SUMMARY OF PRODUCT CHARACTERISTICS

Prograf® Ampoules

1. NAME OF THE MEDICINAL PRODUCT

Prograf Ampoules

5 mg/ml concentrate for solution for I.V. infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml concentrate for solution for infusion contains 5 mg of tacrolimus.

Excipients with known effect: 200 mg of polyoxyethylene hydrogenated castor oil and 638 mg of dehydrated alcohol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

The concentrate is a clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of transplant rejection in liver, kidney or heart allograft recipients.

Treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products.

4.2 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.

General considerations

The recommended initial dosages presented below are intended to act solely as a guideline. Prograf dosing should primarily be based on clinical assessments of rejection and tolerability in each patient individually aided by blood level monitoring (see below for recommended target whole blood trough concentrations). If clinical signs of rejection are apparent, alteration of the immunosuppressive regimen should be considered.

Prograf can be administered intravenously or orally. In general, dosing may commence orally; if necessary, by administering the capsule contents suspended in water, via nasogastric tubing.

Prograf is routinely administered in conjunction with other immunosuppressive agents in the initial post-operative period. The Prograf dose may vary depending upon the immunosuppressive regimen chosen.

Posology

Dosage recommendations - Liver transplantation

Prophylaxis of transplant rejection - adults

Oral Prograf therapy should commence at 0.10 - 0.20 mg/kg/day administered as two divided doses (e.g., morning and evening). Administration should commence approximately 12 hours after the completion of surgery.

If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of 0.01 - 0.05 mg/kg/day should be initiated as a continuous 24-hour infusion.

Prophylaxis of transplant rejection - children

An initial oral dose of 0.30 mg/kg/day should be administered in two divided doses (e.g., morning and evening). If the clinical condition of the patient prevents oral dosing, an initial intravenous dose of 0.05 mg/kg/day should be administered as a continuous 24-hour infusion.

Dose adjustment during post-transplant period in adults and children

Prograf doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to Prograf monotherapy. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Rejection therapy - adults and children

Increased Prograf doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted (e.g., pronounced adverse reactions - see section 4.8) the dose of Prograf may need to be reduced.

For conversion to Prograf, treatment should begin with the initial oral dose recommended for primary immunosuppression.

For information on conversion from ciclosporin to Prograf, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Kidney transplantation

Prophylaxis of transplant rejection - adults

Oral Prograf therapy should commence at 0.20 - 0.30 mg/kg/day administered as two divided doses (e.g., morning and evening). Administration should commence within 24 hours after the completion of surgery.

If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of 0.05 - 0.10 mg/kg/day should be initiated as a continuous 24-hour infusion.

Prophylaxis of transplant rejection - children

An initial oral dose of 0.30 mg/kg/day should be administered in two divided doses (e.g., morning and evening). If the clinical condition of the patient prevents oral dosing, an initial intravenous dose of 0.075 - 0.100 mg/kg/day should be administered as a continuous 24-hour infusion.

Dose adjustment during post-transplant period in adults and children

Prograf doses are usually reduced in the post-transplant period. It is possible in some cases to withdraw concomitant immunosuppressive therapy, leading to Prograf-based dual-therapy. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Rejection therapy - adults and children

Increased Prograf doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes. If signs of toxicity are noted (e.g., pronounced adverse reactions - see section 4.8) the dose of Prograf may need to be reduced.

For conversion to Prograf, treatment should begin with the initial oral dose recommended for primary immunosuppression.

For information on conversion from ciclosporin to Prograf, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Heart transplantation

Prophylaxis of transplant rejection - adults

Prograf can be used with antibody induction (allowing for delayed start of Prograf therapy) or alternatively in clinically stable patients without antibody induction.

Following antibody induction, oral Prograf therapy should commence at a dose of 0.075 mg/kg/day administered as two divided doses (e.g., morning and evening). Administration should commence within 5 days after the completion of surgery as soon as the patient's clinical condition is stabilised. If the dose cannot be administered orally as a result of the clinical condition of the patient, intravenous therapy of 0.01 to 0.02 mg/kg/day should be initiated as a continuous 24-hour infusion.

An alternative strategy was published where oral tacrolimus was administered within 12 hours post transplantation. This approach was reserved for patients without organ dysfunction (e.g., renal dysfunction). In that case, an initial oral tacrolimus dose of 2 to 4 mg per day was used in combination with mycophenolate mofetil and corticosteroids or in combination with sirolimus and corticosteroids.

Prophylaxis of transplant rejection - children

Prograf has been used with or without antibody induction in paediatric heart transplantation.

In patients without antibody induction, if Prograf therapy is initiated intravenously, the recommended starting dose is 0.03 - 0.05 mg/kg/day as a continuous 24-hour infusion targeted to achieve tacrolimus whole blood concentrations of 15 - 25 ng/ml. Patients should be converted to oral therapy as soon as clinically practicable. The first dose of oral therapy should be 0.30 mg/kg/day starting 8 to 12 hours after discontinuing intravenous therapy.

Following antibody induction, if Prograf therapy is initiated orally, the recommended starting dose is 0.10 - 0.30 mg/kg/day administered as two divided doses (e.g., morning and evening).

Dose adjustment during post-transplant period in adults and children

Prograf doses are usually reduced in the post-transplant period. Post-transplant improvement in the condition of the patient may alter the pharmacokinetics of tacrolimus and may necessitate further dose adjustments.

Rejection therapy - adults and children

Increased Prograf doses, supplemental corticosteroid therapy, and introduction of short courses of mono-/polyclonal antibodies have all been used to manage rejection episodes.

In adult patients converted to Prograf, an initial oral dose of 0.15 mg/kg/day should be administered in two divided doses (e.g., morning and evening).

In paediatric patients converted to Prograf, an initial oral dose of 0.20 - 0.30 mg/kg/day should be administered in two divided doses (e.g., morning and evening).

For information on conversion from ciclosporin to Prograf, see below under “Dose adjustments in specific patient populations”.

Dosage recommendations - Rejection therapy, other allografts

The dose recommendations for lung, pancreas and intestinal transplantation are based on limited prospective clinical trial data. In lung-transplanted patients Prograf has been used at an initial oral dose of 0.10 - 0.15 mg/kg/day, in pancreas-transplanted patients at an initial oral dose of 0.2 mg/kg/day and in intestinal transplantation at an initial oral dose of 0.3 mg/kg/day.

Dosage adjustments in specific patient populations

Patients with liver impairment

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

Patients with kidney impairment

As the pharmacokinetics of tacrolimus are unaffected by renal function, no dose adjustment should be required. However, owing to the nephrotoxic potential of tacrolimus, careful monitoring of renal function is recommended (including serial serum creatinine concentrations, calculation of creatinine clearance and monitoring of urine output).

Paediatric population

In general, paediatric patients require doses 1½ - 2 times higher than the adult doses to achieve similar blood levels.

Older people

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

Conversion from ciclosporin

Care should be taken when converting patients from ciclosporin-based to Prograf-based therapy (see sections 4.4 and 4.5). Prograf therapy should be initiated after considering ciclosporin blood concentrations and the clinical condition of the patient. Dosing should be delayed in the presence of elevated ciclosporin blood levels. In practice, Prograf therapy has been initiated 12 - 24 hours after discontinuation of ciclosporin. Monitoring of ciclosporin blood levels should be continued following conversion as the clearance of ciclosporin might be affected.

Target whole blood trough concentration recommendations

Dosing should primarily be based on clinical assessments of rejection and tolerability in each individual patient.

As an aid to optimise dosing, several immunoassays are available for determining tacrolimus concentrations in whole blood including a semi-automated microparticle enzyme immunoassay (MEIA). Comparisons of concentrations from the

published literature to individual values in clinical practice should be assessed with care and knowledge of the assay methods employed. In current clinical practice, whole blood levels are monitored using immunoassay methods.

Blood trough levels of tacrolimus should be monitored during the post-transplantation period. When dosed orally, blood trough levels should be drawn approximately 12 hours post-dosing, just prior to the next dose. The frequency of blood level monitoring should be based on clinical needs. As Prograf is a medicinal product with low clearance, adjustments to the dosage regimen may take several days before changes in blood levels are apparent. Blood trough levels should be monitored approximately twice weekly during the early post-transplant period and then periodically during maintenance therapy. Blood trough levels of tacrolimus should also be monitored following dose adjustment, changes in the immunosuppressive regimen, or following co-administration of substances which may alter tacrolimus whole blood concentrations (see section 4.5).

Clinical study analysis suggests that the majority of patients can be successfully managed if tacrolimus blood trough levels are maintained below 20 ng/ml. It is necessary to consider the clinical condition of the patient when interpreting whole blood levels.

In clinical practice, whole blood trough levels have generally been in the range 5 - 20 ng/ml in liver transplant recipients and 10 - 20 ng/ml in kidney and heart transplant patients in the early post-transplant period. Subsequently, during maintenance therapy, blood concentrations have generally been in the range of 5 - 15 ng/ml in liver, kidney and heart transplant recipients.

Method of administration

The concentrate should be used for intravenous infusion only after it is diluted with suitable carrier media.

The concentration of a solution for infusion should be within the range 0.004 - 0.100 mg/ml. The total volume of infusion during a 24-hour period should be in the range 20 - 500 ml.

The diluted solution should not be given as a bolus (see section 6.6).

Duration of dosing

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.

4.3 Contraindications

Hypersensitivity to tacrolimus or other macrolides.

Hypersensitivity to any of the excipients listed in section 6.1 - in particular polyoxyethylene hydrogenated castor oil or structurally related compounds.

4.4 Special warnings and precautions for use

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

<u>Substances with potential for interaction</u>

Inhibitors or inducers of CYP3A4 should only be co-administered with tacrolimus after consulting a transplant specialist, due to the potential for drug interactions resulting in serious adverse reactions including rejection or toxicity (see section 4.5).

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. It is recommended that concomitant use of strong CYP3A4 inhibitors (such as ritonavir, cobicistat, ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, clarithromycin or josamycin) with tacrolimus should be avoided. If unavoidable, 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 section 4.5).

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. It is recommended that concomitant use of strong CYP3A4 inducers (such as rifampicin, phenytoin, carbamazepine), with tacrolimus should be avoided. If unavoidable, 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 section 4.5).

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 section 4.5).

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 either a decrease in blood concentrations of tacrolimus and reduced clinical effect of tacrolimus, or an increase in blood concentrations of tacrolimus and risk of tacrolimus toxicity (see section 4.5).

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 sections 4.2 and 4.5).

High potassium intake or potassium-sparing diuretics should be avoided (see section 4.5).

Certain combinations of tacrolimus with drugs known to have nephrotoxic or neurotoxic effects may increase the risk of these effects (see section 4.5).

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 4.5). Concurrent use of tacrolimus with drugs known to have nephrotoxic effects should be avoided. When co-administration cannot be avoided, 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 section 4.5).

Lymphoproliferative disorders and malignancies

Patients treated with Prograf have been reported to develop Epstein-Barr virus (EBV)-associated lymphoproliferative disorders (see section 4.8). Patients switched to Prograf therapy should not receive anti-lymphocyte treatment concomitantly. Very young (< 2 years), 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.

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 (see section 4.8).

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.

Eye disorders

Eye disorders, sometimes progressing to loss of vision, have been reported in patients treated with tacrolimus. Some cases have reported resolution on switching to alternative immunosuppression. Patients should be advised to report changes in visual acuity, changes in colour vision, blurred vision, or visual field defect, and in such cases, prompt evaluation is recommended with referral to an ophthalmologist as appropriate.

Infections including opportunistic infections

Patients treated with immunosuppressants, including Prograf are at increased risk for infections including opportunistic 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 including graft rejection that physicians should consider in the differential diagnosis in immunosuppressed 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 thrombocytopenic 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

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 derivatives either by intravenous injection or infusion, and in patients with an allergenic predisposition. The risk of anaphylaxis may be reduced by slow infusion of reconstituted Prograf 5 mg/ml concentrate for solution for infusion or by the prior administration of an antihistamine. Patients should be closely observed during the first 30 minutes of infusion for possible anaphylactoid reaction.

This medicine contains 638 mg of alcohol (ethanol) in 5 mg/ml iv infusion solution which is equivalent to 16 ml beer or 7 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

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.

4.5 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 CYP3A4 metabolism are used concomitantly and to adjust or interrupt the tacrolimus dose if appropriate in order to maintain similar tacrolimus exposure (see sections 4.2 and 4.4). 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 section 4.4]*.	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 section 4.4]*.
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.	Concurrent use of tacrolimus with drugs known to have nephrotoxic effects should be avoided. When co-administration cannot be avoided, monitor renal function and other side effects and adjust tacrolimus dose if needed.
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 section 4.4]*. 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.	It is recommended that concomitant use should be avoided. If co-administration of a strong CYP3A4 inhibitor is unavoidable, consider omitting the dose of tacrolimus the day the strong CYP3A4 inhibitor is initiated. Reinitiate tacrolimus the next day at a reduced dose based on tacrolimus blood concentrations. Changes in both tacrolimus dose and/or dosing frequency should be individualized and adjusted as needed based on tacrolimus trough concentrations, which should be assessed at initiation, monitored frequently throughout (starting within the first few days) and re-evaluated on and after completion of the CYP3A4 inhibitor. Upon completion, appropriate dose and dosing frequency of tacrolimus should be guided by tacrolimus blood concentrations. Monitor renal function, ECG for QT prolongation, and other side effects closely.

Drug/Substance Class or Name	Drug interaction effect	Recommendations concerning co-administration
Moderate or weak CYP3A4 inhibitors: antifungal agents (e.g., fluconazole, isavuconazole, clotrimazole, miconazole), the macrolide antibiotics (e.g., azithromycin), calcium channel blockers (e.g., nifedipine, nicardipine, diltiazem, verapamil), amiodarone, danazol, ethinylestradiol, lansoprazole, omeprazole, the HCV antivirals elbasvir/grazoprevir and glecaprevir/pibrentasvir, the CMV antiviral letermovir, and the tyrosine kinase inhibitors nilotinib, crizotinib, imatinib and (Chinese) herbal remedies containing extracts of *Schisandra sphenanthera*	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see section 4.4]*. 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 section 4.2]*. Monitor renal function, ECG for QT prolongation, and other side effects closely.
In vitro the following substances have been shown to be potential inhibitors of tacrolimus metabolism: bromocriptine, cortisone, dapsone, ergotamine, gestodene, lidocaine, mephenytoin, midazolam, nilvadipine, norethisterone, quinidine, tamoxifen	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see section 4.4]*.	Monitor tacrolimus whole blood trough concentrations and reduce tacrolimus dose if needed *[see section 4.2]*. 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 section 4.4]*. 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.	It is recommended that concomitant use should be avoided. If unavoidable, 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 section 4.4]*.	Monitor tacrolimus whole blood trough concentrations and increase tacrolimus dose if needed *[see section 4.2]*. 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 section 4.2]*. Monitor graft function closely.

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 sections 4.2 and 4.4]*.
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 section 4.2]*.
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 section 4.2]*. 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 section 4.4]*.	Monitor tacrolimus whole blood trough concentrations and increase tacrolimus dose if needed *[see section 4.2]*. 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 section 4.4).

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 section 4.4). 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 sections 4.2 and 4.4).

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 section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Human data show that tacrolimus is able to cross the placenta. Limited data from organ transplant recipients show no evidence of an increased risk of adverse effects on the course and outcome of pregnancy under tacrolimus treatment compared with other immunosuppressive medicinal products. However, cases of spontaneous abortion have been reported. To date, no other relevant epidemiological data are available. Due to the need of treatment, tacrolimus can be considered in pregnant women when there is no safer alternative and when the perceived benefit justifies the potential risk to the foetus. In 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). There is a risk for premature delivery (<37 week) as well as for hyperkalaemia in the newborn, which, however, normalizes spontaneously.

In rats and rabbits, tacrolimus caused embryofoetal toxicity at doses which demonstrated maternal toxicity (see section 5.3).

Breast-feeding

Human data demonstrate that tacrolimus is excreted into breast milk. 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 section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 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).

Infections and infestations

As is well known for other potent immunosuppressive agents, patients receiving tacrolimus are frequently at increased risk for infections (viral, bacterial, fungal, protozoal). The course of pre-existing infections may be aggravated. Both generalised and localised infections can occur.

Cases of CMV infection, BK virus associated nephropathy, as well as cases of JC virus associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including Prograf.

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

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

Blood and lymphatic system disorders

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

Immune system disorders

Allergic and anaphylactoid reactions have been observed in patients receiving tacrolimus (see section 4.4 under Excipients).

Endocrine disorders

rare:	hirsutism

Metabolism and nutrition disorders

very common:	hyperglycaemic conditions, diabetes mellitus, hyperkalaemia
common:	hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, appetite decreased, metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte abnormalities
uncommon:	dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia

Psychiatric disorders

very common:	insomnia
common:	anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders
uncommon:	psychotic disorder

Nervous system disorders

very common:	tremor, headache
common:	seizures, disturbances in consciousness, paraesthesias and dysaesthesias, peripheral neuropathies, dizziness, writing impaired, nervous system disorders
uncommon:	coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia
rare:	hypertonia
very rare:	myasthenia
not known:	posterior reversible encephalopathy syndrome (PRES)

Eye disorders

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

Ear and labyrinth disorders

common:	tinnitus
uncommon:	hypoacusis
rare:	deafness neurosensory
very rare:	hearing impaired

Cardiac disorders

common:	ischaemic coronary artery disorders, tachycardia
uncommon:	ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations
rare:	pericardial effusion
very rare:	*Torsades de pointes*

Vascular disorders

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

Respiratory, thoracic and mediastinal disorders

common:	dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammations
uncommon:	respiratory failures, respiratory tract disorders, asthma
rare:	acute respiratory distress syndrome

Gastrointestinal disorders

very common:	diarrhoea, nausea
common:	gastrointestinal inflammatory conditions, gastrointestinal ulceration and perforation, gastrointestinal haemorrhages, stomatitis and ulceration, ascites, vomiting, gastrointestinal and abdominal pains, dyspeptic signs and symptoms, constipation, flatulence, bloating and distension, loose stools, gastrointestinal signs and symptoms
uncommon:	ileus paralytic, acute and chronic pancreatitis, gastrooesophageal reflux disease, impaired gastric emptying
rare:	subileus, pancreatic pseudocyst

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

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

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, 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

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

Injury, poisoning and procedural complications

common:	primary graft dysfunction

Description of selected adverse reactions

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, 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 potent immunosuppressive agent and has proven activity in both *in vitro* and *in vivo* 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.

Results from published data in other primary organ transplantation

Prograf has evolved into an accepted treatment as primary immunosuppressive medicinal product following pancreas, lung and intestinal transplantation. In prospective published studies tacrolimus was investigated as primary immunosuppressant in approximately 175 patients following lung, 475 patients following pancreas and 630 patients following intestinal transplantation. Overall, the safety profile of tacrolimus in these published studies appeared to be similar to what was reported in the large studies, where tacrolimus was used as primary treatment in liver, kidney and heart transplantation. Efficacy results of the largest studies in each indication are summarised below.

Lung transplantation

The interim analysis of a recent multicentre study discussed 110 patients who underwent 1:1 randomisation to either tacrolimus or ciclosporin. Tacrolimus was started as continuous intravenous infusion at a dose of 0.01 to 0.03 mg/kg/day and oral tacrolimus was administered at a dose of 0.05 to 0.3 mg/kg/day. A lower incidence of acute rejection episodes for tacrolimus- versus ciclosporin-treated patients (11.5% versus 22.6%) and a lower incidence of chronic rejection, the bronchiolitis obliterans syndrome (2.86% versus 8.57%), was reported within the first year after transplantation. The 1-year patient survival rate was 80.8% in the tacrolimus and 83% in the ciclosporin group (Treede et al., 3rd ICI San Diego, US, 2004;Abstract 22).

Another randomised study included 66 patients on tacrolimus versus 67 patients on ciclosporin. Tacrolimus was started 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 and 71% in the ciclosporin group, the 2-year survival rates were 76% and 66%, respectively. Acute rejection episodes per 100 patient-days were numerically fewer in the tacrolimus (0.85 episodes) than in the ciclosporin group (1.09 episodes). Obliterative bronchiolitis developed in 21.7% of patients in the tacrolimus group compared with 38.0% of patients in the ciclosporin group ($p = 0.025$). Significantly more ciclosporin-treated patients ($n = 13$) required a switch to tacrolimus than tacrolimus-treated patients to ciclosporin ($n = 2$) ($p = 0.02$) (Keenan et al., Ann Thoracic Surg 1995;60:580).

In an additional two-centre study, 26 patients were randomised to the tacrolimus versus 24 patients to the ciclosporin group. Tacrolimus was started as continuous intravenous infusion at a dose of 0.05 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. The 1-year survival rates were 73.1% in the tacrolimus versus 79.2% in the ciclosporin group. Freedom from acute rejection was higher in the tacrolimus group at 6 months (57.7% versus 45.8%) and at 1 year after lung transplantation (50% versus 33.3%) (Treede et al., J Heart Lung Transplant 2001;20:511).

The three studies demonstrated similar survival rates. The incidences of acute rejection were numerically lower with tacrolimus in all three studies and one of the studies reported a significantly lower incidence of bronchiolitis obliterans syndrome with tacrolimus.

Pancreas transplantation

A multicentre study included 205 patients undergoing simultaneous pancreas-kidney transplantation who were randomised to tacrolimus ($n = 103$) or to ciclosporin ($n = 102$). The initial oral per protocol dose of tacrolimus was 0.2 mg/kg/day, with subsequent dose adjustments to target trough levels of 8 to 15 ng/ml by Day 5 and 5 to 10 ng/ml after Month 6. Pancreas survival at 1 year was significantly superior with tacrolimus: 91.3% versus 74.5% with ciclosporin ($p < 0.0005$), whereas renal graft survival was similar in both groups. In total 34 patients switched treatment from ciclosporin to tacrolimus, whereas only 6 tacrolimus patients required alternative therapy (Bechstein et al., Transplantation 2004;77:1221).

Intestinal transplantation

Published clinical experience from a single centre on the use of tacrolimus for primary treatment following intestinal transplantation showed that the actuarial survival rate of 155 patients (65 intestine alone, 75 liver and intestine, and 25 multivisceral) receiving tacrolimus and prednisone was 75% at 1 year, 54% at 5 years, and 42% at 10 years. In the early years the initial oral dose of tacrolimus was 0.3 mg/kg/day. Results continuously improved with increasing experience over the course of 11 years. A variety of innovations, such as techniques for early detection of Epstein-Barr (EBV) and CMV infections, bone marrow augmentation, the adjunct use of the interleukin-2 antagonist daclizumab, lower initial tacrolimus doses with target trough levels of 10 to 15 ng/ml, and most recently allograft irradiation were considered to have contributed to improved results in this indication over time (Abu-Elmagd et al., Ann Surg 2001;234:404).

5.2 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 hard capsules, have been shown to be bioequivalent, when administered as equivalent dose.

The rate and extent of absorption of tacrolimus is greatest under fasted conditions. The presence of food decreases both the rate and extent of absorption of tacrolimus, the effect being most pronounced after a high-fat meal. The effect of a high-carbohydrate meal is less pronounced.

In stable liver transplant patients, the oral bioavailability of Prograf was reduced when it was administered after a meal of moderate fat (34% of calories) content. Decreases in AUC (27%) and C_{max} (50%), and an increase in t_{max} (173%) in whole blood were evident.

In a study of stable renal transplant patients who were administered Prograf immediately after a standard continental breakfast the effect on oral bioavailability was less pronounced. Decreases in AUC (2 to 12%) and C_{max} (15 to 38%), and an increase in t_{max} (38 to 80%) in whole blood were evident.

Bile flow does not influence the absorption of 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 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 and biotransformation

Tacrolimus is widely metabolised in the liver, primarily by the cytochrome P450-3A4 (CYP3A4) and the cytochrome P450-3A5 (CYP3A5). Tacrolimus is also considerably metabolised in the intestinal wall. There are several metabolites identified. Only one of these has been shown *in vitro* to have immunosuppressive activity similar to that of tacrolimus. The other metabolites have only weak or no immunosuppressive activity. In systemic circulation only one of the inactive metabolites is present at low concentrations. Therefore, metabolites do not contribute to pharmacological activity of tacrolimus.

Excretion

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

5.3 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 rats and rabbits and was limited to doses that caused significant toxicity in maternal animals. In rats, female reproductive function including birth was impaired at toxic dosages and the offspring showed reduced birth weights, viability and growth.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dehydrated alcohol

Polyoxyethylene hydrogenated castor oil

6.2 Incompatibilities

When diluting, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Tacrolimus is absorbed by PVC plastics. Tubing, syringes and any other equipment used to prepare and administer Prograf 5 mg/ml concentrate for solution for infusion should not contain PVC.

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
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.

6.4 Special precautions for storage

Store ampoule in the original package in order to protect from light.

Do not store above 25°C.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

1 ml concentrate for solution for infusion in 2 ml, type I Ph. Eur. clear colourless glass ampoules.

Each carton contains 10 ampoules.

6.6 Special precautions for disposal and other handling

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

Prograf 5 mg/ml concentrate for solution for infusion must not be injected undiluted.

Prograf 5 mg/ml concentrate for solution for infusion should be diluted in 5% w/v glucose solution or physiological saline solution in polyethylene, polypropylene or glass bottles, but not in PVC containers (see section 6.2). Only transparent and colourless solutions should be used.

The concentration of a solution for infusion should be within the range 0.004 - 0.100 mg/ml. The total volume of infusion during a 24-hour period should be in the range 20 - 500 ml.

The diluted solution should not be given as a bolus.

Any unused concentrate in an opened ampoule or unused reconstituted solution should be disposed of immediately in accordance with local requirements to avoid contamination.

7. LICENSE HOLDER AND MANUFACTURER

License Holder

Astellas Pharma International B.V.
21 Ha'melacha Street, Rosh Ha'ayin, 4809157, Israel

Manufacturer

Astellas Ireland Co. Ltd.,
Killorglin, Ireland

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