NAME OF THE MEDICINAL PRODUCT

Prograf capsules 0.5 mg
Prograf capsules 1 mg
Prograf capsules 5 mg
Prograf concentrate for infusion 5 mg/ml

QUALITATIVE AND QUANTITATIVE COMPOSITION

PROGRAF CAPSULES
Hard gelatin capsules containing 0.5 mg, 1 mg and 5 mg tacrolimus.
Excipient with known effect: Lactose monohydrate.
Other excipients of capsule content: Hypromellose, Croscarmellose sodium, Magnesium stearate.

PROGRAF CONCENTRATE FOR INFUSION 5 mg/ml
Concentrate for intravenous infusion containing tacrolimus 5 mg per 1 ml.
Excipients with known effect: Polyoxyethylene hydrogenated castor oil and dehydrated alcohol.

THERAPEUTIC INDICATION

Primary immunosuppression in liver and kidney allograft recipients and liver and kidney allograft rejection resistant to conventional immunosuppressive agents.

POSOLOGY AND METHOD OF ADMINISTRATION

Only physicians experienced in immunosuppressive therapy and the management of organ transplant patients should prescribe Prograf. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow up of the patient.

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.

Dosing should commence orally, if necessary via an intranasal gastric tube. If the clinical condition of the patient does not allow oral therapy, initial intravenous dosing may be necessary.

Dosage recommendations

Primary Immunosuppression Dose Levels – Adults

Liver and kidney transplantation: Oral tacrolimus therapy should commence at 0.10 – 0.20 mg/kg/day for liver transplantation and at 0.15 – 0.30 mg/kg/day for kidney transplantation administered as two divided doses. Administration should start approximately 6 hours after the completion of liver transplant surgery and within 24 hours after completion of kidney transplant surgery. If clinical condition of the patient does not allow oral dosing, then intravenous tacrolimus therapy should be initiated as a continuous 24 hours infusion at 0.01 to 0.05 mg/kg for liver transplant and 0.05 to 0.10 mg/kg for kidney transplant.

Primary Immunosuppression Dose Levels – Paediatric Patients
Paediatric patients generally require doses 1.5 to 2 times higher than the recommended adult doses to achieve the same blood levels.

Liver and kidney transplantation: An initial dose of 0.3 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 the liver transplantation or 0.1 mg/kg/day for kidney transplantation should be administered as a continuous 24 hours infusion.

Maintenance Therapy Dose Levels
It is necessary to continue immunosuppression with oral Prograf to maintain graft survival. Dose can frequently be reduced during maintenance therapy. Dosing should be primarily based on clinical assessments of rejection and tolerability of the patient.
If progression of disease occurs (e.g. signs of acute rejection) alteration of the immunosuppressive regimen should be considered. Increase the amount of corticosteroids, introduction of short courses of mono/polyclonal antibodies and increase in the dose of Prograf have been used to manage rejection episodes.
If signs of toxicity (e.g. pronounced adverse event) are noted, the dose of Prograf should be reduced.
When Prograf is administered in combination with a corticosteroid these may often be reduced and in rare cases the treatment has continued as monotherapy.

Therapy Dose Levels for Liver and Kidney Allograft Rejection Resistant to Conventional Immunosuppressive Regimens
In patients experiencing rejections episodes which are unresponsive to conventional immunosuppressive therapy, Prograf treatment should begin with the initial dose recommended for primary immunosuppression in that particular allograft.
Prograf should be initiated after considering cyclosporin blood concentrations and the clinical condition of the patient. In practice, Prograf therapy has been initiated 12-24 hours after discontinuation of cyclosporin. Monitoring of cyclosporin blood levels should be continued following conversion as the clearance of cyclosporin may be affected.

Duration of dosing
For oral dosing, the capsules normally have to be taken continuously to suppress graft rejection and no limit for therapy duration can be given. Patients should be converted from intravenous to oral medication as soon as individual circumstances permit. Intravenous therapy should not be continued for more than 7 days.

Mode of Intake
Capsules should generally be administered on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal, to achieve maximal absorption (see Pharmacokinetic properties).

Monitoring of Whole Blood Concentrations
Drug level monitoring is recommended during the early post-transplantation period, following dose adjustment of Prograf therapy after switching from another immunosuppressive regimen or following co-administration of drugs which are likely to lead to a drug interaction. Trough blood levels of Prograf should also be monitored periodically during maintenance therapy. The frequency of blood level monitoring should be based on clinical needs. As tacrolimus has a

long half-life, it can take several days for adjustments in Prograf dosing to be reflected in changes in blood levels.

Patient with Liver Impairment
A dose reduction is necessary.

Patient with Renal Impairment
Careful monitoring of renal function including serial creatinine estimations, calculations of creatinine clearance and monitoring urine output is recommended.

Elderly Patients
There is no evidence currently available to indicate that dosing should be adjusted in older people.

CONTRAINDICATIONS

- Known hypersensitivity to tacrolimus or other macrolides.
- Prograf Capsules 1 mg and Prograf Capsules 5 mg in addition; known hypersensitivity to other ingredients.
- Prograf Concentration for Infusion 5 mg/ml in addition;
  known hypersensitivity to polyoxyethylated castor oil (HCO-60) or structurally related compounds.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

During the initial post-transplant period, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, neurological and visual status, fasting blood glucose levels, electrolytes (particularly potassium), liver and renal function tests, haematology parameters, coagulation values and plasma protein determinations. If clinically relevant changes are seen, adjustments of the immunosuppressive regimen should be considered.

<u>Substances with potential for interaction</u>
Inhibitors or inducers of CYP3A4 should only be co-administered with tacrolimus after consulting a transplant specialist, due to the potential for drug interactions resulting in serious adverse reactions including rejection or toxicity (see Interactions with other medicinal products and other forms of interaction).

CYP3A4 inhibitors
Concomitant use with CYP3A4 inhibitors may increase tacrolimus blood levels, which could lead to serious adverse reactions, including nephrotoxicity, neurotoxicity and QT prolongation. When concomitant use of strong CYP3A4 inhibitors (such as ritonavir, cobicistat,

ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, clarithromycin or josamycin) with tacrolimus is required, tacrolimus blood levels should be monitored frequently, starting within the first few days of co-administration, under the supervision of a transplant specialist, to adjust the tacrolimus dose if appropriate in order to maintain similar tacrolimus exposure. Renal function, ECG including the QT interval, and the clinical condition of the patient should also be closely monitored.
Dose adjustment needs to be based upon the individual situation of each patient. An immediate dose reduction at the time of treatment initiation may be required (see Interactions with other medicinal products and other forms of interaction).

Similarly, discontinuation of CYP3A4 inhibitors may affect the rate of metabolism of tacrolimus, thereby leading to subtherapeutic blood levels of tacrolimus, and therefore requires close monitoring and supervision of a transplant specialist.

CYP3A4 inducers
Concomitant use with CYP3A4 inducers may decrease tacrolimus blood levels, potentially increasing the risk of transplant rejection. When concomitant use of strong CYP3A4 inducers (such as rifampicin, phenytoin, carbamazepine) with tacrolimus is required, tacrolimus blood levels should be monitored frequently, starting within the first few days of co-administration, under the supervision of a transplant specialist, to adjust the tacrolimus dose if appropriate, in order to maintain similar tacrolimus exposure. Graft function should also be closely monitored (see Interactions with other medicinal products and other forms of interaction).

Similarly, discontinuation of CYP3A4 inducers may affect the rate of metabolism of tacrolimus, thereby leading to supratherapeutic blood levels of tacrolimus, and therefore requires close monitoring and supervision of a transplant specialist.

Herbal preparations
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 (see Interactions with other medicinal products and other forms of interaction).

Other interactions
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 Posology and method of administration and Interaction with other medicinal products and other forms of interaction).

High potassium intake or potassium-sparing diuretics should be avoided (see Interaction with other medicinal products and other forms of interaction).

Certain combinations of tacrolimus with drugs known to have neurotoxic effects may increase the risk of these effects (see Interaction with other medicinal products and other forms of interaction.

Vaccination
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.

Gastrointestinal disorders
Gastrointestinal perforation has been reported in patients treated with tacrolimus. As gastrointestinal perforation is a medically important event that may lead to a life-threatening or serious condition, adequate treatments should be considered immediately after suspected symptoms or signs occur.
Since levels of tacrolimus in blood may significantly change during diarrhoea episodes, extra monitoring of tacrolimus concentrations is recommended during episodes of diarrhoea.

Cardiac disorders
Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies, have been observed on rare occasions. Most cases have been reversible, occurring primarily in children with tacrolimus 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, particularly young children and those receiving substantial 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 agent should be considered. Tacrolimus may prolong the QT interval and may cause *Torsades de pointes*. Caution should be exercised in patients with risk factors for QT prolongation, including patients with a personal or family history of QT prolongation, congestive heart failure, bradyarrhythmias and electrolyte abnormalities. Caution should also be exercised in patients diagnosed or suspected to have Congenital Long QT Syndrome or acquired QT prolongation or patients on concomitant medications known to prolong the QT interval, induce electrolyte abnormalities or known to increase tacrolimus exposure (see Interaction with other medicinal products and other forms of interaction).

Lymphoproliferative disorders and malignancies
Patients treated with Prograf have been reported to develop Epstein-Barr virus (EBV)-associated lymphoproliferative disorders (see Undesirable effects).
Patients switched to Prograf therapy should not receive anti-lymphocyte treatment concomitantly. Very young (<2 years old), EBV-VCA-negative children have been reported to be 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.

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

As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown (see Undesirable effects).

Posterior reversible encephalopathy syndrome (PRES)
Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking tacrolimus 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 systemic tacrolimus is advised. Most patients completely recover after appropriate measures are taken.

Opportunistic infections
Patients treated with immunosuppressants, including Prograf are at increased risk for opportunistic infections (bacterial, fungal, viral and protozoal) such as BK virus associated nephropathy, JC virus associated progressive multifocal leukoencephalopathy (PML), and CMV infection. These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions including graft rejection that physicians should consider in patients with deteriorating hepatic or renal function or neurological symptoms.

Nephrotoxicity
Tacrolimus can result 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, hyperkalaemia, 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 Interactions with other medicinal products and other forms of interaction).

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.

Thrombotic microangiopathy (TMA) (including haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP))
Thrombotic microangiopathies may have a multifactorial etiology. Risk factors for TMA that can occur in transplant patients include, for example, severe infections, graft-versus-host disease (GVHD), Human Leukocyte Antigen (HLA) mismatch, the use of calcineurin inhibitors, and mammalian target of rapamycin (mTOR) inhibitors. These risk factors may either alone or as a combination effect contribute to the risk of TMA.

Concurrent use of tacrolimus and mTOR inhibitors may contribute to the risk of TMA.

Excipients

As Prograf capsule contains lactose, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The printing ink used to mark Prograf capsules 0.5 mg and 1.0 mg 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 capsules 0.5 mg and 1.0 mg. This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

Prograf Concentrate for Infusion contains polyoxyethylene hydrogenated castor oil which has been reported to cause anaphylactoid reactions. These reactions consist of 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 preparations containing polyoxyethylene castor oil derivatives either by intravenous injection or infusion, and in patients with an allergenic predisposition. The risk of anaphylaxis may be reduced by slow infusion of reconstituted Prograf concentrate for infusion 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 concentrate for infusion 5 mg/ml should be taken into account.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Metabolic 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 medicinal products or herbal remedies known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels. Similarly, discontinuation of such products or herbal remedies may affect the rate of metabolism of tacrolimus and thereby the blood levels of tacrolimus.

Pharmacokinetics studies have indicated that the increase in tacrolimus blood levels when co-administered with inhibitors of CYP3A4 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.

It is recommended strongly to closely monitor tacrolimus blood levels under supervision of a transplant specialist, as well as monitor for graft function, QT prolongation (with ECG), renal function and other side effects including neurotoxicity, whenever substances which have the potential to alter CYP3A4 metabolism are used concomitantly and to adjust or interrupt the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure (see Posology and method of administration & Special warnings and precautions for use). Similarly, patients should be closely monitored when using tacrolimus concomitantly with multiple substances that affect CYP3A4 as the effects on tacrolimus exposure may be enhanced or counteracted.

Medicinal products which have effects on tacrolimus are listed in the table below. The examples of drug-drug interactions are not intended to be inclusive or comprehensive and therefore the label of each drug that is co-administered with tacrolimus should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regards to co-administration.

Medicinal products which have effects on tacrolimus:

Drug/Substance Class or Name	Drug interaction effect	Recommendations concerning co-administration
Grapefruit or grapefruit juice	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) [see Special warnings and precautions for use].	Avoid grapefruit or grapefruit juice.
Ciclosporin	May increase tacrolimus whole blood trough concentrations. In addition, synergistic/additive nephrotoxic effects can occur.	The simultaneous use of ciclosporin and tacrolimus should be avoided [see Special warnings and precautions for use].
Products known to have nephrotoxic or neurotoxic effects: aminoglycosides, gyrase inhibitors, vancomycin, sulfamethoxazole + trimethoprim, NSAIDs, ganciclovir, acyclovir, amphotericin B, ibuprofen, cidofovir, foscarnet	May enhance nephrotoxic or neurotoxic effects of tacrolimus.	When co-administration is required, monitor renal function and other side effects and adjust tacrolimus dose if needed.

Drug/Substance Class or Name	Drug interaction effect	Recommendations concerning co-administration
Strong CYP3A4 inhibitors: antifungal agents (e.g., ketoconazole, itraconazole, posaconazole, voriconazole), the macrolide antibiotics (e.g., telithromycin, troleandomycin, clarithromycin, josamycin), HIV protease inhibitors (e.g., ritonavir, nelfinavir, saquinavir), HCV protease inhibitors (e.g. telaprevir, boceprevir, and the combination of ombitasvir and paritaprevir with ritonavir, when used with and without dasabuvir), nefazodone, the pharmacokinetic enhancer cobicistat, and the kinase inhibitors idelalisib, ceritinib. Strong interactions have also been observed with the macrolide antibiotic erythromycin.	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., nephrotoxicity, neurotoxicity, QT prolongation) which requires close monitoring [see Special warnings and precautions for use]. Rapid and sharp increases in tacrolimus levels, may occur, as early as within 1-3 days after co-administration, despite immediate reduction of tacrolimus dose. Overall tacrolimus exposure may increase >5 fold. When ritonavir combinations are co-administered, tacrolimus exposure may increase >50 fold. Nearly all patients may require a reduction in tacrolimus dose and temporary interruption of tacrolimus may also be necessary. The effect on tacrolimus blood concentrations may remain for several days after co-administration is completed.	When co-administration of a strong CYP3A4 inhibitor is required, consider omitting the dose of tacrolimus the day the strong CYP3A4 inhibitor is initiated. Reinitiate tacrolimus the next day at a reduced dose based on tacrolimus blood concentrations. Changes in both tacrolimus dose and/or dosing frequency should be individualized and adjusted as needed based on tacrolimus trough concentrations, which should be assessed at initiation, monitored frequently throughout (starting within the first few days) and re-evaluated on and after completion of the CYP3A4 inhibitor. Upon completion, appropriate dose and dosing frequency of tacrolimus should be guided by tacrolimus blood concentrations. Monitor renal function, ECG for QT prolongation, and other side effects closely.

Drug/Substance Class or Name	Drug interaction effect	Recommendations concerning co-administration
Moderate or weak CYP3A4 inhibitors: antifungal agents (e.g., fluconazole, isavuconazole, clotrimazole, miconazole), the macrolide antibiotics (e.g., azithromycin), calcium channel blockers (e.g., nifedipine, nicardipine, diltiazem, verapamil), amiodarone, danazol, ethinylestradiol, lansoprazole, omeprazole, the HCV antivirals elbasvir/grazoprevir and glecaprevir/pibrentasvir, the CMV antiviral letermovir, and the tyrosine kinase inhibitors nilotinib, crizotinib, imatinib and (Chinese) herbal remedies containing extracts of *Schisandra sphenanthera*	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) [see Special warnings and precautions for use]. A rapid increase in tacrolimus level may occur.	Monitor tacrolimus whole blood trough concentrations frequently, starting within the first few days of co-administration. Reduce tacrolimus dose if needed [see Posology and method of administration]. Monitor renal function, ECG for QT prolongation, and other side effects closely.
In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, midazolam, nilvadipine, norethisterone, quinidine, tamoxifen	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) [see Special warnings and precautions for use].	Monitor tacrolimus whole blood trough concentrations and reduce tacrolimus dose if needed [see Posology and method of administration]. Monitor renal function, ECG for QT prolongation, and other side effects closely.

Drug/Substance Class or Name	Drug interaction effect	Recommendations concerning co-administration
Strong CYP3A4 inducers: rifampicin, phenytoin, carbamazepine, apalutamide, enzalutamide, mitotane, or St. John's wort (*Hypericum perforatum*)	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection [see Special warnings and precautions for use]. Maximal effect on tacrolimus blood concentrations may be achieved 1-2 weeks after co-administration. The effect may remain 1-2 weeks after completion of the treatment.	When co-administration of a strong CYP3A4 inducer is required, patients may require an increase in tacrolimus dose. Changes in tacrolimus dose should be individualized and adjusted as needed based on tacrolimus trough concentrations, which should be assessed at initiation, monitored frequently throughout (starting within the first few days) and re-evaluated on and after completion of the CYP3A4 inducer. After use of the CYP3A4 inducer has ended, tacrolimus dose may need to be adjusted gradually. Monitor graft function closely.
Moderate CYP3A4 inducers: metamizole, phenobarbital, isoniazid, rifabutin, efavirenz, etravirine, nevirapine; weak CYP3A4 inducers: flucloxacillin	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection [see Special warnings and precautions for use].	Monitor tacrolimus whole blood trough concentrations and increase tacrolimus dose if needed [see Posology and method of administration]. Monitor graft function closely.
Products known to have high affinity for plasma proteins, e.g.: NSAIDs, oral anticoagulants, oral antidiabetics	Tacrolimus is extensively bound to plasma proteins. Possible interactions with other active substances known to have high affinity for plasma proteins should be considered.	Monitor tacrolimus whole blood trough concentrations and adjust tacrolimus dose if needed [see Posology and method of administration].
Prokinetic agents: metoclopramide, cimetidine and magnesium-aluminium-hydroxide	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation).	Monitor tacrolimus whole blood trough concentrations and reduce tacrolimus dose if needed [see Posology and method of administration]. Monitor closely for renal function, for QT prolongation with ECG, and for other side effects.
Maintenance doses of corticosteroids	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection [see Special warnings and precautions for use].	Monitor tacrolimus whole blood trough concentrations and increase tacrolimus dose if needed [see Posology and method of administration]. Monitor graft function closely.

Drug/Substance Class or Name	Drug interaction effect	Recommendations concerning co-administration
Caspofungin	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection (mechanism not confirmed).	Monitor tacrolimus whole blood trough concentrations and increase tacrolimus dose if needed.
High dose prednisolone or methylprednisolone	May have impact on tacrolimus blood levels (increase or decrease) when administered for the treatment of acute rejection.	Monitor tacrolimus whole blood trough concentrations and adjust tacrolimus dose if needed.
Direct-acting antiviral (DAA) therapy	May have impact on the pharmacokinetics of tacrolimus by changes in liver function during DAA therapy, related to clearance of hepatitis virus. A decrease in tacrolimus blood levels may occur. However, the CYP3A4 inhibiting potential of some DAAs may counteract that effect or lead to increased tacrolimus blood levels.	Monitor tacrolimus whole blood trough concentrations and adjust tacrolimus dose if needed to ensure continued efficacy and safety.

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 Special warnings and precautions for use). Care should be taken when tacrolimus is co-administered with other agents that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole), as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Close monitoring of serum potassium is recommended.

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.

Prograf should not be administered concurrently with ciclosporin. 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 not recommended and care should be taken when administering tacrolimus to patients who have previously received ciclosporin (see Posology and method of administration & Special warnings and precautions for use).

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. Available data suggests 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 phenazone.

Mycophenolic acid. Caution should be exercised when switching combination therapy from ciclosporin, which interferes with enterohepatic recirculation of mycophenolic acid, to tacrolimus, which is devoid of this effect, as this might result in changes of mycophenolic acid exposure. Drugs which interfere with mycophenolic acid's enterohepatic cycle have potential to reduce the plasma level and efficacy of mycophenolic acid. Therapeutic drug monitoring of mycophenolic acid may be appropriate when switching from ciclosporin to tacrolimus or vice versa.
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 Special warnings and precautions for use).

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Human data show that tacrolimus is able to cross the placenta and infants exposed to tacrolimus *in utero* may be at a risk of prematurity, birth defects/congenital anomalies, low birth weight, and fetal distress.

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

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 of appropriate contraception prior to starting treatment of tacrolimus.

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 foetus.

In rats and rabbits, tacrolimus caused embryofoetal toxicity at doses which demonstrated maternal toxicity.

Breastfeeding
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 new born cannot be excluded, women should not breastfeed whilst receiving Prograf.

Fertility
A negative effect of tacrolimus on male fertility in the form of reduced sperm counts and motility was observed in rats (see Preclinical safety data).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Tacrolimus may cause visual and neurological disturbances. This effect may be enhanced if Prograf is administered in association with alcohol.

UNDESIRABLE EFFECTS
The adverse drug reaction profile associated with immunosuppressive agents is often difficult to establish owing to the underlying disease and the concurrent use of multiple medications.

Many of the adverse drug reactions stated below are reversible and/or respond to dose reduction. Oral administration appears to be associated with a lower incidence of adverse events compared with intravenous use. Adverse drug reactions 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); not known (cannot be estimated from the available data).

Infections and infestations
As is well known for other potent immunosuppressive agents, patients receiving tacrolimus are frequently at increased risk for infections (viral, bacterial, fungal, protozoal). The course of pre-existing infections may be aggravated. Both generalised and localised infections can occur. Cases of CMV infection, BK virus associated nephropathy, as well as cases of 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 EBV-associated lymphoproliferative disorders and skin malignancies have been reported in association with tacrolimus treatment.

Blood and lymphatic system disorders

common:	anaemia, leukopenia, thrombocytopenia, leukocytosis, red blood cell analyses abnormal
uncommon:	coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, neutropenia, thrombotic microangiopathy
rare:	thrombotic thrombocytopenic purpura, hypoprothrombinaemia
not known:	pure red cell aplasia, agranulocytosis, haemolytic anaemia, febrile neutropenia

Immune system disorders
Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus (see Special warnings and precautions for use).

Endocrine disorders
rare: hirsutism

Metabolism and nutrition disorders
very common: hyperglycaemic conditions, diabetes mellitus, hyperkalaemia
common: hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, appetite decreased, 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, writing impaired, 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
not known: posterior reversible encephalopathy syndrome (PRES)

Eye disorders
common: vision blurred, photophobia, eye disorders
uncommon: cataract
rare: blindness
not known: optic neuropathy

Ear and labyrinth disorders
common: tinnitus
uncommon: hypoacusis
rare: deafness neurosensory
very rare: hearing impaired

Cardiac disorders

common: ischaemic coronary artery disorders, tachycardia
uncommon: ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations, ECG investigations abnormal, heart rate and pulse investigations abnormal
rare: pericardial effusion
very rare: echocardiogram abnormal, electrocardiogram QT prolonged, *Torsades de pointes*

Vascular disorders
very common: hypertension
common: haemorrhage, thromboembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders
uncommon: infarction, venous thrombosis deep limb, shock

Respiratory, thoracic and mediastinal disorders
common: dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammations
uncommon: respiratory failures, 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: ileus paralytic, acute and chronic pancreatitis, amylase increased, gastrooesophageal reflux disease, impaired gastric emptying
rare: subileus, pancreatic pseudocyst

Hepatobiliary disorders
common: hepatic enzymes and function abnormalities, cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis
rare: hepatic artery thrombosis, venoocclusive liver disease
very rare: hepatic failure, bile duct stenosis

Skin and subcutaneous tissue disorders
common: pruritus, rash, alopecia, acne, sweating increased
uncommon: dermatitis, photosensitivity
rare: toxic epidermal necrolysis (Lyell's syndrome)
very rare: Stevens-Johnson syndrome

Musculoskeletal and connective tissue disorders
common: arthralgia, muscle spasms, pain in extremity, back pain
uncommon: joint disorders
rare: mobility decrease

Renal and urinary disorders
very common: renal impairment
common: renal failure, renal failure acute, oliguria, renal tubular necrosis, nephropathy toxic, urinary abnormalities, bladder and urethral symptoms
uncommon: anuria, haemolytic uraemic syndrome
very rare: nephropathy, cystitis haemorrhagic

Reproductive system and breast disorders
uncommon: dysmenorrhoea and uterine bleeding

General disorders and administration site conditions
common: asthenic conditions, febrile disorders, oedema, pain and discomfort, blood alkaline phosphatase increased, weight increased, body temperature perception disturbed
uncommon: multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling jittery, feeling abnormal, blood lactate dehydrogenase increased, weight decreased
rare: thirst, fall, chest tightness, ulcer
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).

Description of selected adverse reactions
Pain in extremity has been described in a number of published case reports as part of Calcineurin-Inhibitor Induced Pain Syndrome (CIPS). This typically presents as a bilateral and symmetrical, severe, ascending pain in the lower extremities and may be associated with supra-therapeutic levels of tacrolimus. The syndrome may respond to tacrolimus dose reduction. In some cases, it was necessary to switch to alternative immunosuppression.

OVERDOSE

Experience with overdosage is limited. Several cases of accidental overdosage have been reported; symptoms have included 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 protein binding, it is anticipated that tacrolimus will not be dialysable. In isolated patients with very high plasma levels, haemofiltration and diafiltration have been effective in

reducing toxic concentrations. In cases of oral intoxication, gastric lavage and/or the use of absorbents (such as activated charcoal) may be helpful, if used shortly after intake.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Calcineurin inhibitors, ATC code: L04AD02

At the molecular level, the effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP12) which is responsible for the intracellular accumulation of the compound. The FKBP12-tacrolimus complex specifically and competitively binds to and inhibits calcineurin, leading to a calcium-dependent inhibition of T-cell signal transduction pathways, thereby preventing transcription of a discrete set of lymphokine genes.

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

In particular, Prograf inhibits the formation of cytotoxic lymphocytes which are mainly responsible for graft rejection. The drug suppresses T-cell activation and T-helper cell dependant B-cell proliferation as well as the formation of lymphokines such as interleukins-2, -3 and gamma interferon and the expression of the interleukin-2 receptor.

Pharmacokinetic properties

Absorption

In man, tacrolimus has been shown to be able to be absorbed throughout the gastrointestinal tract. Following oral administration of Prograf capsules, peak concentrations (C_{max}) of the tacrolimus in blood are achieved in approximately 1 to 3 hours. In some patients, the drug appears to be continuously absorbed over a prolonged time period yielding more or less a flat absorption profile. The mean oral bioavailability of tacrolimus is in the range of 20% - 25%.

After oral administration (0.30 mg/kg/day) to liver transplant patients, steady state concentrations of tacrolimus were achieved within 3 days in most patients.

In healthy subjects, Prograf 0.5 mg, Prograf 1 mg and Prograf 5 mg hard capsules have been shown to be bioequivalent, when administered as equivalent dose.

The rate and extent of absorption of tacrolimus is greatest under fasted conditions. The presence of food decreases both the rate and extent of absorption of tacrolimus, the effect being most pronounced after a high-fat meal. The effect of a high-carbohydrate meal is less pronounced.
In stable liver transplant patients, the oral bioavailability of Prograf was reduced when it was administered after a meal of moderate fat (34% of calories) content. Decreases in AUC (27%) and C_{max} (50%), and an increase in t_{max} (173%) in whole blood were evident.
In a study of stable renal transplant patients who were administered Prograf immediately after a standard continental breakfast, the effect on oral bioavailability was less pronounced. Decreases in AUC (2 to 12%) and C_{max} (15 to 38%), and an increase in t_{max} (38 to 80%) in whole blood were evident.

Bile flow does not influence the absorption of tacrolimus and therefore commencement of tacrolimus therapy with an oral dose or early conversion of liver transplant patients from

intravenous to oral therapy is possible. There is strong correlation between the area under the curve (AUC) and the whole blood trough levels at steady state. Thus monitoring of whole blood trough levels provides a good estimate of systemic exposure.

Distribution and elimination

In man the disposition of tacrolimus after intravenous infusions may be describes as biphasic. In systemic circulation, tacrolimus binds strongly to erythrocytes resulting in the distribution of whole blood/plasma concentrations of tacrolimus is approximately 20:1. In plasma, the drug is highly plasma bound (>98.8%) to plasma proteins, mainly to serum albumin and (α-1-acid glycoprotein. Tacrolimus is extensively distributed in the body. The steady state volume of distribution based on plasma concentrations is approximately 1300 l (healthy subjects). Corresponding data based on whole blood data averaged 47.6 l.

The total body clearance (TBC) of tacrolimus from blood is low. In healthy subjects the average TBC estimated from whole blood concentrations was 2.25 l/h. In adult liver and kidney transplant patients, values of 4.1 l/h and 6.7 l/h respectively, have been observed. In paediatric liver transplant patients, the TBC is approximately twice that of adult liver transplant patients. Factors such as low haematocrit and protein levels, which result in an increase in the unbound fraction of tacrolimus, or corticosteroid-induced increased metabolism are considered to be responsible for the higher clearance rates observed following transplantation.

There is evidence that pharmacokinetics of tacrolimus change with improving clinical conditions of the patients. In liver transplant patients, the mean oral dose was decreased by 28% from day 7 to month 6 after transplantation to maintain similar mean trough levels of tacrolimus. Change in clearance and/or bioavailability were suggested as probable causes for this effect.

The half-life of tacrolimus is long and variable. In healthy volunteers the main half-life in whole blood is approximately 43 hours. In paediatric and adult liver transplant patients, it averaged 12.4 hours and 11.7 hours respectively. In adult kidney transplant patients, it averaged 15.6 hours. Increased clearance rates contribute to the shorter half-life observed in transplant recipients.

Metabolism and biotransformation

Tacrolimus is widely metabolised in the liver, primarily by the cytochrome P450-3A4 (CYP3A4) and the cytochrome P450-3A5 (CYP3A5). Tacrolimus 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. In systemic circulation only one of the inactive metabolites is present at low concentrations. Therefore, metabolites do not contribute to 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 the faeces. This indicates that tacrolimus is almost completely metabolized prior to elimination from the body and that the bile is the principal route of elimination.

Clinical Studies in Patients with Lupus Nephritis
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 (a dose of 3mg, once daily after supper) 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 the 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 ± S.D.	–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.

The major adverse reactions or abnormalities in clinical laboratory findings due to tacrolimus capsules in 65 patients with lupus nephritis in Phase II and Phase III trials were β_2 microglobulin urine increased (27.3%, 12/44), urinary NAG increased (22.2%, 14/63), nasopharyngitis (15.4%, 10/65), hyperuricaemia (14.1%, 9/64), leukocytosis (14.1%, 9/64), creatinine increased (12.5%, 8/64), diarrhoea (12.3%, 8/65), blood pressure increased (10.8%, 7/65), and hyperglycaemia (10.9%, 7/64).

Preclinical Safety Data
Embryotoxicity was observed in animal studies.

Tacrolimus subcutaneously administered to male rats at a 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.

PHARMACEUTICAL PARTICULARS

Incompatibilities
When diluting, Prograf Concentrate for Infusion must not be mixed with other medicinal products except those mentioned in Instructions for use/handling.

Tacrolimus is not compatible with PVC. Tubing, syringes and any other equipment used to prepare and administer Prograf Concentrate for Infusion and a suspension of Prograf capsule contents should not contain PVC. Tacrolimus is unstable under alkaline conditions. Combination of the reconstituted Prograf Concentrate for Infusion with other pharmaceutical products that produce a marked alkaline solution (e.g. aciclovir and ganciclovir) should be avoided.

SHELF LIFE/SHELF LIFE AFTER OPENING OF CAPSULES POUCH
See outer carton.

SPECIAL PRECAUTIONS FOR STORAGE
Prograf Capsules 0.5 mg, 1 mg and 5 mg
Store below 30ºC.
Store in the original package in order to protect from moisture.
Keep out of reach of children.

Prograf Concentrate for Infusion 5 mg/ml
Store below 25ºC.
Protect from light.
Keep out of reach of children.

INSTRUCTIONS FOR USE/HANDLING
Prograf Capsules should be taken immediately following removal from the blister.

Prograf Concentrate for Infusion must not be injected undiluted.
Prograf Concentrate for Infusion should be diluted in 5% w/v glucose solution or physiological saline solution in polyethylene, polypropylene or glass bottles, but not in PVC containers. Only transparent and colourless solutions should be used.
The concentration of a solution for infusion should be within the range 0.004 - 0.100 mg/ml.
The total volume of infusion during a 24-hour period should be in the range 20 - 500 ml.
The diluted solution should not be given as a bolus.

From a microbiological point of view, the product should be used immediately. Any unused concentrate in an opened ampoule or unused reconstituted solution should be disposed of immediately in accordance with local requirements to avoid contamination.

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.

PRODUCT REGISTRANT

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