PROGRAF™

NAME OF PRODUCT
Prograf Capsules 0.5 mg, Prograf Capsules 1 mg, Prograf Capsules 5 mg and Prograf Concentrate for Infusion 5 mg/mL

QUALITATIVE AND QUANTITATIVE COMPOSITION
Hard gelatin capsules containing 0.5 mg,1 mg and 5 mg tacrolimus on anhydrous basis.
Concentrate for intravenous infusion containing tacrolimus 5 mg per 1 mL.

CLINICAL PARTICULARS
Therapeutic Indications
Primary immunosuppression in liver and kidney allograft recipients and liver and kidney allograft rejection resistant to conventional immunosuppressive agents. It is recommended that Prograf be used concomitantly with adrenal corticosteroids. Because of the risk of anaphylaxis, Prograf Injection should be reserved for patients unable to take Prograf capsules only.

Only for Prograf Capsules 0.5 mg and 1 mg
Lupus nephritis (in a case where the effect of steroids is insufficient or administration of steroids is difficult because of their adverse reactions). For lupus nephritis, the efficacy and safety of this product for patients in an acute phase with high disease activity has not been established.

Posology and Method of Administration
Prograf therapy requires careful monitoring by adequately qualified and equipped personnel. The medicinal product should only be prescribed, and changes in immunosuppressive therapy initiated, by physicians experienced in immunosuppressive therapy and the management of transplant patients. For patients with lupus nephritis, this product should be prescribed by physicians experienced in lupus nephritis therapy.

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 Level Recommendations
Initial dose level recommendation.

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 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 hour 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 liver transplantation or 0.1 mg/kg/day for kidney transplantation should be administered as a continuous 24-hour 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.

Care should be taken when converting patients from ciclosporin-based to Prograf-based therapy (see Special Warnings and Precautions for Use; and Interaction with Other Medicinal Products and Other Forms of Interaction). 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.

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 need. 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.

Only for Prograf Capsules 0.5 mg and 1 mg
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 the 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.

Patient with Liver Impairment
A dose reduction is necessary.

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

Elderly Patients
Limited experience suggests that doses should be the same as for adults.

Contraindications
Prograf capsule:
Hypersensitivity to tacrolimus or other macrolides.
Hypersensitivity to any of the excipients.

Prograf concentrate for infusion:
Hypersensitivity to tacrolimus or other macrolides.
Hypersensitivity to any of the excipients- in particular polyoxyethylene hydrogenated castor oil 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 (see Posology and Method of Administration; and Undesirable Effects).

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.

Substances with potential for interaction
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 Interaction 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 Interaction 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 Interaction 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.

P-glycoprotein
Caution should be observed when co-administering tacrolimus with drugs that inhibit P-glycoprotein, as an increase in tacrolimus levels may occur. Tacrolimus whole blood levels and the clinical condition of the patient should be monitored closely. An adjustment of the tacrolimus dose may be required (see Interactions with Other Medicinal Products and Other Forms of Interactions).

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 Interactions).

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 Interactions with Other Medicinal Products and Other Forms of Interaction).

High potassium intake or potassium-sparing diuretics should be avoided (see Interactions with Other Medicinal Products and Other Forms of Interactions).

Certain combinations of tacrolimus with drugs known to have neurotoxic effects may increase the risk of these effects (see Interactions with Other Medicinal Products and Other Forms of Interactions).

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.

Nephrotoxicity
Tacrolimus can result in renal function impairment in post-transplant patients. Acute renal impairment without active intervention may progress to chronic renal impairment. Patients with impaired renal function should be monitored closely as the dosage of tacrolimus may need to be reduced. The risk for nephrotoxicity may increase when tacrolimus is concomitantly administered with drugs associated with nephrotoxicity (see section Interactions with Other Medicinal Products and Other Forms of Interactions). Concurrent use of tacrolimus with drugs known to have nephrotoxic effects should be avoided. When co-administration is required, tacrolimus trough blood level and renal function should be monitored closely and dosage reduction should be considered if nephrotoxicity occurs.

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 Interactions with Other Medicinal Products and Other Forms of Interactions).

Lymphoproliferative disorders and malignancies
Patients treated with Prograf have been reported to develop Epstein-Barr virus (EBV)-associated lymphoproliferative disorders and other malignancies, including skin cancers and Kaposi's sarcoma (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 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.

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.

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.

As with other potent immunosuppressive compounds, the risk of secondary cancer is unknown.

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 and seizure control and immediate discontinuation of systemic tacrolimus is advised. Most patients completely recover after appropriate measures are taken.

Infections including opportunistic infections
Patients treated with immunosuppressants, including Prograf are at increased risk of infections (bacterial, fungal, viral and protozoal) such as CMV infection, BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). Patients are also at an increased risk of infections with viral hepatitis (for example, hepatitis B and C reactivation and *de novo* infection, as well as hepatitis E, which may become chronic). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in patients with deteriorating hepatic or renal function or neurological symptoms.
Prevention and management should be in accordance with appropriate clinical guidance.

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. If TMA is diagnosed, prompt treatment is required, and discontinuation of tacrolimus should be considered at the discretion of the treating physician.

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.

Excipients
As Prograf 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 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. This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

Prograf 5 mg/mL concentrate for solution for infusion contains polyoxyethylene hydrogenated castor oil, which has been reported to cause anaphylactoid reactions. Caution is therefore necessary in patients who have previously received preparations containing polyoxyethylene castor oil derivative 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 5 mg/mL concentrate for solution for infusion or by the prior administration of an antihistamine.

The ethanol content (638 mg per mL) of Prograf 5 mg/mL concentrate for solution for infusion should be taken into account.

If administered accidentally either arterially or perivasally, the reconstituted Prograf 5 mg/mL concentrate for solution for infusion may cause irritation at the injection site.

Warnings and precautions for patients with Lupus nephritis
The safety of this product in children has not been established in lupus nephritis (no clinical experiences).

Patients with lupus nephritis also need special attention because the renal disorder may become aggravated as the lupus nephritis progresses.

Since patients with lupus nephritis are more likely to suffer from hyperlipidaemia, hypertension, or the like which is considered to be a risk factor for the development of the coronary artery disease associated with systemic lupus erythematosus, the underlying disease, patients being treated with this product should also receive appropriate therapy for these risk factors of the coronary diseases.

In patients with lupus nephritis, creatinine clearance decreased after 28 weeks of treatment. There are only a 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.

Interaction 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 CYP3A metabolism are used concomitantly and to adjust or interrupt the tacrolimus dose if appropriate in order to maintain similar tacrolimus exposure (see Posology and Method of Administration; and 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.
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.

Drug/Substance Class or Name	Drug interaction effect	Recommendations concerning co-administration
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.
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.
Caspofungin	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection. Mechanism of interaction has not been confirmed.	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].

Drug/Substance Class or Name	Drug interaction effect	Recommendations concerning co-administration
Cannabidiol (P-gp inhibitor)	There have been reports of increased tacrolimus blood levels during concomitant use of tacrolimus with cannabidiol. This may be due to inhibition of intestinal P-glycoprotein, leading to increased bioavailability of tacrolimus.	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 [see Posology and Method of Administration and Special Warnings and Precautions for Use].
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.
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.

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) (see Special Warnings and Precautions for Use).

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.

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; and 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
Data from women show that tacrolimus crosses the placenta. There is a risk for hyperkalaemia in the newborn (e.g., incidence in neonates of 7.2%, i.e., 8 of 111) which tends to normalise spontaneously. Tacrolimus treatment 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 case of *in utero* exposure, monitoring of the newborn for the potential adverse effects of tacrolimus is recommended (in particular the effects on the kidneys).

Results from a non-interventional post-authorisation safety study [EUPAS37025]
A post-authorisation safety study analysed 2,905 pregnancies from the Transplant Pregnancy Registry International (TPRI), assessing outcomes in women treated with tacrolimus (383 reported prospectively, including 247 kidney and 136 liver transplant patients), and those on other immunosuppressants. Based on limited data (289 prospectively-reported pregnancies with 1st trimester tacrolimus exposure), study results did not indicate an increased risk of major malformations. A higher prevalence of spontaneous abortion was observed among women treated with tacrolimus compared with alternative immunosuppressants. Among kidney transplant patients there was also a

higher prevalence of pre-eclampsia in women treated with tacrolimus. However, overall, there were insufficient evidence to conclude on the risk of these outcomes. 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, although conclusions were hindered by limited evidence.
In rats and rabbits, tacrolimus caused embryofoetal toxicity at doses which demonstrated maternal toxicity (see Preclinical Safety Data).

Breast-feeding
Based upon reports, tacrolimus is excreted into human 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.

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 drug reactions 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).

Cardiac disorders

Common:	ischaemic coronary artery disorders, tachycardia
Uncommon:	ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations
Rare:	pericardial effusion
Very rare:	*Torsades de pointes*

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

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

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, gastrooesophageal reflux disease, impaired gastric emptying
Rare:	subileus, pancreatic pseudocyst

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

Skin and subcutaneous tissue disorders

Common:	pruritus, rash, alopecias, 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 decreased

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

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.

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).

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, skin malignancies and Kaposi's sarcoma have been reported in association with tacrolimus treatment.

Vascular disorders

Very common:	hypertension
Common:	haemorrhage, thromboembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders
Uncommon:	infarction, venous thrombosis deep limb, shock

General disorders and administration site conditions

Common:	asthenic conditions, febrile disorders, oedema, pain and discomfort, body temperature perception disturbed
Uncommon:	multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling jittery, feeling abnormal
Rare:	thirst, fall, chest tightness, ulcer
Very rare:	fat tissue increased

Immune system disorders
Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus (see Special Warnings and Precautions for Use).

Hepatobiliary disorders

Common:	cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis
Rare:	hepatic artery thrombosis, venoocclusive liver disease
Very rare:	hepatic failure, bile duct stenosis

Reproductive system and breast disorders

Uncommon:	dysmenorrhoea and uterine bleeding

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

Investigations

Very common:	liver function tests abnormal
Common:	blood alkaline phosphatase increased, weight increased
Uncommon:	amylase increased, ECG investigations abnormal, heart rate and pulse investigations abnormal, weight decreased, blood lactate dehydrogenase increased
Very rare:	echocardiogram abnormal, electrocardiogram QT prolonged

Adverse reactions in patients with 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 β2 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).

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

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

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic group: Calcineurin inhibitors, ATC code: L04AD02

Mechanism of Action and Pharmacodynamic Effects
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.

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

In particular, tacrolimus inhibits the formation of cytotoxic lymphocytes, which are mainly responsible for graft rejection. Tacrolimus suppresses T-cell activation and T-helper-cell dependent B-cell proliferation, as well as the formation of lymphokines (such as interleukins-2,-3 and γ-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 tacrolimus in blood are achieved in approximately 1 - 3 hours. In some patients, tacrolimus appears to be continuously absorbed over a prolonged period yielding a relatively 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 Prograf were achieved within 3 days in the majority of patients.

In healthy subjects, Prograf 0.5 mg, Prograf 1 mg and Prograf 5 mg 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 does not influence the absorption of Prograf.

A strong correlation exists between AUC and whole blood trough levels at steady-state. Monitoring of whole blood trough levels therefore provides a good estimate of systemic exposure.

Distribution and Elimination
In man, the disposition of tacrolimus after intravenous infusions may be described as biphasic. In the systemic circulation, tacrolimus binds strongly to erythrocytes resulting in an approximate 20:1 distribution ratio of whole blood/plasma concentrations. In plasma, tacrolimus 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.

Tacrolimus is a low-clearance substance. In healthy subjects, the average total body clearance (TBC) estimated from whole blood concentrations was 2.25 L/h. In adult liver, kidney and heart transplant patients, values of 4.1 L/h, 6.7 L/h and 3.9 L/h, respectively, have been observed. Paediatric liver transplant recipients have a TBC 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.

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

Metabolism and Biotransformation
Tacrolimus is widely metabolized in the liver, primarily by the cytochrome P450-3A4 (CYP3A4) and the cytochrome P450-3A5 (CYP3A5). Tacrolimus is also considerably metabolized 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, indicating that tacrolimus is almost completely metabolised prior to elimination: bile being the principal route of elimination.

Preclinical Safety Data
The kidneys and the pancreas were the primary organs affected in toxicity studies performed in rats and baboons. In rats, tacrolimus caused toxic effects to the nervous system and the eyes. Reversible cardiotoxic effects were observed in rabbits following intravenous administration of tacrolimus.

When tacrolimus is administered intravenously as rapid infusion/bolus injection at a dose of 0.1 to 1.0 mg/kg, QTc prolongation has been observed in some animal species. Peak blood concentrations achieved with these doses were above 150 ng/mL which is more than 6-fold higher than mean peak concentrations observed with Prograf in clinical transplantation.

Embryofoetal toxicity 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.

List of excipients

Prograf 0.5 mg hard capsules

Capsule content:
Hypromellose
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate

Capsule shell:
Titanium dioxide (E 171)
Yellow iron oxide (E 172)
Gelatine

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

Prograf 1 mg hard capsules

Capsule content:
Hypromellose
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate

Capsule shell:
Titanium dioxide (E 171)
Gelatine

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

Prograf 5 mg hard capsules

Capsule content:
Hypromellose
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate

Capsule shell:
Titanium dioxide (E 171)
Red iron oxide (E 172)
Gelatine

Printing ink of capsule shell: Shellac, titanium dioxide (E 171) and propylene glycol.

Prograf Concentrate for Infusion 5 mg/mL

Polyoxyethylene hydrogenated castor oil
Dehydrated alcohol

Incompatibilities

When diluting, this medicinal product 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 or a suspension of Prograf capsule contents should not contain PVC.

Tacrolimus is unstable under alkaline conditions. Combination of the reconstituted Prograf concentrate for infusion 5 mg/mL with other pharmaceutical products that produce a marked alkaline solution (e.g., acyclovir and ganciclovir) should be avoided.

How Supplied
Prograf Capsules 0.5 mg, 1 mg and 5 mg
Ten capsules per blister sheet.
Pack sizes:
Prograf Capsules 0.5 mg: cartons of 50 and 100 capsules
Prograf Capsules 1 mg: cartons of 50 and 100 capsules
Prograf Capsules 5 mg: cartons of 50 capsules

Prograf Concentrate for Infusion 5 mg/mL
Solution in transparent glass ampoules

Shelf Life
Prograf Capsules 0.5 mg, 1 mg and 5 mg
Recommended shelf life is 36 months.

Prograf Concentrate for Infusion 5 mg/mL
Recommended shelf life is 24 months.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless the dilution has taken place in controlled and validated aseptic conditions.

Storage Conditions
Prograf Capsules 0.5 mg, 1 mg and 5 mg
Store below 30°C in a dry place.
After opening of the aluminium wrapper, the capsules are stable for 3 months.

Prograf Concentrate for Infusion 5mg/mL
Store below 25°C.
Store ampoule in the original package in order to protect from light.

For storage conditions of the diluted medicinal product, see Shelf Life.

Instructions for Use/Handling/Disposal
Capsules should be taken immediately following removal from the blister. Patients should be advised not to swallow the desiccant.

Tubing, syringes and other equipment used to administer Prograf should not contain PVC (see Incompatibilities).

Prograf Concentrate for Infusion must not be injected undiluted.

Prograf Concentrate for Infusion should be prepared for infusion with 5% dextrose solution or physiological saline in polyethylene, polypropylene or glass containers. Only transparent and colorless 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.
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.

SOURCE OF GELATIN
Bovine

DATE OF REVISION OF TEXT
19 Jan 2026
(CCDS v8.0/9.0)

NAME AND ADDRESS OF MANUFACTURER
Astellas Ireland Co., Ltd.
Killorglin, Co. Kerry.
V93 FC86, Ireland

KEEP OUT OF REACH OF CHILDREN/JAUHI DARIPADA KANAK-KANAK

For any enquiry, please write to pv.my@astellas.com.