rare: hypertonia

very rare: myasthenia

Eye disorders

common: blurred vision, photophobia, eye disorders

uncommon: cataract

rare: blindness

Ear and labyrinth disorders

common: tinnitus

uncommon: hypoacusis

rare: neurosensory deafness

very rare: impaired hearing

Cardiac disorders

common: ischaemic coronary artery disorders, tachycardia

uncommon: ventricular dysrhythmias and cardiac arrest, heart failure, cardiomyopathies, ventricular hypertrophy, supraventricular dysrhythmias, palpitations, abnormal ECG investigations, abnormal heart rate and pulse investigations

rare: pericardial effusion

very rare: abnormal echocardiogram, QT prolonged

Vascular disorders

very common: hypertension

common: haemorrhage, thrombembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders

uncommon: infarction, deep limb venous thrombosis, shock

Respiratory, thoracic and mediastinal disorders

common: dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammation

uncommon: respiratory failure, respiratory tract disorders, asthma

rare: acute respiratory distress syndrome

Gastrointestinal disorders

very common: diarrhoea, nausea

common: gastrointestinal inflammatory conditions, gastrointestinal ulceration and perforation, gastrointestinal haemorrhages, stomatitis and ulceration, ascites, vomiting, gastrointestinal and abdominal pains, dyspeptic signs and symptoms, constipation, flatulence, bloating and distension, loose stools, gastrointestinal signs and symptoms

uncommon: paralytic ileus, peritonitis, acute and chronic pancreatitis, increased blood amylase, gastro-oesophageal reflux disease, impaired gastric emptying

rare: subileus, pancreatic pseudocyst

Hepatobiliary disorders

very common: abnormal liver function tests

common: bile duct disorders, hepatocellular damage and hepatitis, cholestasis and jaundice

rare: venoocclusive liver disease, hepatitic artery thrombosis

very rare: hepatic failure

Skin and subcutaneous tissue disorders

common: pruritus, rash, alopecia, acne, increased sweating

uncommon: dermatitis, photosensitivity

rare: toxic epidermal necrolysis (Lyell's syndrome)

very rare: Stevens Johnson syndrome

Musculoskeletal and connective tissue disorders

common: arthralgia, back pain, muscle spasms, pain in extremity

uncommon: joint disorders

Renal and urinary disorders

very common: renal impairment

common: renal failure, acute renal failure, oliguria, renal tubular necrosis, toxic nephropathy, urinary abnormalities, bladder and urethral symptoms

uncommon: anuria, haemolytic uraemic syndrome

very rare: nephropathy, haemorrhagic cystitis

Reproductive system and breast disorders

uncommon: dysmenorrhoea, uterine bleeding

General disorders and administration site conditions

common: febrile disorders, pain and discomfort, asthenic conditions, oedema, body temperature perception disturbed,

uncommon: influenza like illness, feeling jittery, feeling abnormal, multi-organ failure, chest pressure sensation, temperature intolerance

rare: fall, ulcer, chest tightness, thirst

very rare: fat tissue increased

Injury, poisoning and procedural complications

common: primary graft dysfunction

Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have been observed. A number of associated cases of transplant rejection have been reported (frequency cannot be estimated from available data).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Experience of overdosage is limited.

Earlier clinical experience (when initial induction doses were 2 or 3 times greater than those currently recommended) suggested that symptoms of overdosage may include renal, neurological and cardiac disturbances, glucose intolerance, hypertension and electrolyte disorders (e.g. hyperkalaemia). Over-immunosuppression may increase the risk for severe infections.

Liver function clearly influences all pre- and post-operative pharmacokinetic variables. Patients with failing liver grafts or those switched from other immunosuppressive therapy to Prograf should be monitored carefully to avoid overdosage.

No specific antidote to Prograf therapy is available. If overdosage occurs general supportive measures and symptomatic treatment should be conducted.

Based on the poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is anticipated that Prograf will not be dialysable.

In isolated patients with very high plasma concentrations of tacrolimus, haemofiltration and haemodiafiltration have been reported to considerably decrease the tacrolimus levels.

In cases of oral intoxication, gastric lavage and/or the use of absorbents (such as activated charcoal) may be helpful.

IDENTIFICATION

Prograf 0,5 mg (Capsules)

Hard gelatin capsules, red imprinted with “0.5 mg” on capsule cap and “[f]607” on capsule body. Capsule cap and capsule body light yellow and capsule content a white powder.

Prograf 1 mg (Capsules)

Hard gelatin capsules, red imprinted with “1 mg” on capsule cap and “[f]617” on capsule body. Capsule cap and capsule body opaque white and capsule content a white powder.

Prograf 5 mg (Capsules)

Hard gelatin capsules, white imprinted with “5 mg” on capsule cap and “[f]657” on capsule body. Capsule cap and capsule body opaque greyish-red and capsule content a white powder.

Prograf Concentrate for Infusion 5 mg/ml

Colourless, clear liquid, practically free from foreign insoluble matter, in transparent glass ampoules.

PRESENTATION

Prograf 0,5 mg (Capsules)/Prograf 1 mg (Capsules)/Prograf 5 mg (Capsules)

Ten capsules per blister sheet.

Three, five or ten blister sheets with one desiccant sachet in an aluminium wrapper.

Prograf Concentrate for Infusion 5 mg/ml

Containers of ten transparent glass ampoules.

STORAGE INSTRUCTIONS

Prograf 0,5 mg (Capsules)/Prograf 1 mg (Capsules)/Prograf 5 mg (Capsules)

Aluminium-wrapped blisters: Store at or below 30 °C. Protect from light and moisture. Keep out of reach of children.

After opening the aluminium wrapper, the capsules in the blister strips are stable for 12 months when stored at room temperature. The individual blister strips should be kept in a dry place. The patients should be instructed accordingly.

Prograf Concentrate for Infusion 5 mg/ml

Store below 25 °C. Protect from light. Keep out of reach of children.

To be used within 24 hours when reconstituted with 5 % glucose solution in polyethylene or glass containers or in physiological saline in polyethylene containers. Opened ampoules should be disposed of immediately if not used to avoid contamination.

REGISTRATION NUMBERS

	South Africa:	**Namibia:**	**Botswana:**
Prograf 0,5 mg (Capsules):	A39/34/0647	10/34/0465	
Prograf 1 mg (Capsules):	32/34/0559	04/34/1668	BOT0701038
Prograf 5 mg (Capsules):	32/34/0560	04/34/1670	BOT0801181
Prograf Concentrate for Infusion 5 mg/ml:	32/34/0561	04/34/1669	

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE

Astellas Pharma (Pty) Ltd, 7 Mirage Road, Bedfordview, 2007, South Africa

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION

Date of registration: 14 Aug 2009

Date of most recently revised professional information: 24 April 2020