AUSTRALIAN PRODUCT INFORMATION
PROGRAF® (tacrolimus) CAPSULES and CONCENTRATED INJECTION
PROGRAF® XL (tacrolimus) PROLONGED-RELEASE CAPSULES

1 NAME OF THE MEDICINE

Tacrolimus

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PROGRAF CAPSULES

Each 0.5 mg capsule contains 0.5 mg tacrolimus
Each 1 mg capsule contains 1 mg tacrolimus
Each 5 mg capsule contains 5 mg tacrolimus

Contains: lactose
The printing ink used to mark the capsule contains trace amounts of soya lecithin

For the full list of excipients, see Section 6.1 List of excipients.

PROGRAF XL PROLONGED-RELEASE CAPSULES

Each 0.5 mg prolonged-release capsule contains 0.5 mg tacrolimus
Each 1 mg prolonged-release capsule contains 1 mg tacrolimus
Each 5 mg prolonged-release capsule contains 5 mg tacrolimus

Contains: lactose
The printing ink used to mark the capsule contains trace amounts of soya lecithin

For the full list of excipients, see Section 6.1 List of excipients.

PROGRAF CONCENTRATED INJECTION

Each mL of Concentrated Injection contains 5 mg tacrolimus.

Contains: ethanol

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

PROGRAF CAPSULES

Capsule

Supplied as:
PROGRAF capsules 0.5 mg: light yellow hard gelatine capsules with ‘0.5 mg’ and ‘[f]607’ printed in red.

PROGRAF capsules 1 mg: white, hard gelatine capsules with '1 mg' and '[f]617' printed in red.

PROGRAF capsules 5 mg: greyish-red, hard gelatine capsules with '5 mg' and '[f]657' printed in white.

PROGRAF XL PROLONGED-RELEASE CAPSULES

Prolonged release capsule

Supplied as:

PROGRAF XL 0.5 mg prolonged-release capsules: oblong capsules with a light yellow cap imprinted with “0.5 mg” and an orange body imprinted with “ 647”.

PROGRAF XL 1 mg prolonged-release capsules: oblong capsules with a white cap imprinted with “1 mg” and an orange body imprinted with “ 677”.

PROGRAF XL 5 mg prolonged-release capsules: oblong capsules with a greyish red cap imprinted with “5 mg” and an orange body imprinted with “ 687”.

PROGRAF CONCENTRATED INJECTION

Injection, concentrated

Supplied as:

PROGRAF Concentrated Injection 5 mg/mL: colourless, clear, sterile liquid in transparent glass ampoules.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PROGRAF and PROGRAF XL are indicated for use as an adjunct to liver, kidney, lung or heart allograft transplantation in adults and children.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

If allograft rejection or adverse events occur, alteration in the immunosuppressive regimen should be considered.

Method of Administration

It is recommended that the oral daily dose of PROGRAF be administered as two divided doses, in the morning and in the evening.

It is recommended that the oral daily dose of PROGRAF XL be administered once daily in the morning.

PROGRAF and PROGRAF XL 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 maximum absorption (Refer to Section 5.2 - PHARMACOKINETIC PROPERTIES - Absorption).

PROGRAF and PROGRAF XL capsules should be taken immediately following removal from the blister. The capsules should be swallowed with fluid (preferably water).

Oral administration of PROGRAF or PROGRAF XL should commence as soon as practicable. In some transplantation patients, therapy has commenced orally by administering the PROGRAF capsule contents suspended in water via an intranasal gastric tube.

In patients unable to take oral capsules, therapy may be initiated with PROGRAF Concentrated Injection as a continuous IV infusion.

PROGRAF Concentrated Injection should be diluted in 5% glucose solution in polyethylene or glass bottles or in 0.9% sodium chloride injection solution in polyethylene bottles. The concentration of a solution for final infusion produced in this way should be in the range 0.004 - 0.1 mg/mL. The solution should not be given as a bolus.

If IV therapy is necessary, conversion from IV to oral tacrolimus is recommended as soon as oral therapy can be tolerated. This usually occurs within 2 – 3 days. In patients receiving an IV infusion, the first dose of oral therapy should be given 8 – 12 hours after discontinuing the IV infusion.

Liver Transplantation

Oral tacrolimus therapy should commence at 0.10 – 0.20 mg/kg/day administered as two divided doses for PROGRAF or as a total daily dose for PROGRAF XL. Administration should start approximately 6 hours after the completion of liver transplant surgery. If the clinical condition of the patient does not allow for oral dosing then intravenous tacrolimus therapy should be initiated as a continuous 24 hour infusion, at 0.01 to 0.05 mg/kg/day.

Kidney Transplantation

Oral tacrolimus therapy should commence at 0.15 – 0.30 mg/kg/day administered as two divided doses for PROGRAF or as a total daily dose for PROGRAF XL. Administration should start within 24 hours of kidney transplant surgery. If the clinical condition of the patient does not allow for oral dosing then intravenous tacrolimus therapy should be initiated as a continuous 24 hour infusion, at 0.04 to 0.06 mg/kg/day.

Lung Transplantation

Oral tacrolimus therapy should commence at 0.10 – 0.30 mg/kg/day administered as two divided doses for PROGRAF or as a total daily dose for PROGRAF XL. Administration should start within 24 hours of lung transplant surgery. If the clinical condition of the patient does not allow for oral dosing then intravenous tacrolimus therapy should be initiated as a continuous 24 hour infusion, at 0.01 to 0.05 mg/kg/day.

Heart Transplantation

Oral tacrolimus therapy should commence at 0.075 mg/kg/day administered as two divided doses for PROGRAF or as a total daily dose for PROGRAF XL. Administration should start within 24 hours of heart transplant surgery. If the clinical condition of the patient does not allow for oral dosing then intravenous tacrolimus therapy should be initiated as a continuous 24 hour infusion, at 0.01 to 0.02 mg/kg/day.

Further information for all indications follows:

Children
Higher mg/kg doses may be required in children compared with adults to achieve the same tacrolimus blood concentration. It is recommended that the initial intravenous dose if needed should be 0.05 – 0.06mg/kg/day: initial oral doses should be 0.15 – 0.30 mg/kg/day as two divided doses.

Therapy Dose Levels for Kidney, Liver, Lung or Heart Allograft Rejection Resistant to Existing Immunosuppressive Regimens
In patients experiencing rejection episodes, which are unresponsive to conventional immunosuppressive therapy, PROGRAF and PROGRAF XL treatment should begin with the initial dose recommended for primary immunosuppression in that particular allograft.

Conversion

Conversion of PROGRAF treated patients to PROGRAF XL
Allograft transplant patients maintained on twice daily PROGRAF capsules dosing requiring conversion to once daily PROGRAF XL should be converted on a 1:1 (mg:mg) total daily dose basis. PROGRAF XL should be administered in the morning. Following conversion, tacrolimus trough levels should be monitored and if necessary dose adjustments made to maintain similar systemic exposure.

In stable patients converted from PROGRAF (twice daily dosing) to PROGRAF XL (once daily dosing) on a 1:1 (mg:mg) total daily dose basis, the systemic exposure to tacrolimus (AUC_{0-24}) for PROGRAF XL was approximately 10% lower than that for PROGRAF. The relationship between tacrolimus trough levels (C_{24}) and systemic exposure (AUC_{0-24}) for PROGRAF XL is similar to that of PROGRAF. When converting from PROGRAF capsules to PROGRAF XL tacrolimus trough levels should be measured prior to conversion and within two weeks after conversion. Dose adjustments should be made to ensure that similar systemic exposure is maintained.

In *de novo* kidney and liver transplant patients AUC_{0-24} of tacrolimus for PROGRAF XL on Day 1 was 30% and 50% lower respectively, when compared with that for PROGRAF at equivalent doses. By Day 4, systemic exposure as measured by trough levels is similar for both kidney and liver transplant patients with both formulations. Careful and frequent monitoring of tacrolimus trough levels is recommended in the first two weeks post-transplant with PROGRAF XL to ensure adequate drug exposure in the immediate post-transplant period. As tacrolimus is a substance with low clearance, adjustments to the PROGRAF XL dose regimen may take several days before steady state is achieved.

Conversion from cyclosporin to PROGRAF or PROGRAF XL
Care should be taken when converting patients from cyclosporin-based to tacrolimus-based therapy (Refer to Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Conversion between agents; and Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). Tacrolimus-based therapy should be initiated after considering cyclosporin blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated cyclosporin blood levels. In practice, tacrolimus-based 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 might be affected.

Conversion between tacrolimus formulations
Differences between oral formulations of tacrolimus can lead to important differences in systemic exposure to tacrolimus. Inadvertent or unsupervised switching between formulations is unsafe and could lead to graft rejection or increased incidence of side effects. Therefore, it is appropriate to prescribe and dispense tacrolimus by tradename, taking care to specify appropriate daily dosing (e.g. PROGRAF - twice daily dosing, PROGRAF XL – once daily dosing). Patients must only be switched from one tacrolimus formulation to another under the close supervision of a transplant specialist.

Dose adjustments in special populations

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

Patients with Renal Impairment
No dose adjustment is required. However, careful monitoring of renal function is recommended.

Patients with Liver Impairment
Tacrolimus is extensively metabolised by the liver. In patients with liver impairment dose reduction is recommended.

Tacrolimus is normally administered together with other immunosuppressive drugs. In isolated cases, successful maintenance therapy with tacrolimus alone has been described. Tacrolimus should not be given concurrently with cyclosporin.

Race
In comparison to Caucasians, black patients may require higher tacrolimus doses to achieve similar trough levels.

Gender
There is no evidence that male and female patients require different doses to achieve similar trough levels.

Monitoring Advice

Monitoring of tacrolimus WHOLE BLOOD trough concentrations in conjunction with other laboratory and clinical parameters is considered an essential aid to patient management for the evaluation of rejection, toxicity, dose adjustments and compliance. Factors influencing frequency of monitoring include but are not limited to hepatic or renal dysfunction, the addition or discontinuation of potentially interacting drugs and the post-transplant time. Blood trough concentration monitoring is not a replacement for renal or liver function monitoring and tissue biopsies.

Various assays have been used to measure blood or plasma concentrations of tacrolimus. Comparison of the concentrations in published literature to patient concentrations should be made with care and knowledge of the assay methods employed.

Trough blood concentrations should be measured at 12 hours after a PROGRAF dose or 24 hours after a PROGRAF XL dose. The majority of patients (adults and children) can be successfully managed if the trough blood concentrations are maintained within the following range:

- Liver transplant: 5 – 20 ng/mL for the first 3 months, 5 – 15 ng/mL thereafter.
- Kidney transplant: 10 – 20 ng/mL for the first 3 months, 5 – 15 ng/mL thereafter
- Heart transplant: 10 – 20 ng/mL for the first 3 months, 5 – 15 ng/mL thereafter
- Lung transplant: 10 – 20 ng/mL for the first month, then 5 – 15 ng/mL thereafter

During the first months post-transplant, monitoring of the following parameters should be undertaken on a routine basis: blood pressure, ECG, visual status, blood glucose levels, electrolytes (particularly potassium), creatinine, BUN, urinary output, haematology parameters, coagulation values, and liver and renal function tests. If clinically relevant changes are seen, adjustment of the immunosuppressive regimen should be considered.

Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of PROGRAF and PROGRAF XL. This should be considered when deciding upon a maintenance regimen.

4.3 CONTRAINDICATIONS

PROGRAF and PROGRAF XL are contraindicated in patients hypersensitive to tacrolimus or other macrolides, or to other ingredients of the capsules.

PROGRAF Concentrated Injection should not be used in patients known to be hypersensitive to polyoxyethylene hydrogenated castor oils.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Tacrolimus therapy requires careful monitoring in hospital units equipped and staffed with adequate laboratory and supportive medical resources. The drug should only be prescribed, and changes in immunosuppressive therapy should be initiated, by physicians experienced in immunosuppressive therapy and the management of transplant patients. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

Post-transplant diabetes mellitus (PTDM)

Post-transplant insulin dependent diabetes mellitus (PTDM - use of insulin for 30 or more consecutive days, with < 5 day gap, by patients without a prior history of insulin or non-insulin-dependent diabetes mellitus) was reported in 20% (30/151) and 6% (17/281) of tacrolimus treated kidney transplant patients in the US and European randomised trials respectively. The median time to onset of PTDM was 68 days. Insulin dependence was reversible in 15% of these patients at one year and in 50% at two years post-transplant. Black and Hispanic patients were found to be at increased risk of development of PTDM in the US trial. The risk benefit ratio should be carefully considered before using tacrolimus in kidney transplant patients with a pre-transplant diabetic condition.

In liver transplantation PTDM was reported in 18% (42/239) and 11% (26/239) of PROGRAF treated patients and was reversible in 45% and 31% of these patients at one year post transplant in the US and European randomised trials respectively.

Insulin-dependent post-transplant diabetes mellitus was reported in 13% (10/75) and 22% (29/132) of tacrolimus-treated heart transplant patients receiving mycophenolate mofetil or azathioprine and

was reversible in 30% and 17% of these patients at one year post transplant, in the US and European randomised studies, respectively.

Neurotoxicity

Neurological and CNS disorders have been reported with tacrolimus therapy. Symptoms include tremor, headache, changes in motor function, sensory function or mental status, insomnia, seizures, coma and delirium. Patients experiencing such events should be carefully monitored. In cases of severe or worsening neurological disorder, adjustment of the immunosuppressive regimen should be considered.

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.

Pure red cell aplasia (PRCA)

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.

Nephrotoxicity

Tacrolimus can cause renal impairment charactered by increases in serum creatinine as a result of a reduced glomerular filtration rate, particularly when used in high doses. These changes have been observed to be dose dependent and improvements have been associated with reduced dosing. The mechanism leading to these changes is not fully understood. Use of tacrolimus with sirolimus in heart transplantation patients in a US study was associated with increased risk of renal function impairment, and is not recommended. Patients with impaired renal function should be monitored closely as the dosage of tacrolimus may need to be reduced.

Care should be taken in using tacrolimus with other nephrotoxic drugs. In particular, tacrolimus should not be used simultaneously with cyclosporin. Tacrolimus or cyclosporin should be discontinued at least 24 hours prior to initiating the other. In the presence of elevated tacrolimus or cyclosporin concentrations, dosing with the other drug usually should be further delayed.

Hyperkalaemia

Mild to severe hyperkalaemia was reported in patients treated with tacrolimus, especially in patients with renal impairment. Patients may require treatment, and should avoid high dietary potassium intake. Serum potassium levels should be monitored and potassium-sparing diuretics should not be used during tacrolimus therapy.

Vaccinations

As with other immunosuppressants, response to 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, although all cases were considered a complication of transplant surgery or accompanied by infection, diverticulum, or malignant neoplasm. As gastrointestinal perforation is a medically important event that may lead to a life-threatening or serious condition, adequate treatments including surgery should be considered immediately after a suspect symptom occurs.

Anaphylaxis with IV administration

PROGRAF Concentrated Injection contains PEG-60 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, by intravenous injection or infusion, preparations containing PEG-60 hydrogenated castor oil and in patients with an allergenic predisposition. Studies in dogs have shown that the risk of anaphylaxis may be reduced by slow infusion of PROGRAF Concentrated Injection or by prior administration of an H1 antihistamine. PROGRAF or PROGRAF XL capsules 1mg and 5mg do not contain PEG-60 hydrogenated castor oil.

Potential interactions

When substances with a potential for interaction (Refer to Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS) – particularly strong inhibitors of CYP3A4 (such as telaprevir, boceprevir, ritonavir, ketoconazole, voriconazole, itraconazole or clarithromycin) or inducers of CYP3A4 (such as rifampin, rifabutin) – are being combined with tacrolimus, tacrolimus blood levels should be monitored to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure.

Malignancies

As with other potent immunosuppressive compounds, patients treated with tacrolimus are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Lymphoproliferative disorder (LPD) related to Epstein-Barr Virus (EBV) infection has been reported in immunosuppressed organ transplant recipients. In patients switched to tacrolimus, this may be attributable to over-immunosuppression before commencing therapy with this agent. Very young (< 2 years), EBV-sero-negative children have been reported to have an increased risk of developing lymphoproliferative disorders. Therefore, in this patient group, EBV serology should be ascertained before starting treatment with tacrolimus. During treatment, careful monitoring is recommended.

Infections

Like other immunosuppressants, tacrolimus predisposes patients to the development of a variety of bacterial, fungal, parasitic and viral infections. Over suppression of the immune system can also increase susceptibility to opportunistic infections, sepsis and fatal infections. Among these conditions are BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML). These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions that physicians should consider in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms.

Hypertension

Hypertension is a common adverse effect of tacrolimus therapy. Antihypertensive therapy may be required; the control of blood pressure can be accomplished with any of the common antihypertensive agents. Since tacrolimus may cause hyperkalemia, potassium-sparing diuretics should be avoided. While calcium-channel blocking agents can be effective in treating tacrolimus-associated hypertension, care should be taken since interference with tacrolimus metabolism may require a dosage reduction.

Myocardial Hypertrophy

Ventricular hypertrophy or hypertrophy of the septum, reported as cardiomyopathies have been observed in a few cases in association with administration of tacrolimus. Most of these have been reversible, occurring primarily in patients having tacrolimus blood trough levels higher than the recommended level. Mean tacrolimus whole blood trough concentrations during the period prior to diagnosis of myocardial hypertrophy in 20 patients with pre and post treatment echo cardiograms ranged from 10.6 to 53.3 ng/mL in infants (N = 10, age 0.4 to 2 years), 4.0 to 45.7 ng/mL in children (N = 7, age 2 to 15 years) and 10.9 to 24.3 ng/mL in adults (N = 3, age 37 to 45 years). Other factors observed to increase the risk of these clinical conditions are, for example, previously existing heart diseases, corticosteroid usage, hypertension, renal or hepatic dysfunction, and fluid overload. Accordingly, high-risk patients should be monitored, e.g., with echocardiography or ECG. If abnormalities develop, dose reduction of tacrolimus therapy, or change of treatment to other immunosuppressive agent should be considered.

QT Interval Prolongation

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

Conversion between agents

Conversion between tacrolimus formulations

Various formulations of tacrolimus are available. Medication errors have resulted in incorrect dosing or unsupervised switching between tacrolimus formulations. This has led to serious adverse events, including graft rejection, or other side effects which could be a consequence of either under exposure or over exposure to tacrolimus. Therefore, it is appropriate to prescribe and dispense

tacrolimus by tradename, taking care to specify appropriate daily dosing (e.g. PROGRAF - twice daily dosing, PROGRAF XL – once daily dosing). It should be emphasised that patients, once titrated to an effective dose of a particular formulation of tacrolimus, should not be changed to another formulation of tacrolimus without blood trough level monitoring, clinical assessment and re-titration (Refer to Section 4.2 - DOSE AND METHOD OF ADMINISTRATION - Conversion).

Conversion with cyclosporin
Tacrolimus should not be administered concurrently with cyclosporin as the half-life of the latter may be increased. Synergistic/additive nephrotoxic effects can also occur. Care should be taken when administering tacrolimus to patients who have previously received cyclosporin and when converting patients from cyclosporin- to tacrolimus -based therapy. It is recommended that cyclosporin blood levels are monitored prior to the administration of tacrolimus. The most appropriate time to initiate tacrolimus therapy should be based upon information on cyclosporin blood levels and the clinical condition of the patient. Dosing may be delayed in the presence of elevated cyclosporin levels. Monitoring of cyclosporin blood levels should be continued following conversion as the clearance of cyclosporin may be affected. A 24 hour interval between stopping cyclosporin and starting tacrolimus has been commonly used.

Patients switched to tacrolimus rescue therapy should not be given anti-lymphocyte treatment concomitantly.

Use in hepatic impairment

Tacrolimus is extensively metabolised by the liver. In patients with liver impairment dose reduction is recommended. (Refer to Section 4.2 - DOSE AND METHOD OF ADMINISTRATION – Dose adjustments in special populations.)

Use in renal impairment

No dose adjustment is required. However, careful monitoring of renal function is recommended. (Refer to Section 4.2 - DOSE AND METHOD OF ADMINISTRATION – Dose adjustments in special populations.)

Use in the elderly

Experience in the elderly is limited. There is no evidence presently available to suggest that doses should be altered in elderly patients. (Refer to Section 4.2 - DOSE AND METHOD OF ADMINISTRATION – Dose adjustments in special populations.)

Paediatric use

Higher mg/kg doses may be required in children compared with adults to achieve the same tacrolimus blood concentration. It is recommended that the initial intravenous dose if needed should be 0.05 – 0.06mg/kg/day: initial oral doses should be 0.15 – 0.30 mg/kg/day as two divided doses. (Refer to Section 4.2- DOSE AND METHOD OF ADMINISTRATION.)

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 drugs or herbal remedies known to inhibit or induce CYP3A4 may affect the metabolism of tacrolimus and thereby increase or decrease tacrolimus blood levels. It is strongly recommended to closely monitor tacrolimus blood levels, as well as QT prolongation (with ECG), renal function and other side effects, whenever drugs which have the potential to alter CYP3A metabolism are used concomitantly and to adjust the tacrolimus dose as appropriate in order to maintain similar tacrolimus exposure.

Inhibitors of Metabolism

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

Strong interactions have been observed with antifungal agents such as ketoconazole, fluconazole, itraconazole and voriconazole, the macrolide antibiotic erythromycin, HIV protease inhibitors (e.g. ritonavir, nelfinavir, saquinavir), HCV protease inhibitors (e.g. telaprevir, boceprevir) and amiodarone. Concomitant use of these drugs may require decreased tacrolimus doses in nearly all patients.

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

The herbal remedy schisandra sphenanthera extract inhibits CYP3A4 and may increase the blood levels of tacrolimus.

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

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

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

Inducers of Metabolism

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

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

High dose prednisolone or methylprednisolone administered for the treatment of acute rejection have the potential to increase or decrease tacrolimus blood levels.

Carbamazepine, metamizole and isoniazid have the potential to decrease tacrolimus concentrations.

Effect of Tacrolimus on the Metabolism of Other Drugs

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

The half-life of cyclosporin is prolonged when tacrolimus is given concomitantly. In addition, synergistic/additive nephrotoxic effects can occur. For these reasons, the combined administration of cyclosporin and tacrolimus is not recommended and care should be taken when administering tacrolimus to patients who have previously received cyclosporin.

Tacrolimus have 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 antipyrine.

Other potential interactions that may increase systemic exposure of tacrolimus:

Prokinetic agents such as metoclopramide and cisapride.
Cimetidine.
Magnesium-aluminum-hydroxide.

Other Interactions which have led to Clinically Detrimental Effects

Concurrent use of tacrolimus with drugs known to have nephrotoxic or neurotoxic effects may increase these effects (e.g. aminoglycosides, gyrase inhibitors, vancomycin, cotrimoxazole, NSAIDs, ganciclovir or aciclovir).

Enhanced nephrotoxicity has been observed following the administration of amphotericin B and ibuprofen in conjunction with tacrolimus.

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

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.

Protein Binding Considerations

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Tacrolimus subcutaneously administered to male rats at doses of 2 or 3 mg/kg/day resulted in a dose-related decrease in sperm count.

Use in pregnancy - Pregnancy Category C

In reproduction studies in rats and rabbits, adverse effects on the fetus were observed mainly at dose levels that were toxic to the dams.

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.

Human data show that tacrolimus is able to cross the placenta.

There are no adequate and well-controlled studies in pregnant women. There is data from a voluntary pregnancy exposure registry (Transplantation Pregnancy Registry International (TPRI)) that monitors outcomes of pregnancy in female transplant recipients and those fathered by male transplant recipients exposed to immunosuppressants including tacrolimus.

Safety data from postmarketing surveillance and the TPRI suggest infants of organ transplant recipients using immunosuppressive medications including tacrolimus have an increased risk for miscarriage, pre-term delivery (< 37 weeks), low birth weight (< 2500 g), birth defects/congenital anomalies and fetal distress.

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

Tacrolimus use may also be associated with hyperglycemia or diabetes in pregnancy in the absence of pre-existing diabetes or gestational. 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 with tacrolimus.

Tacrolimus should be used during pregnancy only if the potential benefit to the mother justifies potential risk to the fetus.

Use in lactation

Tacrolimus is excreted into breast milk. It is therefore recommended that mothers should not breast-feed while receiving tacrolimus.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Tacrolimus may cause visual and neurological disturbances. Patients treated with tacrolimus who are affected by such disorders should not drive a car or operate dangerous machinery.

4.8 ADVERSE EFFECTS (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.

The most commonly reported adverse drug reactions (occurring in > 10% of patients) are tremor, renal impairment, hyperglycaemic conditions, diabetes mellitus, hyperkalaemia, infections, hypertension and insomnia.

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, including isolated reports).

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 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 tacrolimus.

Neoplasms benign, malignant and unspecified

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

rare: thrombotic thrombocytopenic purpura, hypoprothrombinaemia

unknown frequency: agranulocytosis, haemolytic anaemia, pure red cell aplasia (observed during post-marketing)

Immune system disorders

Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus

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, anorexia, metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte abnormalities

uncommon: dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia

Psychiatric disorders

very common: insomnia

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

uncommon: psychotic disorder

Nervous system disorders

very common: tremor, headache

common: seizures, disturbances in consciousness, paraesthesias and dysaesthesias, peripheral neuropathies, dizziness, 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

Eye disorders

common: vision blurred, photophobia, eye disorders

uncommon: cataract

rare: blindness

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, QT prolongation, Torsades de pointes.

rare: pericardial effusion

very rare: echocardiogram abnormal

Vascular disorders

very common: hypertension

common: haemorrhage, thrombembolic 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, peritonitis, acute and chronic pancreatitis, blood amylase increased, gastrooesophageal reflux disease, impaired gastric emptying

rare: subileus, pancreatic pseudocyst

Hepatobiliary disorders

very common: liver function test abnormal

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

rare: hepatitic artery thrombosis, venoocclusive liver disease

very rare: hepatic failure

Skin and subcutaneous 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 cramps, pain in limb*, back pain

uncommon: joint disorders

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, mobility decreased, ulcer

very rare: fat tissue increased

Injury, poisoning and procedural complications

common: primary graft dysfunction

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

<u>Post Marketing Experience</u>

The following adverse events have been reported in association with tacrolimus use during worldwide post-marketing experience:

Blood and lymphatic system disorders
Musculoskeletal and connective tissue disorders
unknown frequency: Calcineurin-inhibitor induced pain syndrome (CIPS)*

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).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Experience of overdosage is limited.

Early clinical experience (when initial induction doses were 2 – 3 times greater than those currently recommended) suggested that symptoms of overdosage may include glucose intolerance, renal, neurological and cardiac disorders, hyperkalaemia and hypertension. Over immunosuppression may increase risk of severe infections.

Liver function clearly influences all pre- and post-operative pharmacokinetic variables. Patients with failing liver grafts or those switched from other immunosuppressive therapy to PROGRAF or PROGRAF XL should be monitored carefully to avoid overdosage.
No specific antidote to tacrolimus therapy is available. If overdosage occurs, general supportive measures and symptomatic treatment should be conducted.

Based on the poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is anticipated that PROGRAF or PROGRAF XL will not be dialysable. Data on haemoperfusion are not available. Activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Tacrolimus is a macrolide lactone with potent in vitro and in vivo immunosuppressive activity. Studies suggest that tacrolimus inhibits the formation of cytotoxic lymphocytes which are regarded as being primarily 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 and -3 and gamma-interferon and the expression of the interleukin-2 receptor. At the molecular level, the effects of tacrolimus appear to be mediated by binding to a cytosolic protein (FKBP), which is responsible for the intracellular accumulation of the compound. A complex of tacrolimus-FKBP-12, calcium, calmodulin and calcineurin is formed and the phosphatase activity of calcineurin inhibited.

Studies in animals and man have shown that PROGRAF is able to prevent and treat graft rejection following transplantation of the liver, kidney, and other solid organs.

Clinical trials

PROGRAF

Liver

The efficacy and safety of a PROGRAF based immunosuppressive regimen following orthotopic liver transplantation was assessed in two prospective, randomised, non-blinded multicentre trials. The active control groups were treated with a cyclosporin based regimen. In a European trial, patients received a tacrolimus-steroid based regimen (n = 264) or a cyclosporin-azathioprine-steroid (with or without anti-lymphocyte globulin) based regimen (n = 265).

Equivalent graft survival (77.5 vs. 72.69%) and patient survival (82.9 vs. 77.5%) was seen. Significant reductions were seen in the tacrolimus treated patients for incidence of acute rejection (40.5 vs. 49.8%), refractory acute rejection (0.8 vs. 5.3%) and chronic rejection (1.5 vs. 5.3%). In American trial patients received a tacrolimus-steroid regimen (n = 263) or a cyclosporin (mainly triple therapy) based regimen (n = 266). Equivalent graft survival (82 vs. 79%) and patient survival (88 vs. 88%) rates were observed. Tacrolimus was associated with significant reductions in the incidence of acute rejection (68 vs. 76%), steroid resistant rejection (19 vs. 36%) and refractory rejection (3 vs. 15%).

Kidney

Two randomised, multicentre non-blinded comparative trials were performed in cadaveric kidney transplantation. In an American trial patients received a tacrolimus based (n = 205) or cyclosporin based (n = 207) regimen. All patients also received maintenance azathioprine and corticosteroids and an induction course of an antilymphocyte antibody preparation. Equivalent graft survival (91.2 vs. 87.9%) and patient survival (95.6 vs. 96.6%) was seen for the tacrolimus and cyclosporin treated patients respectively. A significantly reduced one year incidence rate of biopsy confirmed acute rejection (30.7 vs. 46.4%), moderate to severe acute rejection (10.7 vs. 26.6%) and use of antilymphocyte antibody preparation for treatment of rejection (10.7 vs. 25.1%) was seen in the tacrolimus treated patients.

A European trial compared triple drug based immunosuppression with tacrolimus or cyclosporin centred regimens, with 303 and 145 patients randomised to the tacrolimus and cyclosporin arms respectively. Equivalent one year graft survival (82.5 vs. 86.2%) and one year patient survival (93.0 vs. 96.5%) rates were observed, but with significantly reduced one year acute rejection rate (32.3 vs. 54.5%), rate of corticosteroid sensitive rejections (24.4 vs. 42.1%) and rate of corticosteroid resistant rejections (10.2 vs. 20.7%).

Heart

Two open-label, randomised, comparative studies evaluated the safety and efficacy of tacrolimus-based and cyclosporin-based immunosuppression in primary orthotopic heart transplantation. In a Phase 3 study conducted in Europe, 314 patients received a regimen of antibody induction, corticosteroids and azathioprine in combination with tacrolimus or cyclosporin modified for 18 months. In a 3-arm study conducted in the US, 331 patients received corticosteroids and tacrolimus plus sirolimus, tacrolimus plus mycophenolate mofetil (MMF) or cyclosporin modified plus MMF for 1 year.

In the European Phase 3 study, patient / graft survival at 18 months post-transplant was similar between treatment arms, 91.7% in the tacrolimus group and 89.2% in the cyclosporin group. In the

US study, patient and graft survival at 12 months was similar with 93.5% survival in the tacrolimus plus MMF group and 86.1% survival in the cyclosporin modified plus MMF group. In the European study, the cyclosporin trough concentrations were above the pre-defined target range (i.e. 100-200 ng/mL) at Day 122 and beyond in 32 – 68% of the patients in the cyclosporin treatment arm, whereas the tacrolimus tough concentrations were within the pre-defined target range (i.e. 5 –15 ng/mL) in 74 – 86% of the patients in the tacrolimus treatment arm.

The US study contained a third arm of a combination regimen of sirolimus, 2mg per day, and full-dose tacrolimus; however, this regimen was associated with increased risk of wound healing complications, renal function impairment, and insulin dependent post-transplant diabetes mellitus, and is not recommended in de novo heart transplant patients (Refer to Section 4.4 - SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Lung
In a prospective, 2-centre, open-label randomised trial, 74 lung transplant patients (aged 20 –66 years old) were randomised to tacrolimus-based (n = 37) and cyclosporin-based (n = 37) immunosuppression. The drugs were given in combination with mycophenolate mofetil and corticosteroids. Tacrolimus was started immediately after transplantation as continuous intravenous infusion at a dose of 0.015 mg/kg/day and oral tacrolimus was administered at a dose of 0.1 to 0.3 mg/kg/day with subsequent dose adjustments to target trough levels of 12 to 15 ng/mL in the first month and 9 to 12 ng/mL thereafter. The 6-months and 1-year patient survival data was similar in both groups (89% vs. 84% and 82% vs. 71%, cyclosporin vs. tacrolimus respectively). Freedom from acute rejection was comparable at 1 year, 35% in the cyclosporin group and 46% in the tacrolimus group.

Another prospective, randomised, open-label study included 66 patients on tacrolimus versus 67 patients on cyclosporin, aged 20 to 66 years old. The drugs were given in combination with azathioprine and corticosteroids. Tacrolimus was started 6 to 8 hours after transplantation as continuous intravenous infusion at a dose of 0.025 mg/kg/day and oral tacrolimus was administered at a dose of 0.15 mg/kg/day with subsequent dose adjustments to target trough levels of 10 to 20 ng/mL. The 1-year patient survival was 83% in the tacrolimus group and 71% in the cyclosporin group, the 2-year survival rates were 76% and 66%, respectively. The differences between groups were not statistically significant. Freedom from acute rejection after at least 37 weeks follow-up was also comparable (14% in the tacrolimus group and 11.5% in the cyclosporin group).

A number of published, open, uncontrolled studies have examined the use of tacrolimus in lung transplant patients who have developed refractory acute rejection or bronchiolitis obliterans syndrome while receiving cyclosporin-based immunosuppressive regimens. In these studies, conversion from cyclosporin to tacrolimus has been associated with improved clinical outcomes such as reduced frequency of further acute rejection episodes and stabilisation or improvement in declining FEV_1 values.

PROGRAF XL
Three Phase III non-inferiority studies have been conducted, confirming the safety and efficacy of PROGRAF XL is comparable to PROGRAF in de novo kidney transplant patients aged 12 years and older (n = 638 and 667) and de novo liver transplant patients aged 18 years and older (n = 471). Patient survival and graft survival at 1 year post transplant ranged from 91% to 99%. In these

studies tacrolimus was used in combination with corticosteroids (liver transplant), with corticosteroids and mycophenolate mofetil (kidney), or with corticosteroids, mycophenolate mofetil and basiliximab (kidney).

The results of all conversion studies demonstrate that conversion from PROGRAF-based immunosuppression regimens to PROGRAF XL-based immunosuppression regimens on 1:1 (mg:mg) basis has been performed in adult kidney, liver and heart transplant recipients without any increase in incidences of acute rejection, graft loss or effects on patient survival rates. Long-term following up of patients in the conversion studies (up to 2 years) confirm patient survival and graft survival with PROGRAF XL were consistent across all conversion studies, ranging from 97% to 100%.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

In man tacrolimus has been shown to be able to be absorbed throughout the gastrointestinal tract. Available tacrolimus is generally rapidly absorbed.

Following oral administration of PROGRAF capsules peak concentrations (Cmax) of tacrolimus in blood are achieved in approximately 1 - 3 hours. PROGRAF XL is a prolonged-release formulation of tacrolimus resulting in an extended oral absorption profile with an average time to Cmax of approximately 2 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 PROGRAF 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 Cmax (50%), and an increase in tmax (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 Cmax (15 to 38%), and an increase in tmax (38 to 80%) in whole blood were evident.

Bile flow does not influence the absorption of PROGRAF.

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

Distribution

In man, the disposition of tacrolimus after intravenous infusion 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 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 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

Tacrolimus is widely metabolised in the liver, primarily by the cytochrome P450-3A4. 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 14C-labelled tacrolimus, most of the radioactivity was eliminated in the faeces. Approximately 2% of the radioactivity was eliminated in the urine. Less than 1% of unchanged tacrolimus was detected in the urine and faeces, indicating that tacrolimus is almost completely metabolised prior to elimination: bile being the principal route of elimination.

Pharmacokinetics in special populations
The pharmacokinetics of tacrolimus in special populations have not been studied in detail. For dose adjustments in special populations, Refer to Section 4.2 – Dose and method of administration.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No evidence of genotoxicity was seen in a series of assays for gene mutations and clastogenicity. Tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes but high concentrations

of tacrolimus have been reported to increase the frequency of sister chromatid exchanges in human lymphocytes *in vitro*.

Carcinogenicity

Tacrolimus did not show any tumourigenic effects in long term carcinogenicity studies using the mouse and rat. The maximum dose tested in the rat resulted in a blood exposure less than, and a plasma exposure 1.4 times the exposure achieved after the maximum recommended clinical dose, 0.3 mg/kg, based on AUC. In mice the maximum dose was 0.8 times the recommended clinical dose based on body surface area.

Patients receiving long-term immunosuppressive therapy are at an increased risk of developing lymphomas and other malignancies (Refer to Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Malignancies.)

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

PROGRAF CAPSULES

PROGRAF capsules contain hypromellose 2910, croscarmellose sodium, lactose and magnesium stearate. The capsule shell contains gelatin, purified water and titanium oxide and a dye (ferric oxide yellow E172 for 0.5 and 1 mg capsules, and ferric oxide red E172 for 5 mg capsules). The capsules have a trace of printing ink (that used in the 0.5 and 1 mg capsules contains shellac, soya lecithin, dimethylpolysiloxane and ferric oxide red E172; that used in the 5 mg capsules contains shellac, propylene glycol and titanium dioxide E171).

PROGRAF XL PROLONGED-RELEASE CAPSULES

PROGRAF XL prolonged-release capsules contain hypromellose, ethylcellulose, lactose and magnesium stearate. The capsule shells contain gelatin, titanium dioxide, iron oxide yellow CI77492, iron oxide red CI77491 and sodium lauryl sulfate. The capsules also have a trace of printing ink, Opacode S-1-15083 red, which contains shellac, soya lecithin, simethicone and iron oxide red CI77491.

PROGRAF CONCENTRATED INJECTION

PROGRAF Concentrated Injection contains PEG-60 hydrogenated castor oil and ethanol.

6.2 INCOMPATIBILITIES

Tacrolimus is incompatible with PVC plastics. Tubing, syringes, and other equipment used to administer PROGRAF Concentrated Injection should not contain PVC.

See also Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

PROGRAF capsules should be stored below 30°C. After opening the aluminium wrapper, PROGRAF capsules are stable for 12 months when stored at room temperature. The blister strips should be kept in a dry place and the capsules should be left in the blister until required for use.

PROGRAF XL prolonged-release capsules should be stored below 25°C. After opening the aluminium wrapper, PROGRAF XL prolonged-release capsules are stable for 12 months when stored at room temperature. The blister strips should be kept in a dry place and the capsules should be left in the blister until required for use.

PROGRAF Concentrated Injection should be protected from light and stored below 25°C. Once an ampoule is opened, the contents should be used immediately. Following reconstitution in either 5% w/v glucose solution in polyethylene or glass containers or in 0.9% Sodium Chloride Injection in polyethylene containers, the resulting infusion mixture should be used immediately

6.5 NATURE AND CONTENTS OF CONTAINER

PROGRAF capsules are supplied as blister strips each containing 10 capsules packed within a protective aluminium wrapper.

Package Quantities

PROGRAF capsules 0.5 mg	Cartons of 100 capsules
PROGRAF capsules 1 mg	Cartons of 100 capsules
PROGRAF capsules 5 mg	Cartons of 50 capsules

PROGRAF XL prolonged-release capsules are supplied as blister strips each containing 10 capsules packed within a protective aluminium wrapper.

Package Quantities

PROGRAF XL Prolonged-Release Capsules 0.5 mg	Cartons of 30 and 50* capsules
PROGRAF XL Prolonged-Release Capsules 1 mg	Cartons of 30*, 50* and 60 capsules
PROGRAF XL Prolonged-Release Capsules 5 mg	Cartons of 30 and 50* capsules

(* not marketed in Australia)

PROGRAF Concentrated Injection 5 mg/mL: colourless, clear, sterile liquid in transparent glass ampoules.

Package Quantities

PROGRAF Concentrated Injection 5 mg/mL	Cartons of 10 ampoules

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

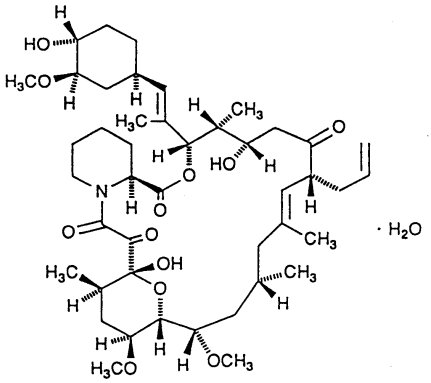
6.7 PHYSICOCHEMICAL PROPERTIES

Tacrolimus appears as white crystals or a crystalline powder, very soluble in methanol, and chloroform, freely soluble in acetone and ethanol and practically insoluble in hexane and water.

Tacrolimus is obtained by fermentation as a single enantiomer but exists in tautomeric equilibration in aqueous solution.

Chemical structure

[3S-[3R[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a*-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy- 3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido [2,1-c] [1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate.



Molecular Formula: $C_{44}H_{69}NO_{12}.H_20$
Molecular Weight: 822.03

CAS number

CAS 104987-11-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

8 SPONSOR

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6 Eden Park Drive
Macquarie Park NSW 2113

Tel: 1800 751 755 (Medical Information)
Email: aaumedinfo@astellas.com (Medical Information)
Website: www.astellas.com/au

9 DATE OF FIRST APPROVAL

25 August 1997

10 DATE OF REVISION

14 December 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.6	Effects on 'fertility' and 'use in pregnancy' sections revised
4.8	Post Marketing section added