PROGRAF®

Tacrolimus capsules

COMPOSITION

Each capsule contains 0.5 mg and 1 mg of tacrolimus

PROPERTIES

Pharmacodynamic

Pharmacotherapeutic Group

Immunosuppressive macrolide lactone

Mechanism of action and Pharmacodynamic Effects

Prograf®, a macrolide, calcineurin phosphatase inhibitor.

Prograf® is a highly potent immunosuppressive agent and has proven activity in both *in vitro* and *in vivo* studies.

In particulars, Prograf® inhibits the formation of cytotoxic lymphocytes which are mainly responsible for graft rejection. The drug suppresses calcium-dependent signaling for transcription and synthesis of cytokines, such as interleukin-2 and gamma interferon, which are involved in early T-cell activation and T-helper-cell dependent B-cell proliferation, as well as the formation of lymphokines such as interleukin-2, 3 and –interferon and the expression of the interleukin-2 receptor. On the molecular level, the effects of Prograf® appear to be mediated by binding to a cytosolic protein (FKBP), which is also responsible for the intracellular accumulation of the compound.

In vivo studies Prograf® has been shown to be efficacious in transplantations of liver and kidney.

Pharmacokinetics

General characteristic

Absorption

In the rat, the major site of absorption was identified as the upper GI tract. Absorption of Prograf® is incomplete and highly variable following oral administration. After oral administration, Prograf® is rapidly absorbed in certain patients with peak plasma concentrations reached within 0.5 hours, while in other patients the drug appears to be continuously absorbed over a prolonged time period yielding more or less a flat absorption profile. Possibly the poor dissolution of Prograf® in gastric fluids, due to low aqueous solubility and alterations in gastric motility, may be partially responsible for this observation.

In kidney transplant recipients 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 from Prograf® capsules was estimated to be 21.8% in liver transplant patient, 20.1% in kidney transplant patients, and 14.4 to 17.4% in healthy volunteers. The oral bioavailability of Prograf® was reduced when it was administered after food containing a moderate fat content. There was a decrease in AUC (plasma 35%, whole blood 27%), C_{max} (plasma 57%, whole blood 50%) and an increase in T_{max} (both plasma and whole blood 173%). The rate and extent of absorption of Prograf® is greatest under fasted conditions.

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

Distribution and elimination

Distribution of Prograf® is extensive. It is highly bound to erythrocytes and to plasma proteins.

Following intravenous infusion of Prograf® peak plasma concentrations are reached at the end of the infusion. The drug concentration declines rapidly after the end of infusion indicating rapid distribution

of the drug outside the plasma compartment. Once distribution equilibrium is reached, Prograf® concentrations decline at a slower rate, corresponding to the disposition of the drug.
The pharmacokinetics of Prograf® 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 through level concentrations of Prograf® remained relatively stable up to 6 months post-transplant.
Based on plasma data in transplant patients, the volume of distribution averaged 1342 L, suggesting extensive distribution of the drug in the body. In liver transplant patients, based on whole blood concentrations, the volume of distribution averaged 64.4 L (0.85 L/kg when normalized to body weight) and based on the plasma concentrations 1094.5 L (16.1 L/kg when normalized to body weight).
Measurement of minimum blood or plasma levels, which were correlated with AUC, provided an accurate reflection of total drug exposure.
Prograf® strongly binds to erythrocytes. In plasma, the drug is highly bound to plasma proteins (>98.8%) in rat, dog monkey and man. The whole blood/plasma ratio appears to be approximately 20 to 1 (volunteer studies). Prograf® binds strongly to erythrocytes. This effect is dependent on temperature, lower temperatures resulting in lower plasma concentrations.
After oral administration (0.15 mg/kg bid) in liver transplant patients, steady state concentrations of Prograf® were achieved within 3 days in most patients.
The half-life of Prograf® is long and variable clearance low.
The average total body clearance amounts to approximately 2.43 L/h (1.88-3.0 L/h) in healthy volunteers. In liver transplant patients, the total body clearance observed was 4.1 L/h (1.8-7.7 L/h) (whole blood concentrations) and 150.1 L/h (range 67.5-265 L/h) (plasma concentrations).
The plasma half-life of Prograf® ranges between 3.5 and 40.5 h, other reference starting 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 to 20.9 h) and based on the plasma concentration 6.7 h (range 2.7-13.3 h).
The renal clearance is less than 1 mL/min. The metabolites of Prograf® are primarily excreted via the bile.
After oral administration of tacrolimus capsules at 3 mg to 25 adult patients with lupus nephritis, the mean blood level reached 4.35 ng/mL (1.70-7.30 ng/mL) during 8-16 hours after administration.

Metabolism and biotransformation
Prograf® widely metabolised in the liver, primarily by the cytochrome P450-3A4 (CYP3A4) and the cytochrome P450-3A5 (CYP3A5). In man, less than 1% of unchanged tacrolimus was detected in the urine.
This indicates the drug is almost completely metabolized prior to elimination from the body.
Prograf® has a high affinity for the hepatic cytochrome P450 3A system.
The drug has a strong inhibitory effect on cytochrome P450 1A and 3A.
In vitro data with animal and human hepatocytes suggest that at least 9 metabolites can occur. Whether or not they are pharmacologically active is not known.
There is evidence that Prograf® is also metabolized by the gut wall when given orally.
Possible hepatic metabolic phase-I reactions of Prograf® appear to include mono-demethylation, hydroxylation, and a combination of mono-demethylation and hydroxylation. Data on phase-II pathways of the drug are not available.

Characteristic in patients
Relationship between plasma/blood concentrations and therapeutic activity
As stated in Dosage and Administration, individual dose adjustment controlled by monitoring of Prograf® levels in whole blood may be helpful to achieve optimal therapy.

Several immunoassays are available for determining Prograf® concentration in whole blood, including a fully automatic microparticle enzyme immunoassay (MEIA). Details are available on request.

Variations with respect to confounding factors, age, polymorphism, metabolism and concomitant pathological situations (renal failure, hepatic insufficiency)
Based on preliminary clinical experience, the kinetic properties of Prograf® are not altered in elderly patients.
Children require a higher dose of Prograf®, approximately 1.5 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 Prograf® concentrations (and correspondingly longer half-lives and smaller clearance values) compared with patients with normal liver function.
As the drug is extensively metabolized by the liver, patients with impaired liver function should be carefully monitored and dose adjustment may be necessary.

Patients with kidney dysfunction
Since the drug is nearly completely metabolized, highly lipid-soluble and has a molecular weight of 822, it is not expected to be dialyzable. 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 drug-induced impairment of kidney function.

Preclinical Safety Data
Acute toxicity
The oral LD50 value in rats was 134 mg/kg for the male and 194 mg/kg for the female animal, respectively, whereas the minimal lethal dose for both sexes was approximately 100 mg/kg. After intravenous administration, the LD50, values were 57 mg/kg for the male and 23.6 mg/kg for the female animals, respectively. The minimal lethal doses were 32 and 18 mg/kg, respectively. After oral single dose application of 250 mg/kg in baboons only minimal signs of an acute toxicity were seen. After an intravenous administration of 50 mg/kg in baboons, acute shock symptoms were seen.

Repeated-dose-toxicity
In repeated-dose studies in rats and baboons, Prograf® induced at oral doses of 1.5 and 10.0 mg/kg/day, respectively, and at intravenous doses of 0.32 and 1.0 mg/kg/day, respectively, minimal and probably reversible nephrotoxicity. Furthermore, an impairment of the endocrine parts of the pancreas was seen. This alteration was also reversible.
The minimal toxic doses after oral administration in rats and baboons were 1.5 and 10.0 mg/kg/day, respectively and after intravenous administration ca 0.1 and 0.5 mg/kg/day, respectively. Only in rats doses above 0.5 mg/kg/day showed minimal toxic effects on the eyes and peripheral nerves, whereas doses above 3.2 mg/kg/day affected the central nervous system.
Rabbits were shown to be especially susceptible to intravenous administration of Prograf®. Above doses of 2 x 0.05 mg/kg/day, cardiotoxic effects were observed.

Mutagenicity
Relevant *in vitro* and *in vivo* tests showed no signs of a mutagenic potential of Prograf®.

Carcinogenicity
In chronic, 1-year toxicity studies (rats and baboons) and in long-term carcinogenicity studies (mouse, 18 months, and rat, 24 months) no signs of a direct tumorigenic potential of Prograf® were seen.

However, as known from other immunosuppressive drugs, malignancies such as lymphomas and skin cancers can be expected and were seen rarely in patients.

Reproduction toxicity
Embryotoxicity was observed in animal studies.
Tacrolimus subcutaneously administered to male rats at doses of 2 or 3 mg/kg/day (1.6 to 6.4 times the clinical dose range based on body surface area) resulted in a dose-related decrease in sperm count. Tacrolimus given orally at 1.0 mg/kg (0.8 to 2.2 times the clinical dose range based on body surface area) to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryolethality and adverse effects on female reproduction which were indicated by a higher rate of post-implantation loss and increased numbers of undelivered and nonviable pups. When given at 3.2 mg/kg (2.6 to 6.9 times the clinical dose range based on body surface area), tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on estrus cycles, parturition, pup viability, and pup malformations.

Clinical Studies
Patients with lupus nephritis who were refractory to steroid monotherapy and exhibited clinical signs of chronic nephritis with immunological activity were treated with tacrolimus capsules for 28 weeks in the Phase III trial. The rate of change in the total score* of disease activity at the final measurement was -32.9%. The rate of change in actual values of daily urinary protein excretion and complement (C3), which are indices of chronic nephritis and immunological activity, respectively, were -60.8% and 16.4%, and the change in creatinine clearance CCr) was -22.0%.

	Tacrolimus group [n=27]	Placebo group [n=34]	95% confidence intervals for the differences between groups
The rate of change in the total score of disease activity* (%) mean ± SD.	-32.9 ± 31.0	2.3 ± 38.2	-
The rate of change in the actual value of daily urinary protein excretion (%) median (1st quartile, 3rd quartile).	-60.8 (-73.7, -37.2)	8.7 (-14.0, 90.0)	[-115.0 to -48.7]
The rate of change in the actual value of complement (C3) (%) median (1st quartile, 3rd quartile).	16.4 (10.3, 27.5)	-2.8 (-11.1, 18.2)	[8.5 to 26.7]
The rate of change in the actual value of CCr (%), median (1st quartile, 3rd quartile).	-22.0** (-33.5, -4.2)	-1.4 (-19.3, 16.9)	[-30.5 to -3.4]

* Total score of disease activity consists of the sum of the scores (a 4-point scale, ranging from 0 to 3 per item) of 5 items: daily urinary protein excretion, urinary red blood cells, serum creatinine, anti-ds DNA antibody, and complement (C3).
** As for the evaluation of CCr only, the number of cases for the tacrolimus group was 26.

INDICATIONS
Prevention of graft rejection following transplantation of liver or kidney.
Treatment of liver or kidney allograft rejection in patients previously having received other immunosuppressive agents.

Lupus Nephritis (Tacrolimus to be added on, in a case of patient who has received steroids and meets any of the following conditions):

- Failure to control disease activity with steroids
- Difficulty of reducing the steroid dose due to a concern about disease recurrence
- Difficulty of increasing the steroid dose because of adverse drug reactions of steroids

For lupus nephritis, the efficacy and safety of this product for patients in an induction therapy with high disease activity has not been established.

DOSAGE AND ADMINISTRATION

1.General statement

The dosage recommendations given below are intended to act as a guideline. Prograf® doses should be adjusted according to individual patient requirements.

If the clinical condition of the patient allows oral dosing, administration of oral Prograf® should start as soon as clinically practicable. In some liver transplantation patients therapy has commenced orally via an intranasal gastric tube.

The capsules should be taken out of the blister only immediately before intake.

After opening of the aluminum wrapper, the capsules from the blisters must be used within 3 months. Patients should be cautioned not to swallowed desiccant contained additionally in the aluminum wrapper.

For patients with lupus nephritis, Prograf® should be prescribed by physicians experienced in lupus nephritis therapy.

2.Transplantation

Mode of intake

It is recommended that the oral daily dose should be taken in two divided doses (morning and evening). 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 2-3 hours after a meal to achieve maximal absorption (see Interaction and Properties-pharmacokinetic).

<u>Maintenance therapy in liver and kidney transplant recipients (adults and children)-general consideration</u>

Prograf® is normally administered together with other immunosuppressive agents. In isolated cases successful maintenance therapy with Prograf® alone has also been described. Prograf® should not be given together with cyclosporine A.

If allograft rejection or adverse event occurs, alteration in the immunosuppressive regimen should be considered.

Continuous immunosuppressive with Prograf® is recommended to maintain graft survival. If progression of disease (e.g. Signs of acute rejection) occurs alteration of the immunosuppressive regime 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 Prograf® should be reduced. Patients should be instructed not to decrease the dose without the consent of the treating physician.

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.

<u>Whole Blood Concentration Monitoring</u>

N.B. Various assays have been used to measure blood or plasma levels of Prograf®. Comparison of the levels in published literature to patient levels should be undertaken with care and knowledge of the assay methods employed. In Europe, most experience is available with whole blood ELISA assays.

Prograf® whole blood trough levels can be measured using an immunoassay. Through blood levels of Prograf® should be monitored periodically during the 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.
Drug level monitoring is recommended during the early post-transplantations period, following dose adjustment after switching from another immunosuppressive regimen and following co-administration of drugs which are likely to lead to drug-drug interactions.
Clinical experience suggests that in majority of patients can be successfully managed if the body 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 conditions is satisfactory, then the dose should not be adjusted.

Primary immunosuppression-adult patients
Liver transplantation
Oral administration
Initially, an oral dose in a range from 0.10-0.20 mg/kg/day should be administered in two divided doses. Initial oral doses have been administered in a range from 0.02-0.30 mg/kg/day.

Primary immunosuppression-adult patients
Kidney transplantation
Initial administration
Initially, an oral dose in a range from 0.15-0.30 mg/kg per day should be administered in two divided doses (morning and evening).

Primary immunosuppression-paediatric liver or kidney transplant recipients
Initial administration
Experience with initial oral administration in pediatric patients is limited. An initial oral dose of 0.30 mg/kg per day should be administered in two divided doses (e.g. morning and evening).
It is recommended that all paediatric patients (excepts those with impaired liver or kidney function) receive doses at about one and half to two times higher than the recommended adult doses.

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.

Allograft rejection resistant to conventional immunosuppressive therapy
In patients experiencing rejection episodes which are unresponsive to conventional immunosuppressive therapy, treatment should begin with the initial dose recommended for primary immunosuppression in that particular allograft.
Patient converted from cyclosporine A to Prograf® should receive the first Prograf® dose no sooner than 24 hours after the last cyclosporine A dose.
Dosing may be further delayed in the presence of elevated cyclosporine A levels.

Duration and onset of intake
For onset of treatment see above.
To suppress graft rejection the capsules normally have to be taken continuously. Therefore, no limitation of duration can be given.

Dose in special populations

Patients with liver impairment

Dose reduction may be necessary in patients with severe liver impairment in order to maintain the through blood levels within the recommended target range.

Patients with renal 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.

Elderly patients

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

3.Lupus nephritis

For adults, usually, a dose of 3 mg as tacrolimus is orally administered, once daily after supper.

In order to avoid the development of adverse reactions in patients with lupus nephritis, it is recommended that the blood levels should be monitored monthly for 3 months after the start of tacrolimus therapy; thereafter, the blood levels approximately 12 hours after administration should be monitored periodically, and the dosage should be adjusted. If this product does not improve the clinical signs of nephritis, such as urinary protein excretion, or the immunological findings after continuous treatment for 2 months or more, the treatment with this product should be discontinued, or the patient should be switched to another product. In cases where this product is sufficiently effective, it is recommended that the dose should be reduced to a level at which the effect can be maintained.

UNDESIRABLE EFFECTS

The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to 1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Infections and infestations

As it is well known for the potent immunosuppressive agents, patients receiving tacrolimus are at an increased risk for infections (viral, bacterial, fungal, and protozoal). The course of pre-existing infections may be aggravated. Overall, infections have been reported frequently in patients being treated with tacrolimus. Both generalised and localised infections can occur.

Injury, poisoning and procedureal complications

Common: Graft dysfunction
Rare: Fall

Immune system disorder

Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus.

Investigations

Very common: Blood creatinine increased, Liver function test abnormal
Common: Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood bilirubin increased, Blood calcium decreased, Blood glucose increased, Blood magnesium decreased, Blood potassium increased, Blood pressure increased, Blood triglycerides increased, Blood urea increased, Blood uric acid increased, Gamma-glutamyltransferase increased, Platelet count decreased, Transaminases increased, Weight increased, White blood cell count decreased, White blood cell count increased

Uncommon: Activated partial thromboplastin time prolonged, Amilase increased, Blood cholesterol increased, Blood culture positive, Blood lactate dehydrogenase increased, Blood phosphorus decreased, Blood potassium decreased, ECG signs of ventricular hypertrophy, Electrocardiogram abnormal, Electrocardiogram QRS complex prolonged, Electrocardiogram QT prolonged, Electrocardiogram T wave abnormal, Haematocrit decreased, Haemoglobin decreased, Prothrombin time prolonged, Weight decreased

Rare: Activated partial thromboplastin time shortened, Antithrombin III decreased, Blood fibrinogen decreased, Blood fibrinogen increased, Coagulation time prolonged, Electrocardiogram QRS complex abnormal, Electrocardiogram ST segment abnormal, Electrocardiogram ST segment depression, Electrocardiogram ST segment elevation, Electrocardiogram T wave inversion, Electrocardiogram T wave peaked, Glucose urine present, Haematocrit increased, Haemoglobin abnormal, Heart rate decreased, Heart rate increased, Heart rate irregular, International normalised ratio increased, Protein urine present

Not known: Echocardiogram abnormal, Hepatic enzyme increased, Prothrombin level decreased

Metabolism and nutrition disorders

Very common: Hyperglycaemia

Common: Acidosis, Decreased appetite, Diabetes mellitus, Fluid overload, Hypercholesterolaemia, Hyperkalemia, Hyperlipidaemia, Hyperuricaemia, Hypocalcaemia, Hypokalaemia, Hypomagnesaemia, Hyponatraemia, Hypophosphataemia

Uncommon: Dehydration, Diabetes mellitus inadequate control, Glucose tolerance impaired, Hypertriglyceridaemia, Hypoproteinaemia, Metabolic acidosis, Type 1 diabetes mellitus, Type 2 diabetes mellitus

Nervous system disorders

Very common: Headache, Tremor

Common: Convulsion, Dizziness, Dysgraphia, Hypoaesthesia, Lethargy, Paraesthesia

Uncommon: Aphasia, Cerebral haemorrhage, Clonic convulsion, Coma, Depressed level of consciousness, Dysarthria, Encephalopathy, Epilepsy, Grand mal convulsion, Hemiparesis, Loss of consciousness, Nervous system disorder, Neuropathy peripheral, Neurotoxicity, Peroneal nerve palsy, Polyneuropathy, Somnolence, Speech disorder, Status epilepticus, Syncope

Rare: Aphonia, Brachial plexopathy, Carpal tunnel syndrome, Cerebral infarction, Haemorrhagic stroke, Mononeuropathy multiplex, Motor dysfunction, Paralysis flaccid, Peripheral nerve lesion, Peripheral sensory neuropathy, Psychomotor skills impaired, Quadriparesis, Radial nerve palsy, Stupor

Not known: Monoparesis, Nerve compression, Quadriplegia, Posterior reversible encephalopathy syndrome (PRES)

Psyciatric disorders

Very common: Insomnia

Common: Agitation, Anxiety, Confusional state, Depressed mood, Depression, Hallucination, Nightmare

Uncommon: Disorientation, Elevated mood, Emotional disorder, Euphoric mood, Mental disorder, Mental status changes, Mood altered, Mood swings, Psychotic disorder

Rare: Crying, Mutism

Cardiac disorders

Common: Angina pectoris, Tachycardia
Uncommon: Atrial fibrillation, Cardiac arrest, Cardiac failure, Myocardial infarction, Palpitations, Sinus tachycardia, Supraventicular extrasystoles, Supraventricular tachycardia, Ventricular extrasystoles, Ventricular hypertrophy
Rare: Angina unstable, Atrial flutter, Cardiac failure congestive, Cardiac fibrillation, Cardiomyopathy, Cardiopulmonary failure, Hypertropic cardiomyopathy, Left ventricular failure, Myocardial ischaemia, Pericardial effusion, Sinus arrhytmia, Sinus bradycardia, *Torsades de pointes*, Ventricular fibrillation

Blood and lymphatic system disorders
Common: Anaemia, Leukocytosis, Leukopenia, Thrombocytopenia
Uncommon: Coagulopathy, Haemolytic uraemic syndrome, Neutropenia, Pancytopenia, Thrombotic microangiopathy
Rare: Disseminated intravascular coagulation, Hypoprothrombinaemia, Thrombotic thrombocytopenic purpura
Not known: Agranulocytosis*, Pure red cell aplasia*, Haemolytic anaemia*, Febrile neutropenia*

Gastrointestinal disorders:
Very common: Diarrhoea, Nausea
Common: Abdominal pain, Abdominal pain upper, Ascites, Constipation, Dyspepsia, Flatulence, Gastritis, Loose stools, Vomiting
Uncommon: Abdominal discomfort, Abdominal distension, Colitis, Duodenitis, Dysphagia, Epigastric discomfort, Gastric ulcer, Gastrointestinal haemorrhage, Gastrooesophageal reflux disease, Haematemesis, Ileus paralytic, Impaired gastric emptying, Mouth ulceration, Oesophagitis, Pancreatitis, stomatitis
Rare: Aphthous stomatitis, Enterocolitis, Gastritis erosive, Gastrooesophagitis, Melaena, Oesophageal discomfort, Oesophagitis ulcerative, Pancreatitis pseudocyst, Pancreatitis necrotising, Subileus, Upper gastrointestinal haemorrhage
Not known: Gastrointestinal perforation*, Pancreatitis chronic, Pancreatitis haemorrhagic

Renal and urinary disorders:
Very common: Renal impairment
Common: Nephropathy toxic, Oliguria, Renal failure, Renal failure acute, Renal tubular necrosis
Uncommon: Anuria, Bladder spasm, Dysuria, Glycosuria, Haematuria, Micturition urgency, Pollakiuria, Proteinuria, Urinary incontinence
Rare: Bladder pain, Cylindruria, Leukocyturia, Micturition disorder, Myoglobinuria, Urge incontinence, Urinary retention, Urine flow decreased
Not known: Cystitis haemorrhagic, Nephropathy

Respiratory, thoracic and mediastinal disorders:
Common: Cough, Dyspnoea, Pleural effusion
Uncommon: Atelectasis, Hiccups, Lung disorder, Lung infiltration, Nasal congestion, Pulmonary oedema, Respiratory distress, Respiratory failure
Rare: Acute respiratory distress syndrome, Emphysema, Lung consolidation, Respiratory disorder, Rhinitis allergic

Ear and labyrinth disorders
Common: Tinnitus
Uncommon: Hypoacusis
Rare: Deafness neurosensory
Not known: Hearing impaired

Eye disorders
Common: Photophobia, Vision blurred
Rare: Blindness unilateral
Not known: Blindness cortical, Blindness transient, Optic neuropathy*

Skin and subcutaneous tissue disorders:
Common: Acne, Alopecia, Hyperhidrosis, Hypotrichosis, Pruritus, Rash
Uncommon: Dermatitis
Rare: Toxic epidermal necrolysis
Not known: Stevens-Johnson syndrome

Musculoskeletal and connective tissue disorders:
Common: Arthralgia, Back pain, Muscle spasms, Pain in extremity**
Rare: Mobility decreased

Neoplasms benign, malignant and unspecified (incl. cysts and polyps):
Patients receiving immunosuppressive agents are at an increased risk of developing malignancies, particularly of the skin. Benign as well as malignant neoplasms including EBV-associated lymphoproliferative disorders, skin malignancies and Kaposi's sarcoma have been reported in association with tacrolimus treatment.

General disorders and administration site conditions:
Common: Asthenia, Chest pain, Fatigue, Oedema, Oedema peripheral, Pain, Pyrexia
Uncommon: Chest discomfort, Chills, Feeling abnormal, Feeling hot, Feeling jittery, Feeling of body temperature change, Hyperpyrexia, Influenza like illness, Malaise, Multi-organ failure, Temperature intolerance
Rare: Feeling cold, Generalised oedema, Thirst, Ulcer
Not known: Fat tissue increased, Hyperthermia malignant

Hepatobiliary disorders:
Common: Cholangitis, Cholestasis
Uncommon: Chronic hepatitis, Hepatic function abnormal, Hepatitis, Hepatitis acute, Jaundice steatosis, Hepatotoxicity, Hiperbilirubinaemia, Jaundice cholestatic, Venoocclusive liver disease
Not known: Bile duct stenosis, Hepatic failure, Hepatocellular injury

Vascular disorders:
Very common: Hypertension
Uncommon: Deep vein thrombosis, Flushing, Hot flush, Hypotension, Orthostatic hypotension
Rare: Haemorrhage, Peripheral vascular disorder

**In isolated cases, pain in extremity has been reported as part of Calcineurin-Inhibitor Induced Pain Syndrome (CIPS), which typically presents as a bilateral and symmetrical, severe, ascending pain in the lower extremities.

The above mentioned listed adverse reactions have been observed during clinical studies and/or during marketed use. (*: post-marketing experience)

Lupus Nephritis
The major adverse reactions or abnormalities in clinical laboratory findings due to this product in 65 patients with lupus nephritis (capsules 65) were increased urinary β_2-microglobulin (27.3%, 12/44), increased urinary NAG (22.2%, 14/63), nasopharyngitis (15.4%, 10/65), hyperuricemia (14.1%, 9/64), leukocytosis (14.1%, 9/64), increased creatinine (12.5%, 8/64), diarrhoea (12.3%, 8/65), increased blood pressure (10.8%, 7/65), and hyperglycemia (10.9%, 7/64).
(At the time of latest approval of indications in Japan on January 2007)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

- email to pv@id.astellas.com or
  Pusat Farmakovigilans/MESO Nasional
  Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika,
  Psikotropika, Prekursor dan Zat Adiktif
  Badan Pengawas Obat dan Makanan
  Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
  Email: pv-center@pom.go.id
  Website: https://e-meso.pom.go.id/ADR

WARNINGS AND PRECAUTIONS
Prograf® therapy requires careful monitoring in units equipped and staffed with adequate laboratory and supportive medical resources. The drug should only be prescribed, and changes in immunosuppressive therapy should only be initiated by physician experienced in immunosuppressive therapy and the management of transplant patients. The physician responsible for maintenance therapy should have complete information requisite for the follow up patient.
Dose and/or blood level adjustment should only be undertaken by the transplant center responsible for the transplant patients.
Several types of neurological and CNS disorders have been reported in association with Prograf® therapy. For this reason, patients exhibiting such adverse events should be controlled carefully. Occurrence of severe CNS symptoms should prompt immediate dose review. It has been reported that in some cases severe tremor and/or motoric (expressive) aphasia may be indicators for severe CNS disorders.
Prograf® should not be administered together with cyclosporin.

During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis:

- Blood pressure for possible hypertension
- Neurological status
- Fasting blood glucose levels for possible hyperglycemia or diabetes mellitus
- Serum potassium for possible hyperkalemia and other electrolites
- Liver and kidney function tests
- ECG
- Visual status
- Haematologic parameter, coagulation value

If clinically relevant changes are seen, adjustment of the immunosuppressive regimen should be considered.

Medication Error
Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have been observed. This has led to serious adverse events, including graft rejection, or other side effects which could be a consequence of either under- or over-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.

Use in the patients who receive ciclosporin
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.

Cardiac disorders
Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies, have been observed. Most cases have been reversible. If hypertrophy is suspected, echocardiographic monitoring should be done as clinically warranted. If myocardial hypertrophy develops, dose reduction of tacrolimus treatment, or change of treatment to another immunosuppressive agent should be considered.

Tacrolimus may prolong the QT interval and may cause *Torsades de pointes*. Caution should be exercised in patients with known risk factors for QT prolongation (including but not limited to, congenital or acquired QT prolongation, concomitant medications known to prolong the QT interval or known to increase tacrolimus exposure).

Malignancies including lymphoproliferative disorders
Patients treated with tacrolimus have been reported to develop malignant neoplasms including Epstein Barr Virus (EBV)- associated lymphoproliferative disorders, skin cancers and Kaposi's sarcoma.

A combination of immunosuppressives such as antilymphocytic antibodies given concomitantly increases the risk of EBV-associated lymphoproliferative disorders. Very young (< 2 years) EBV sero-negative children have been reported to have an increased risk of developing lymphoproliferative disorders. Therefore, in this patient group, EBV serology should be ascertained before starting treatment with tacrolimus. During treatment, careful monitoring of EBV serology is recommended.

As with other immunosuppressive agents, owing to the potential risk of malignant skin changes, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Kaposi's sarcoma, including cases with aggressive forms of disease and fatal outcomes, has been reported in patients receiving tacrolimus. In some cases, regression of Kaposi's sarcoma has been observed after reducing the intensity of immunosuppression.

Infections
Patients receiving immunosuppressants, including tacrolimus, are at increased risk of developing bacterial, viral, fungal, and protozoal infections, including infection reactivation (for e.g. Hepatitis B reactivation) and opportunistic infections (for e.g. JC virus associated progressive multifocal leukoencephalopathy, CMV infection). These infections may lead to serious, including fatal, outcomes.

Nephrotoxicity
Tacrolimus can results in both acute and chronic renal function impairment in transplant patients due to its vasoconstrictive effect on renal vasculature, toxic tubulopathy and tubularinterstitial effects. Acute renal impairment can result in high serum creatinine, hyperkalemia, decreased secretion of urea and hyperuricaemia, and is usually reversible. Chronic renal impairment is characterized by progressive renal dysfunction, increased blood urea and proteinuria. Patients with impaired renal function should be monitored closely to adjust the dosage of tacrolimus and may need transient reduction or discontinuation. Acute renal impairment without active intervention may progress to chronic renal impairment.
Concurrent use of tacrolimus with other known nephrotoxic drugs could result in potentiation of nephrotoxicity. When concurrent use of tacrolimus with other known nephrotoxic drugs is required, monitor renal function and tacrolimus blood concentrations frequently, and dose adjustments of both tacrolimus and/or concomitant medications should be considered upon initiation, throughout concurrent treatment and at discontinuation of such concomitant drugs (see INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION).

Hyperkalemia
Hyperkalemia has been reported with tacrolimus use. Serum potassium levels should be monitored. Concomitant use with potassium-sparing diuretics or high intake of potassium should be avoided.

Immunizations
As with other immunosuppressants, response to vaccination during treatment with tacrolimus may be less effective. The use of live attenuated vaccines should be avoided.

Neurotoxicity
Patients treated with tacrolimus have been reported to develop encephalopathies such as posterior reversible encephalopathy syndrome (PRES). If suspect symptoms are observed, immediate confirmatory medical imaging and other suitable measures including tacrolimus discontinuation should be considered.

Thrombotic microangiopathy (TMA) (including haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopaenic purpura (TTP))
The diagnosis of TMA, including thrombotic thrombocytopaenic purpura (TTP) and haemolytic uraemic syndrome (HUS), sometimes leading to renal failure or a fatal outcome, should be considered in patients presenting with haemolytic anaemia, thrombocytopenia, fatigue, fluctuating neurological manifestation, renal impairment, and fever.

The concomitant administration of tacrolimus with a mammalian target of rapamycin (mTOR) inhibitor (e.g. sirolimus, everolimus) may increase the risk of thrombotic microangiopathy (including haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura).

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

Use with CYP3A4 inhibitors and inducers
When substances with a potential for interaction particularly strong inhibitors of CYP3A4 (such as telaprevir, boceprevir, ritonavir, ketoconazole, voriconazole, itraconazole, or clarithromycin) or inducers of CYP3A4 (such as rifampin, rifabutin) are being combined with tacrolimus, tacrolimus blood levels should be monitored to adjust the tacrolimus dose as appropriate in order to maintain

similar tacrolimus exposure. Early and frequent continued monitoring of tacrolimus blood levels within the first few days of co-administration, as well as monitoring for renal function, for QT prolongation with ECG, and for other side effects is strongly recommended when co-administered with CYP3A4 inhibitors.

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

Gastrointestinal disorders
Gastrointestinal perforation has been reported in patients treated with tacrolimus, although all cases were considered a complication of transplant surgery or accompanied by infection, diverticulum, or malignant neoplasm. As gastrointestinal perforation is a medically important event that may lead to a life-threatening or serious condition, adequate treatments including surgery should be considered immediately after a suspect symptom occurs.

For lupus nephritis, the efficacy and safety of this product for patients in an acute phase with high disease activity have not been established.

Since heart failure, arrhythmia, myocardial infarction, angina pectoris, myocardial disorder (including failed cardiac function and hypertrophy of the ventricular wall), etc. have been observed during administration of this product, patients should be observed carefully using ECG, echocardiography, chest X-ray and other examinations. Since patients with lupus nephritis are more likely to suffer from hyperlipidemia, hypertension, or the like which is considered to be a risk factor for the development of the coronary artery disease associated with systemic erythematosus, the underlying disease, patients being treated with this product should also receive appropriate therapy for these coronary diseases.

Since this product frequently causes renal disorder, patients with lupus nephritis should be observed carefully using frequent laboratory tests (serum creatinine, BUN, creatinine clearance, urinary NAG, urinary β2-microglobulin, etc.) or some other appropriate measures. The renal disorder may become aggravated as the lupus nephritis progresses.

The safety of this product in children and elderly patients has not been established in lupus nephritis. (No clinical experiences in lupus nephritis.)

In patients with lupus nephritis, creatinine clearance decreased after 28 weeks of treatment. There are only few results from clinical trials in patients with lupus nephritis lasting longer than 28 weeks, and therefore the long-term safety of this product has not been established.

CONTRAINDICATIONS
Patients receiving ciclosporin or bosentan
Patients receiving potassium-sparing diuretics
Known hypersensitivity to Prograf® or other macrolides
Known hypersensitivity to other ingredients of the capsules

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Potential Interactions:

[Pharmacokinetic Interaction]

Tacrolimus is extensively metabolised via the hepatic microsomal cytochrome P-450 3A4 isoenzyme (CYP3A4). Concomitant use of drugs or herbal remedies known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease the blood level of tacrolimus.

Based on *in vitro* studies, the following drugs can be regarded as potential inhibitors of Prograf® metabolism: bromocriptine, ergotamine, gastodene, miconazole, midazolam, nilvadipine, tamoxifen, triacethyloleandromycin.

Based on theoretical considerations, concomitant use of the following drugs known to induce the metabolic turnover of the cytochrome P-450 system might lead to decrease Prograf® blood levels; carbamazepine, matamizole, isoniazide.

In *in vitro* models, no inhibitory effects on Prograf® metabolism were observed with aspirin, captopril, cimetidine, ciprofloxacin, diclofenac, doxicycline, furosemide, glibenclamide, imipramine, paracetamol, progesterone, ranitidine, sulphamethoxazole, trimethoprim and vancomycin.

Tacrolimus also shown a broad and powerful inhibitory effect on CYP3A4-dependent metabolism, thus, concomitant use of tacrolimus with drugs known to be metabolised by CYP3A4-dependent pathways may affect the metabolism of such drugs. Tacrolimus is extensively bound to plasma proteins. Possible interactions with other drugs known to have high affinity for plasma proteins (e.g. oral anticoagulants and oral antidiabetics) should be considered.

Prograf® may increase blood levels of bosentan and adverse reactions of bosentan may occur. In addition, the blood levels of tacrolimus may be altered. Since Prograf® and bosentan are metabolized by CYP3A4, the concomitant use of these drugs may increase the blood levels of bosentan. In addition, the blood levels of tacrolimus may be altered when used concomitantly with bosentan because bosentan is not only metabolized by CYP3A4 but also induces CYP3A4. Prograf® should not be co-administered with bosentan.

[Pharmacodynamic Interactions (synergistic effects)]

Concurrent use of tacrolimus with drugs known to have nephrotoxic or neurotoxic effects may increase the level of toxicity. As tacrolimus treatment may be associated with hyperkalemia, or may increase pre-existing hyperkalemia, therefore, the following should be avoided:

- High-potassium intake or
- Potassium-sparing diuretics (e.g. amiloride, triamterene and spironolactone)

[Other Interactions]

During treatment with tacrolimus, vaccinations may be less effective and the use of live attenuated vaccines should be avoided.

Clinically Relevant Interactions:

Systemic tacrolimus therapy requires careful monitoring when co-administered with drugs having a potential interaction and when necessary interruption or dose adjustment of tacrolimus should be made.

1. The following drugs and herbal remedy inhibit CYP3A4 and have been shown or expected, to increase the blood levels of tacrolimus. Grapefruit juice has also been reported to increase the blood level of tacrolimus by inhibiting the activity of CYP3A4.
    - Ketoconazole, fluconazole, itraconazole, clotrimazole, voriconazole
    - Nifedipine, nicardipine, diltiazem

- Amiodarone
- Erythromycin, clarithromycin, josamycin
- Danazol, ethynylestradiol
- Omeprazol, lansoprazole
- Nefazodone
- HIV protease inhibitors (for example but not limited to ritonavir, nelfinavir, saquinavir)
- HCV protease inhibitors (for example but not limited to telaprevir, boceprevir)
- Letermovir
- *Schisandra sphenanthera* extracts
- Verapamil

Significant tacrolimus dose reduction and prolongation of dosing interval may be required in order to maintain similar tacrolimus exposure when co-administered with strong CYP3A inhibitors, particularly telaprevir. Rapid increase in tacrolimus level may occur when co-administered with CYP3A4 inhibitors. Cases have been reported in which a sharp rise in tacrolimus levels occurred very rapidly, as early as within 1-3 days after co-administration with a strong CYP3A4 inhibitor, clarithromycin, despite immediate reduction of tacrolimus dose. Therefore early, within the first few days of co-administration, and frequent continued monitoring of tacrolimus blood levels, as well as monitoring for renal function, for QT prolongation with ECG, and for other side effects is strongly recommended.

2. The following drugs induce CYP3A4 and have been shown to decrease the blood levels of tacrolimus:
   - Rifampicin (rifampin)
   - Phenytoin
   - Phenobarbital
   - St. John's wort (*Hypericum perforatum*)

3. Concomitant administration of cannabidiol has been shown to increase the blood levels of tacrolimus (mechanism not confirmed). Tacrolimus and cannabidiol should be co-administered with caution, closely monitoring for side effects. Monitor tacrolimus whole blood trough concentrations and adjust the tacrolimus dose if needed.

4. Concomitant administration of caspofungin has been shown to decrease the blood levels of tacrolimus (mechanism not confirmed).

5. Enhanced nephrotoxicity has been observed following the administration of the following drugs in conjunction with tacrolimus:
   - Amphotericin B
   - NSAIDs (Ibuprofen)
   - Aminoglycosides
   - Gyrase inhibitors
   - Vancomycin
   - Co-trimoxazole
   - Ganciclovir
   - Acyclovir

6. The half-life of ciclosporin has been shown to increase when tacrolimus is given simultaneously. In addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration of ciclosporin and tacrolimus is not recommended and

care should be taken when administering tacrolimus to patients who have previously received ciclosporin.

7. Concomitant administration of methylprednisolone has been reported to increase and to decrease plasma levels of Prograf®.

8. Effects of Prograf® on the cytochrome P-450 system-mediated metabolism of other drugs: 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. 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.

9. Combination therapy with mycophenolic acid (MPA) products: Caution should be exercised when switching combination therapy from ciclosporin to tacrolimus and vice versa. Exposure to MPA is higher with tacrolimus co-administration than with ciclosporin co-administration because ciclosporin interrupts the enterohepatic recirculation of MPA while tacrolimus does not. Therapeutic drug monitoring of MPA is recommended.

10. Impact of direct-acting antiviral (DAA) therapy: The pharmacokinetics of tacrolimus may be impacted by changes in liver function during DAA therapy, related to clearance of HCV virus. A close monitoring and potential dose adjustment of tacrolimus is warranted to ensure continued efficacy and safety.

Pregnancy and Lactation

Human data shows that tacrolimus is able to cross the placenta. Due to the need of treatment, tacrolimus can be considered in pregnant women when there is no safer alternative and when the perceived benefit justifies the potential risk to the fetus.

The use of tacrolimus during pregnancy has been associated with preterm delivery, neonatal hyperkalemia and renal dysfunction.

A cumulative review of evidence related to the safety of the use of tacrolimus suggests that infants exposed to tacrolimus *in utero* may be at risk of prematurity, birth defect/congenital anomalies, low birth weight, and fetal distress. Tacrolimus may increase hyperglycemia in pregnant women with diabetes (including gestational diabetes). Monitor maternal blood glucose levels regularly. Tacrolimus may exacerbate hypertension in pregnant women and increase pre-eclampsia. Monitor and control blood pressure. Females and males of reproductive potential should consider the use appropriate contraception prior to starting treatment with Prograf®.

Complementary evidence from a non-interventional post-authorization safety study

A post-authorization safety study analyzed 2,905 pregnancies from the Transplant Pregnancy Registry International (TPRI), assessing outcomes of pregnancies in women treated with regimens containing tacrolimus (383 reported prospectively, including 247 kidney and 136 liver transplant patients), and those on other immunosuppressants. The study results did not indicate an increased risk of major malformations. There was a trend towards a higher prevalence of spontaneous abortion among women treated with tacrolimus compared with alternative immunosuppressants. Among kidney transplant patients, there was also a trend towards a higher prevalence of pre-eclampsia in women treated with tacrolimus. Among kidney and liver transplant patients exposed to tacrolimus, 45%-55% of their live births were premature, with 75%-85% having a normal birth weight for gestational age. Similar results were observed for other immunosuppressants.

In rats and rabbits, tacrolimus caused embryofetal toxicity at doses which also demonstrated maternal toxicity.
Preclinical data in rats suggest that Prograf® is excreted into breast milk.
Human data demonstrate that tacrolimus is excreted into breast milk.
The effects of tacrolimus on the breastfed infant, or on milk production have not been assessed. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving 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.

Overdosage
Experience of Overdosage is limited.
Several cases of accidental overdose have been reported with tacrolimus. Symptoms with overdose are consistent with the adverse drug reactions listed in UNDESIRABLE EFFECTS section (including tremor, headache, nausea and vomiting, infections, urticaria, lethargy, increased blood urea nitrogen and elevated serum creatinine concentrations, and increase in alanine aminotransferase levels).
No specific antidote to Prograf® therapy is available. If overdosage occurs, general supportive measures and symptomatic treatment should be conducted.
Based on its high molecular weight, poor aqueous solubility, and extensive erythrocyte and plasma proteins binding, it is anticipated that Prograf® will not be dialysable. The oral use of activated charcoal has been reported in treating acute overdoses, but experience has not been sufficient to warrant recommending its use.

PHARMACEUTICAL PARTICULARS
List of excipients
Capsule content: Hypromellose, Croscarmellose sodium, Lactose monohydrate, Magnesium stearate

Incompatibility
Tacrolimus is not compatible with PVC. Tubing, syringes and other equipment used to prepare or administer the tacrolimus products (infusion or suspension of capsule contents) should not contain PVC.

Shelf life
Unopened pouch: 3 years

Special precaution for storage
Do not store above 30°C
Aluminum wrapped blisters: store in the original package

Nature and contents of container
Prograf® 0.5 mg Capsule
Box, 1 pouch @ 5 blisters @ 10 capsules
Reg. No.: DKI1108000201A1

Prograf® 1 mg Capsule
Box, 1 pouch @ 5 blisters @ 10 capsules
Reg. No.: DKI1108000201B1

Special precaution for disposal and other handling
Based on immunosuppressive effects of tacrolimus, inhalation or direct contact with skin or mucous membranes by the formulations for injection or powder contained in tacrolimus products should be avoided during preparation. If such contact occurs, wash the skin and flush the affected eye or eyes.

HARUS DENGAN RESEP DOKTER

Manufactured by Astellas Ireland Co., Ltd., Killorglin, County Kerry, V93 FC86, Ireland

Marketing Authorisation Holder: PT. Combiphar, JI. Raya Simpang 383, Padalarang 40553, Jawa Barat, Indonesia

Imported and distributed by: PT. Astellas Pharma Indonesia, Jakarta, Indonesia

Informasi Untuk Pasien
Kapsul Prograf® 0.5 mg
Kapsul Prograf® 1mg
tacrolimus

Bacalah leaflet ini dengan seksama sebelum anda mengonsumsi obat ini karena berisi informasi yang sangat penting untuk anda.

- Simpanlah leaflet ini. Anda mungkin perlu untuk membacanya lagi.
- Jika anda memiliki pertanyaan lebih lanjut, silahkan menghubungi dokter atau apoteker anda.
- Obat ini diresepkan hanya untuk anda. Jangan memberikan kepada orang lain. Hal tersebut mungkin dapat membahayakan mereka, walaupun tanda gejala dan penyakit mereka sama dengan anda.
- Jika anda mengalami efek samping segera hubungi dokter atau apoteker anda. Termasuk jika anda mengalami efek samping yang tidak tercantum dalam leaflet ini. Lihat nomor 4.

Apa saja yang terdapat dalam leaflet ini:

1. Apa itu Prograf® dan digunakan untuk apa

Prograf® termasuk dalam golongan obat yang disebut imunosupresan (obat yang menekan sistem kekebalan/sistem imun tubuh). Sejalan dengan transplantasi organ anda (contohnya hati, ginjal, jantung), sistem imun tubuh anda akan mencoba menolak organ baru tersebut. Prograf® digunakan untuk mengontrol respon kekebalan tubuh anda sehingga tubuh anda dapat menerima organ tranplan. Prograf ® sering digunakan secara kombinasi dengan obat lain yang juga dapat menekan sistem kekebalan tubuh.

Anda juga mungkin akan diberikan Prograf® untuk penolakan berkelanjutan terhadap transplantasi hati, ginjal, jantung atau organ lain atau jika pengobatan sebelumnya tidak dapat mengontrol respon kekebalan tubuh setelah proses transplantasi.

Prograf® juga dapat untuk mengobati lupus nephritis (peradangan pada ginjal yang terjadi akibat sistem kekebalan tubuh keliru menyerang ginjal sendiri).

2. Apa yang perlu diketahui sebelum menggunakan Prograf®

Jangan menggunakan Prograf®

- Jika anda alergi (hipersensitif) terhadap tacrolimus atau zat lain yang terkandung dalam Prograf® (dapat dilihat pada nomor 6)
- Jika anda alergi (hipersensitif) terhadap antibiotik golongan makrolida (contohnya eritromisin, klaritomisin, josamisin)
- Pasien yang menggunakan ciclosporin atau bosentan
- Pasien yang menerima diuretik hemat kalium (obat yang membuang kelebihan cairan namun tetap mempertahankan kadar kalium dalam tubuh)

Peringatan dan perhatian

Bicarakan dengan dokter atau apoteker anda sebelum menggunakan Prograf®

- Anda perlu menggunakan Prograf® setiap hari selama anda membutuhkan imunosupresan untuk mencegah penolakan dari organ transplantasi anda. Anda perlu untuk berkonsultasi dengan dokter anda secara teratur.
- Sementara anda menggunakan Prograf® dokter anda mungkin akan melakukan beberapa tes (termasuk tes darah, urin, fungsi hati, penglihatan dan syaraf) dari waktu ke waktu. Hal ini termasuk biasa dan akan menolong dokter anda untuk memutuskan dosis Prograf® yang paling tepat untuk anda.
- Jika anda memiliki masalah hati atau penyakit yang dapat mempengaruhi hati anda, harap sampaikan kepada dokter anda karena hal tersebut dapat mempengaruhi dosis Prograf® yang anda gunakan.
- Jika anda merasakan nyeri perut hebat disertai atau tidak dengan gejala lain, seperti menggigil, demam, mual atau muntah.
- Jika anda mengalami diare selama lebih dari sehari, hubungi dokter anda, karena mungkin saja diperlukan penyesuaian dosis Prograf® yang anda gunakan.
- Batasi dalam terpapar sinar matahari dan sinar UV sementara anda menggunakan Prograf® dengan menggunakan pakaian yang sesuai dan menggunakan krim pelindung matahari dengan faktor pelindung matahari yang tinggi. Hal ini karena ada potensi risiko terjadinya perubahan kulit dengan terapi imunosupresif.
- Jika anda memerlukan vaksinasi, informasikan kepada dokter anda sebelumnya. Dokter anda akan menyaranlan tindakan yang paling tepat.
- Pasien yang diterapi dengan Prograf® telah dilaporkan mempunyai risiko tinggi terkena gangguan limfoproliferatif (pertumbuhan sel darah putih yang tidak terkendali). . Tanyakan kepada dokter anda untuk saran yang jelas mengenai gangguan ini.
- Jika Anda memiliki atau memiliki riwayat kerusakan pada pembuluh darah terkecil, yang diketahui dengan *thrombotic microangiopathy/thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome*. Bicarakan pada dokter Anda jika anda mengalami demam, memar pada bagian bawah kulit (seperti bintik merah), kelelahan tanpa sebab, kebingungan, kulit atau menguning, penurunan volume urin, kehilangan pandangan dan kejang (lihat nomor 4). Ketika tacrolimus digunakan bersamaan dengan sirolimus atau everolimus, risiko mengalami gejala-gejala tersebut dapat meningkat.

Yang Perlu Diperhatikan saat Penanganan

Kontak langsung dengan setiap bagian tubuh Anda seperti kulit atau mata, atau menghirup cairan injeksi, atau bubuk yang terkandung dalam produk tacrolimus harus dihindari selama penanganan. Jika kontak seperti itu terjadi, cucilah kulit dan mata.

Obat-obatan lain dan Prograf®

Informasikan kepada dokter atau apoteker anda jika anda sedang menggunakan atau baru saja akan atau mungkin akan menggunakan obat-obatan lain, termasuk obat-obatan yang digunakan tanpa resep dokter dan obat herbal (obat tradisional)

Prograf® tidak dapat digunakan bersamaan dengan siklosporin.

Jika Anda harus bertemu dokter lain selain spesialis transplantasi Anda, beritahukan kepada dokter

Anda bahwa Anda sedang mengonsumsi tacrolimus. Dokter Anda mungkin perlu untuk berkonsultasi kepada spesialis transplantasi Anda apabila Anda harus menggunakan obat-obatan lain yang dapat meningkatkan atau menurunkan kadar tacrolimus dalam darah Anda.

Kadar Prograf® dalam darah dapat dipengaruhi oleh obat-obatan lain yang anda gunakan, dan kadar darah obat lain dapat dipengaruhi oleh Prograf® sehingga mungkin memerlukan penyesuaian, kenaikan atau penurunan dosis Prograf®.
Beberapa pasien mengalami peningkatan kadar tacrolimus dalam darah ketika menggunakan obat-obatan lain. Hal ini dapat menyebabkan efek samping serius, seperti gangguan ginjal, gangguan sistem saraf, dan gangguan ritme jantung (lihat nomor 4). Sebuah efek yang menyebabkan peningkatan kadar Prograf® dalam darah dapat terjadi sangat cepat setelah penggunaan obat-obatan lain, sehingga pemantauan lanjutan secara terus menerus terhadap kadar Prograf® dalam darah mungkin perlu dilakukan dalam beberapa hari pertama penggunaan obat-obatan lain dan lebih sering ketika penggunaan obat-obatan lain dilanjutkan. Beberapa obat yang dapat menyebabkan penurunan kadar tacrolimus dalam darah dapat meningkatkan resiko penolakan organ transplantasi. Khususnya, informasikan kepada dokter jika anda menggunakan atau baru saja menggunakan obat-obatan dengan zat aktif seperti:

- Obat-obatan anti jamur dan antibiotik, khususnya yang disebut antibiotik golongan makrolida, digunakan untuk mengobati infeksi seperti ketokonazol, flukonazol, itrakonazol, voriconazole, clotrimazole, miconazole, caspofungin, eritromisin, klaritromisin, josamisin,rifampisin, rifabutin, dan isoniazid
- Letermovir, digunakan untuk mencegah penyakit yang disebabkan oleh *human cytomegalovirus*
- Penghambat enzim protease pada human imunodeficiency virus (misalnya ritonavir, nelfinavir, saquinavir), digunakan untuk mengobati infeksi HIV

- Penghambat enzim protease pada virus hepatitis C (misalnya telaprevir, boceprevir), digunakan untuk mengobati infeksi hepatitis C
- Mycophenolic acid, digunakan untuk menekan sistem imun untuk mencegah penolakan transplantasi
- Obat-obatan untuk ulkus lambung dan peningkatan asam lambung (contohnya omeprazol atau simetidin)
- Terapi hormonal dengan etinilestradiol (contohnya pil kontrasepsi oral) atau danazol
- Obat-obatan untuk tekanan darah tinggi atau ganguan jantung seperti nifedipin, diltiazem dan verapamil.
- Obat anti-aritmia (amiodaron) digunakan untuk mengontrol aritmia (detak jantung yang tidak teratur)
- Obat-obatan anti epilepsi seperti karbamazepin, fenitoin atau fenobarbital
- Kortikosteroid prednisolon dan metilprednisolon
- Antidepresan nefazodone
- Obat herbal yang mengandung St. John wort (*Hypericum perforatum*) atau ekstrak *Schisandra sphenanthera*
- Cannabidiol (yang digunakan antara lain sebagai obat kejang).

Informasikan ke dokter Anda jika anda menerima pengobatan untuk Hepatitis C. Obat-obatan untuk Hepatitis C dapat mengubah fungsi hati anda dan dapat mempengaruhi kadar tacrolimus dalam darah. Kadar tacrolimus dalam darah dapat berkurang atau meningkat tergantung pada obat-obatan yang diresepkan untuk Hepatitis C. Dokter anda mungkin perlu untuk meninjau kadar tacrolimus dalam darah dan membuat penyesuaian dosis Prograf® setelah anda memulai pengobatan Hepatitis C.

Informasikan ke dokter anda jika anda menggunakan atau membutuhkan amfoterisin B, antibiotik (kotrimoksazol, vankomisin, atau antibiotik lain golongan aminoglikosida seperti gentamisin), atau antiviral (seperti asiklovif, gansiklovir). Hal ini dapat memperburuk fungsi ginjal atau gangguan sistem syaraf jika digunakan bersamaan dengan Prograf®.
Dokter anda juga perlu mengetahui jika anda menggunakan suplemen kalium atau diuretik hemat kalium (seperti amilorid, triamteren atau spironolakton), beberapa pereda rasa sakit (sering disebut NSAIDs), antikoagulan (obat pengencer darah), atau obat oral untuk terapi diabetes, selama anda menggunakan Prograf®.

Jika anda memerlukan vaksinasi, informasinya sebelumnya kepada dokter anda.

Penggunaan Prograf® dengan makanan dan minuman
Untuk transplantasi: secara umum anda harus menggunakan Prograf® dalam kondisi perut kosong atau setidaknya 1 jam sebelum atau 2 sampai 3 jam setelah makan. Jeruk bali *dan* jus jeruk bali harus dihindari saat menggunakan Prograf®. Untuk Lupus nephritis: secara umum, gunakan Prograf® setelah makan malam.

Kehamilan dan menyusui
Jika anda sedang hamil atau sedang menyusui, jika anda berfikir sedang hamil atau berencana untuk memiliki bayi, tanyakan kepada dokter atau apoteker anda untuk saran sebelum menggunakan obat ini. Sebuah studi menilai hasil kehamilan pada wanita yang diobati dengan takrolimus dan mereka yang diobati dengan imunosupresan lainnya. Meskipun tidak ada bukti yang cukup dalam studi ini

untuk menarik kesimpulan, tingkat keguguran yang lebih tinggi dilaporkan di antara pasien transplantasi hati dan ginjal yang diobati dengan takrolimus, serta tingkat yang lebih tinggi di antara pasien transplantasi ginjal dengan preeklamsia (hipertensi persisten yang terkait dengan kehilangan protein dalam urin yang berkembang selama kehamilan atau periode pasca persalinan).. Tidak ditemukan peningkatan risiko cacat lahir mayor (kelainan yang mempengaruhi struktur organ vital dan membutuhkan tindakan segera untuk bertahan hidup) antara penggunaan takrolimus dengan immunosupresan lain.

Takrolimus dapat dikeluarkan melalui air susu ibu. Sehingga anda tidak boleh menyusui selama menggunakan Prograf®.

Mengemudi dan menggunakan mesin

Jangan mengendarai atau menggunakan alat atau mesin jika anda merasa pusing atau mengantuk, atau mengalami masalah dalam melihat secara jelas setelah menggunakan Prograf®. Efek ini sering terlihat jika Prograf® digunakan bersamaan dengan alkohol.

3. Bagaimana menggunakan Prograf®

Selalu gunakan Prograf® seperti petunjuk dokter anda. Anda harus berkonsultasi dengan dokter atau apoteker jika anda tidak yakin.

Pastikan anda menerima obat tacrolimus yang sama setiap kali anda menerima resep, kecuali dokter anda setuju untuk mengganti dengan obat tacrolimus yang lain.

Penjadwalan dosis

<Untuk transplantasi>

Obat ini harus digunakan dua kali sehari. Jika tampilan obat ini tidak sama dengan biasanya, atau petunjuk penggunaanya berubah, hubungi dokter atau apoteker anda secepat mungkin untuk meyakinkan bahwa anda menerima obat yang tepat.

Dosis awal untuk mencegah penolakan dari organ yang ditranplantasi akan ditentukan oleh dokter dihitung berdasarkan berat badan anda. Dosis awal setelah ditansplantasi secara umum akan berada pada rentang dosis

0.1 – 0.30 mg per kg berat badan per hari

tergantung dari organ yang ditransplantasi.

Dosis anda tergantung dari kondisi umum dan obat imunosupresan lain yang digunakan. Tes darah rutin diperlukan dokter anda untuk menentukan dosis yang tepat dan untuk menyesuaikan dosis dari waktu ke waktu. Dokter anda biasanya akan mengurangi dosis Prograf® ketika kondisi sudah stabil. Dokter anda akan mengatakan dengan jelas berapa kapsul yang anda butuhkan dan berapa sering. Untuk menekan penolakan organ yang ditransplan kapsul sebaiknya dikonsumsi secara terus menerus. Sehingga, tidak ada batas waktu yang dapat diberikan.

Prograf® digunakan secara oral dua kali sehari, biasanya pada pagi dan sore. Anda biasanya harus menggunakan Prograf® pada saat perut kosong atau setidaknya 1 jam sebelum atau 2 sampai 3 jam setelah makan. Kapsul harus ditelah seutuhnya dengan segelas air. Hindari buah jeruk bali dan jus buah jeruk bali selama menggunakan Prograf®. Jangan menelan pengering yang terdapat dalam pembungkus foil .

<u>Pasien dengan gangguan hati</u>

Pengurangan dosis mungkin diperlukan pada pasien dengan gangguan hati bertujuan untuk menjaga kadar obat dalam darah sesuai dengan kisaran yang disarankan.

<u>Pasien dengan gangguan ginjal</u>

Tidak ada penyesuaian dosis berdasarkan prinsip farmakokinetik (proses yang terjadi dalam tubuh setelah pemberian obat). Walaupun demikian pengawasan yang ketat terhadap fungsi ginjal termasuk pemeriksaan kreatinin (senyawa kimia dalam darah yang berasal dari proses produksi energi pada otot) secara berkala, perhitungan bersihan kreatinin dan pengawasan dari jumlah urin yang dikeluarkan tetap direkomendasikan.

<u>Pasien lanjut usia</u>

Tidak tersedia data pendukung yang menganjurkan bahwa dosis harus diubah pada pasien lanjut usia.

< Untuk lupus nephritis >

Secara umum, untuk dewasa, gunakan 3 mg Prograf® sehari sekali setelah makan malam.

Untuk menghindari terjadinya efek samping pada pasien lupus nephritis, dianjurkan untuk memeriksa kadar obat dalam darah setiap bulan selama 3 bulan pertama setelah diberikan tacrolimus; kemudian, kadar obat dalam darah selama kurang lebih 12 jam setelah pemberian obat harus diawasi secara berkala, dan dosis harus disesuaikan. Jika obat ini tidak memberikan perbaikan pada gejala klinis dari *lupus nephritis*, seperti pengeluaran protein dalam urin, atau dalam pemeriksaan imunologi (pemeriksaan terkait kekebalan tubuh) setelah pengobatan selama 2 bulan atau lebih, pengobatan dengan obat ini harus dihentikan, atau diganti dengan obat lain. Jika produk ini efektif dalam pengobatan, direkomendasikan penurunan dosis sampai dengan efek obat tersebut dapat terjaga.

Jika anda menggunakan Prograf® lebih banyak dari yang seharusnya
Jika anda secara tidak sengaja menggunakan Prograf® lebih banyak temui dokter anda atau hubungi unit gawat darurat rumah sakit terdekat.

Jika anda lupa menggunakan Prograf®
Jangan menggandakan dosis anda untuk menutupi dosis yang terlupa.
Jika anda lupa untuk menggunakan Prograf®, tunggu hingga waktu berikutnya, dan selanjutnya lanjutkan seperti sebelumnya.

Jika anda berhenti menggunakan Prograf®
Menghentikan pengobatan Prograf® dapat meningkatkan risiko penolakan dari organ yang ditransplan. Jangan hentikan pengobatan kecuali dokter anda menyarankan hal tersebut.

Jika anda memiliki pertanyaan lebih lanjut mengenai obat ini, tanyakan kepada dokter atau apoteker anda.

4. Kemungkinan efek samping yang dapat terjadi
Seperti halnya obat lain, obat ini dapat menyebabkan efek samping, walaupun tidak semua orang mengalaminya.

Prograf® mengurangi mekanisme pertahanan tubuh anda untuk menghentikan penolakan terhadap organ yang ditransplantasi atau untuk mengobati lupus nephritis. Sebagai akibatnya, tubuh anda akan tidak sebaik biasanya dalam melawan infeksi. Sehingga jika anda menggunakan Prograf® anda mungkin akan mengalami infeksi lebih sering dari biasanya pada bagian kulit, mulut, perut, usus, paru-paru dan saluran kemih.

Efek samping yang parah dapat terjadi, termasuk salah satu dalam daftar dibawah. Informasikan segera kepada dokter anda jika anda mengalami atau mencurigai mengalami beberapa efek samping serius dibawah:

Efek samping serius umum (dapat terjadi pada 1 dari 10 orang):
- Luka pada saluran cerna: nyeri perut yang parah disertai atau tidak dengan gejala lain, seperti menggigil, demam, mual atau muntah.
- Kurangnya fungsi organ hasil transplantasi
- Penglihatan kabur

Efek samping serius yang tidak biasa (dapat terjadi pada 1 dari 100 orang):

- *Thrombotic microangiopathy* (kerusakan pada pembuluh darah terkecil), h*aemolytic uraemic syndrome* (HUS), suatu kondisi dengan gejala berikut: rendah atau tidak ada output urin (gagal ginjal akut), kelelahan ekstrim, menguningnya kulit atau mata (jaudince) dan memar abnormal atau perdarahan dan tanda-tanda infeksi.

Efek samping serius yang jarang terjadi (dapat terjadi pada 1 dari 1.000 orang):
- Trombotik trombositopenik purpura: suatu kondisi yang melibatkan perusakan pada pembuluh darah terkecil dan ditandai dengan demam dan memar di bawah kulit yang mungkin muncul sebagai bintik-bintik merah, dengan atau tanpa disertai rasa lelah yang ekstrim yang tidak dapat dijelaskan, kebingungan, menguningnya kulit atau mata (*jaundice*), dengan gejala gagal ginjal akut (output urin rendah atau tidak ada), kehilangan penglihatan dan kejang.
- *Toxic epidermal necrolysis*: pengelupasan dan melepuh pada kulit atau selaput lendir, peradangan pada kulit yang dapat terjadi pada area tubuh yang luas
- Kebutaan

Efek samping serius yang sangat jarang (dapat terjadi pada 1 dari 10.000 orang):
- Sindrom Stevens-Johnson: nyeri pada kulit yang meluas, wajah bengkak, penyakit serius dengan kulit, mulut, mata dan area kelamin yang melepuh, gatal-gatal, lidah bengkak, ruam kulit yang menyebar berwarna merah atau ungu, ganti kulit.
- *Torsades de Pointes*: perubahan frekuensi jantung yang dapat disertai atau tidak dengan gejala, seperti nyeri dada (angina), pingsan, vertigo atau mual, palpitasi (detak jantung terasa) dan kesulitan bernapas.

Efek samping serius – frekuensi tidak diketahui (frekuensi tidak dapat dihitung dari data yang tersedia):
- Infeksi oportunistik (infeksi yang disebabkan bakteri, jamur, virus dan protozoa yang tidak berbahaya pada orang sehat namun menyerang orang dengan kekebalan tubuh lemah): diare berkepanjangan, demam dan sakit tenggorokan.
- Tumor jinak dan ganas telah dilaporkan sebagai akibat pengobatan dengan imunosupresi, termasuk kanker kulit ganas dan kanker kulit langka yang dapat meliputi lesi (luka) kulit yang dikenal sebagai sarkoma Kaposi. Gejalanya termasuk perubahan kulit seperti muncul warna baru atau perubahan warna kulit yang sudah ada, lesi, atau benjolan.Kasus aplasia sel darah merah murni (pengurangan jumlah sel darah merah yang sangat parah) dan anemia hemolitik (penurunan jumlah sel darah merah karena kerusakan abnormal disertai dengan kelelahan) telah dilaporkan. Anda mungkin tidak memiliki gejala atau tergantung pada keparahan kondisi, anda dapat merasakan: kelelahan, apatis, kulit pucat, sesak napas, pusing, sakit kepala, nyeri dada dan rasa dingin di tangan dan kaki.
- Kasus agranulositosis (penuruanan sel darah putih yang tinggi disertai dengan ulkus di mulut, demam dan infeksi). Anda mungkin tidak memiliki gejala atau Anda mungkin merasa demam mendadak, menggigil dan sakit tenggorokan.
- Reaksi alergi dan anafilaksis dengan gejala berikut: ruam gatal mendadak (gatal-gatal), pembengkakan tangan, kaki, pergelangan kaki, wajah, bibir, mulut atau tenggorokan (yang dapat menyebabkan kesulitan dalam menelan atau bernapas) dan Anda mungkin merasa akan pingsan.
- *Posterior Reversible Encephalopathy Syndrome* (PRES): sakit kepala, kebingungan, perubahan perasaan, kejang, dan gangguan penglihatan. Hal ini dapat menjadi gejala dari gangguan yang

dinamakan sindrom *posterior reversible encephalopathy*, yang telah dilaporkan pada beberapa pasien yang menggunakan tacrolimus.

- Neuropati optik (ketidaknormalan saraf mata): gangguan dengan penglihatan Anda seperti penglihatan kabur, gangguan pada saat melihat warna, kesulitan untuk melihat detil atau batasan pada jarak pandang anda.

Efek samping yang tercantum di bawah ini juga dapat terjadi setelah menggunakan Prograf® dan dapat menjadi serius:

Efek samping yang sangat umum (dapat mempengaruhi lebih dari 1 dari 10 orang):

- Peningkatan gula darah, diabetes mellitus, peningkatan kalium dalam darah
- Sulit tidur
- Gemetar, sakit kepala
- Peningkatan tekanan darah
- Tes fungsi hati yang tidak normal
- Diare, mual
- Masalah ginjal

Efek samping yang umum (dapat mempengaruhi hingga 1 dari 10 orang):

- Berkurangnya hasil hitung sel darah (keping darah, sel darah merah atau putih), meningkatnya hasil hitung sel darah putih, perubahan pada hasil hitung sel darah merah (terlihat pada hasil tes darah).
- Pengurangan magnesium, fosfat, kalium, kalsium atau natrium dalam darah, kelebihan cairan, peningkatan asam urat atau lipid dalam darah, penurunan nafsu makan, peningkatan keasaman darah, perubahan lain dalam garam darah
- Gejala cemas, kebingungan dan disorientasi, depresi, perubahan suasana hati, mimpi buruk, halusinasi, gangguan mental
- Pusing, gangguan dalam kemampuan menulis, gangguan sistem saraf
- Peningkatan sensitifitas terhadap cahaya, gangguan mata
- Denging suara di telinga

- Berkurangnya aliran darah di pembuluh jantung, detak jantung lebih cepat
- Perdarahan, penyumbatan sebagian atau lengkap dari pembuluh darah, penurunan tekanan darah
- Sesak napas, perubahan dalam jaringan paru-paru, pengumpulan cairan di area paru-paru, radang tenggorokan, batuk, gejala seperti flu
- Radang atau maag yang menyebabkan sakit perut atau diare, pendarahan di perut, radang atau ulkus di mulut, pengumpulan cairan di area perut, muntah, nyeri perut, gangguan pencernaan, sulit buang air besar, perut kembung, mencret, masalah perut
- Kulit menguning karena masalah hati, kerusakan jaringan hati dan radang hati
- Gatal, ruam, rambut rontok, jerawat, peningkatan keringat
- Nyeri pada sendi, kaki atau punggung, kejang otot
- Kurangnya fungsi ginjal, berkurangnya produksi urin, gangguan atau nyeri buang air kecil
- Lemah, demam, pengumpulan cairan dalam tubuh, rasa sakit dan tidak nyaman, peningkatan enzim alkali fosfatase dalam darah, peningkatan berat badan, perasaan perubahan suhu tubuh yang menggangu

Efek samping tidak umum (dapat mempengaruhi hingga 1 dalam 100 orang):
- Perubahan dalam pembekuan darah, penurunan semua jumlah sel darah
- Dehidrasi, berkurangnya protein atau gula dalam darah, peningkatan fosfat dalam darah
- Koma, perdarahan di otak, stroke, kelumpuhan, gangguan otak, kelainan dalam berbicara dan bahasa, masalah memori
- Pandangan kabur karena kelainan pada lensa mata
- Pendengaran terganggu
- Denyut jantung tidak teratur, denyut jantung berhenti, penurunan kinerja jantung, gangguan otot jantung, pembesaran otot jantung, peningkatan detak jantung, EKG tidak normal, denyut jantung dan denyut nadi tidak normal
- Pembekuan darah dalam pembuluh vena pada anggota tubuh, *shock* (kondisi darurat yang mengancam jiwa)
- Kesulitan bernapas, gangguan saluran pernapasan, asma
- Obstruksi usus (kelainan pada usus), peningkatan level darah dari enzim amilase, refluks (kembalinya isi lambung ke tenggorokan, penundaan proses pengosongan lambung
- Dermatitis (peradangan pada kulit), sensasi rasa terbakar di bawah sinar matahari
- Gangguan sendi
- Ketidakmampuan untuk buang air kecil, nyeri haid dan perdarahan haid yang tidak normal
- Kerusakan pada beberapa organ, seperti penyakit influenza, peningkatan sensitifitas terhadap panas dan dingin, rasa tertekan pada dada, gelisah, peningkatan enzim laktat dehidrogenase dalam darah, penurunan berat badan

Efek samping yang jarang (dapat mempengaruhi hingga 1 dari 1.000 orang):
- Pendarahan kecil pada kulit karena pembekuan darah
- Peningkatan kekakuan otot
- Ketulian
- Pengumpulan cairan di sekitar jantung
- Sesak napas akut

- Pembentukan kista/benjolan di pankreas
- Masalah dengan aliran darah di hati
- Pertumbuhan rambut tidak normal
- Haus, pingsan, rasa sesak di dada, mobilitas menurun, ulkus

Efek samping yang sangat jarang terjadi (dapat mempengaruhi hingga 1 dari 10.000 orang):
- Melemahnya otot
- EKG tidak normal
- Kerusakan pada hati, penyempitan pembuluh empedu
- Nyeri saat buang air kecil disertai darah dalam urin
- Peningkatan jaringan lemak

Efek samping utama pada pasien dengan Lupus Nefritis:
- Peningkatan β2 mikroglobulin dalam urin, peningkatan enzim N-acetyl-beta-D-glucosaminidase (NAG) dalam urin, radang nasofaring (bagian atas tenggorokan), hiperuresemia (kadar asam urat tinggi dalam darah), leukositosis (kondisi sel darah putih melebihi batas normal) dan peningkatan kadar kreatinin

Pelaporan efek samping
Jika Anda mengalami efek samping, segera hubungi dokteratau apoteker Anda. Hal ini termasuk kemungkinan efek samping yang tidak tercantum pada leaflet ini. Anda dapat melaporkan efek samping secara langsung melalui email pv@id.astellas.com. Dengan melaporkan efek samping yang terjadi, Anda dapat membantu memberikan informasi lebih lanjut mengenai keamanan obat ini.

5. Bagaimana cara menyimpan Prograf®

Jauhkan Prograf® dari pandangan dan jangkauan anak-anak.

Gunakan kapsul segera setelah dikeluarkan dari blister.

Jangan gunakan Prograf® setelah tanggal kadaluarsa yang tercantum pada dus dan blister setelah kata *Exp. Date*. Tanggal kadaluarsa mengacu pada hari terakhir pada bulan tersebut.

Simpan pada kemasan asli untuk menjaga dari kelembaban dan jangan melebihi 30°C.
Setelah membuka kemasan aluminum, kapsul dari blister harus digunakan dalam waktu 3 bulan.

6. Isi kemasan da informasi lainnya Apa yang terkandung dalam Prograf®

Prograf® 0.5 mg hard capsules

- Zat aktifnya adalah tacrolimus. Setiap kapsul mengandung 0.5 mg tacrolimus sebagai tacrolimus monohydrate.
- Zat tambahan lainnya:

Dalam kapsul terkandung: Hypromellose, croscarmellose sodium, lactose monohydrate, magnesium stearate.

Prograf® 1 mg hard capsules

- Zat aktifnya adalah tacrolimus. Setiap kapsul mengandung 1 mg tacrolimus sebagai tacrolimus monohydrate.

- Zat tambahan lainnya:
  Dalam kapsul terkandung: Hypromellose, croscarmellose sodium, lactose monohydrate, magnesium stearate.

Seperti apa tampilan Prograf®

Prograf® 0.5 mg hard capsules

Kapsul berwarna kuning muda buram tercetak merah “0.5 mg” dan “[f] 607”, mengandung bubuk putih.

Prograf ®1 mg hard capsules

Kapsul berwarna putih buram tercetak merah “1 mg” dan “[f] 617”, mengandung bubuk putih.

Batas kadaluarsa

Kemasan tertutup: 3 tahun

Perhatian khusus untuk penyimpanan

Jangan disimpan pada suhu di atas 30°C

Kemasan blister yang dibungkus aluminium: simpan dalam kemasan aslinya.

HARUS DENGAN RESEP DOKTER.

Nomor Ijin Edar:
Prograf 0.5mg : DKI1108000201A1
Prograf 1mg : DKI1108000201B1

Pemegang izin edar dan produsen

Pemegang izin edar:
PT. Combiphar
Jl. Raya Simpang 383, Padalarang 40553,
Jawa Barat, Indonesia

Produsen:
Astellas Ireland Co., Ltd.
Killorglin
County Kerry
V93 FC86, Irlandia

Diimpor dan didistribusikan oleh:
PT. Astellas Pharma Indonesia
Jakarta, Indonesia

untuk informasi lebih lanjut mengenai obat ini, harap menghubungi:
PT. Astellas Pharma Indonesia

Website: www.astellas.com/id