PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]Prograf®
Tacrolimus

tacrolimus for injection
5 mg/mL, for intravenous use

tacrolimus immediate-release capsules, USP
0.5 mg, 1 mg and 5 mg, for oral use

Immunosuppressant

Astellas Pharma Canada, Inc.
Markham, ON
L3R 0B8

Date of Authorization:
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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Carcinogenesis and Genotoxicity	2025/12
7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnancy	2025/12

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PART 1: HEALTHCARE PROFESSIONAL INFORMATION

1 INDICATIONS

Transplantation

Prograf® (tacrolimus) is indicated for:

- prophylaxis of organ rejection in patients receiving allogeneic liver, kidney or heart transplants.
- treatment of refractory rejection in patients receiving allogeneic liver or kidney transplants.

Prograf is to be used concomitantly with adrenal corticosteroids and other immunosuppressive agents. The safety and efficacy of the use of Prograf with sirolimus has not been established.

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

Rheumatoid Arthritis

Prograf (tacrolimus immediate-release capsules, USP) is indicated for:

- treatment of active rheumatoid arthritis in adult patients for whom disease modifying anti-rheumatic drug (DMARD) therapy is ineffective or inappropriate.

Prograf may be used as monotherapy or in combination with non-steroidal anti-inflammatory drugs (NSAIDs) and/or steroids, although the possibility of increased toxicity has not been fully explored (see 7 Warnings and Precautions and 9 Drug Interactions).

Combined use of Prograf with gold, penicillamine, hydroxychloroquine, sulfasalazine or azathioprine has not been studied.

There is currently insufficient data to support the concomitant use of Prograf and methotrexate.

Careful monitoring of Prograf-treated patients is mandatory. Prograf should only be prescribed for rheumatoid arthritis by physicians experienced with the use of immunosuppressants.

1.1 Pediatrics

Pediatrics (< 18 years of age): Experience with Prograf in pediatric kidney and heart transplant patients is limited. Successful liver transplants have been performed in pediatric patients (ages 4 months up to 16 years) using Prograf, with the majority of these patients under 5 years of age (see 7 Warnings and Precautions).

Prograf is not indicated for the use of rheumatoid arthritis in children younger than 18 years of age.

1.2 Geriatrics

Geriatrics (> 65 years of age): The safety and efficacy of Prograf in patients older than 65 years of age has not been established.

2 CONTRAINDICATIONS

- Prograf (tacrolimus) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see the **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** sections.
- Prograf (tacrolimus for injection) is contraindicated in patients with a hypersensitivity to HCO-60 (polyoxyl 60 hydrogenated castor oil).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Increased susceptibility to infection and the possible development of lymphoma and skin cancer may result from immunosuppression (see **7 WARNINGS AND PRECAUTIONS**, **Carcinogenesis and Genotoxicity**, and **Immune**).

- **Transplant Patients**
  Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Prograf (tacrolimus). Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient and should be consulted if a patient is converted to an alternative formulation so that therapeutic drug monitoring can be instituted.

- **Rheumatoid Arthritis**
  Careful monitoring of Prograf-treated patients is mandatory. Prograf should only be prescribed for rheumatoid arthritis by physicians experienced with the use of immunosuppressants. Prograf is indicated for the treatment of active rheumatoid arthritis in adult patients for whom disease-modifying anti-rheumatic drug (DMARD) therapy is ineffective or inappropriate.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Due to intersubject variability following dosing with tacrolimus, individualization of the dosing regimen is necessary for optimal therapy.

Additional factors that may impact dosing include pre-existing conditions, such as renal or hepatic impairment, race, pediatric use and the concomitant use of other medications.

Prograf has been used in combination with azathioprine. Prograf has been used in combination with mycophenolate mofetil (MMF) in patients receiving deceased donor kidney transplants and heart

transplants. Because of the risk of anaphylaxis, intravenous Prograf should be reserved for patients unable to take Prograf capsules orally.

Medication errors, including inadvertent, unintentional or unsupervised substitution of Prograf (immediate-release) or Advagraf (extended-release) tacrolimus formulations, have been observed. This has led to serious adverse events, including graft rejection, or other side effects which could be a consequence of either under- or over-exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist.

Following conversion to any alternative formulation, therapeutic drug monitoring must be performed and dose adjustments made to ensure that systemic exposure to tacrolimus is maintained.

4.2 Recommended Dose and Dosage Adjustment

Prograf (tacrolimus for injection) is for intravenous (IV) use in transplant patients only. **Anaphylactic reactions have occurred with injectables containing castor oil derivatives (see 7 WARNINGS AND PRECAUTIONS).**

In patients unable to take oral Prograf (tacrolimus immediate-release capsules, USP), therapy may be initiated with IV Prograf (tacrolimus for injection). The initial dose of Prograf should be administered no sooner than 6 hours after transplantation. The recommended starting dose of Prograf given intravenously is 0.01 mg/kg/day (heart) or 0.03 - 0.05 mg/kg/day (liver, kidney) as a continuous intravenous infusion (see Table 1). Adult patients should receive doses at the lower end of the dosing range. Concomitant adrenal corticosteroid therapy is recommended early post-transplantation.

Continuous intravenous infusion of Prograf (tacrolimus for injection) should be continued until the patient can tolerate oral administration of Prograf (tacrolimus immediate-release capsules, USP).

Kidney Transplantation
The recommended starting oral dose of Prograf is 0.2 - 0.3 mg/kg/day administered every 12 hours in two divided doses. The initial dose of Prograf may be administered within 24 hours of transplantation but should be delayed until renal function has recovered (as indicated, for example, by a serum creatinine ≤ 4 mg/dL). Black patients may require higher doses to achieve comparable blood levels. Dosage and typical tacrolimus whole blood trough concentrations are shown in the table below; blood concentration details are described under 7 Warnings and Precautions– Monitoring and Laboratory Tests - Blood Concentration Monitoring.

Table 1: Recommended Tacrolimus Oral Dosing in Kidney Transplant Patients

Dosage	
Initial Oral Dose	0.2 - 0.3 mg/kg/day
Dosing Regimen	two divided doses, q12h
Typical tacrolimus whole blood trough concentrations	
Month 1-3 Month 4-12	7 - 20 ng/mL 5 - 15 ng/mL

Liver Transplantation
It is recommended that patients be converted from IV to oral Prograf as soon as oral therapy can be tolerated. This usually occurs within 2-3 days. The first dose of oral therapy should be given 8-12 hours after discontinuing the IV infusion. The recommended starting oral dose of Prograf capsules is 0.1 - 0.15 mg/kg/day administered in two divided daily doses every 12 hours. The initial dose of Prograf should be administered no sooner than 6 hours after transplantation. Adult patients should receive doses at the lower end of the dosing range.

Some centres use lower Prograf doses during maintenance therapy post-transplantation. Dosing should be titrated based on clinical assessment of rejection and tolerability. Adjunct therapy with adrenal corticosteroids is recommended early post-transplant.

Heart Transplantation
The recommended starting oral dose of Prograf is 0.075 mg/kg/day administered every 12 hours in two divided doses. It is recommended that patients initiate oral therapy with Prograf capsules if possible. If IV therapy is necessary, conversion from IV to oral Prograf is recommended as soon as oral therapy can be tolerated. This usually occurs within 2-3 days. The initial dose of Prograf should be administered no sooner than 6 hours after transplantation. In a patient receiving an IV infusion, the first dose of oral therapy should be given 8-12 hours after discontinuing the IV infusion.

Dosing should be titrated based on clinical assessments of rejection and tolerability. Lower Prograf dosages may be sufficient as maintenance therapy. Adjunct therapy with adrenal corticosteroids is recommended early post-transplant.

Rheumatoid Arthritis
The recommended adult oral dose of Prograf is 3 mg, administered once a day.
Regular monitoring of Prograf-treated patients for occurrence of adverse events is mandatory.

Patients with Hepatic or Renal Dysfunction
Due to the potential for nephrotoxicity, patients with renal or hepatic impairment should receive doses at the lowest value of the recommended intravenous and oral dosing ranges. Further reductions in dose below these ranges may be required.

Conversion from Cyclosporine to Prograf
Tacrolimus should not be used simultaneously with cyclosporine. Patients converted from cyclosporine to Prograf should receive the first Prograf dose no sooner than 24 hours after the last cyclosporine dose. Dosing may be further delayed in the presence of elevated cyclosporine levels.

Conversion from Prograf to Cyclosporine
Patients converted from Prograf to cyclosporine should receive the first cyclosporine dose no sooner than 24 hours after the last Prograf dose. Dosing may be further delayed in the presence of elevated tacrolimus levels.

Pediatric Patients
Pediatric liver transplantation patients without pre-existing renal or hepatic dysfunction have required and tolerated higher doses than adults to achieve similar blood concentrations. Therefore, it is recommended that therapy be initiated in pediatric patients at a starting IV dose of

0.03 - 0.05 mg/kg/day and a starting oral dose of 0.15 - 0.20 mg/kg/day. Dose adjustments may be required. Experience in pediatric kidney and heart transplantation patients is limited.

Race
Although a formal study to evaluate the pharmacokinetics of tacrolimus in Black transplant patients has not been conducted, a retrospective comparison of Black and Caucasian kidney transplant patients indicated that Black patients required higher tacrolimus doses to attain similar trough concentrations.

4.3 Reconstitution

Table 2: Reconstitution of Prograf Injection 5 mg/mL

Vial Size	Diluent to be Added to Vial	Approximate Available Volume in Ampoule	Nominal Concentration per mL
1 mL (2 mL capacity)	0.9% Sodium Chloride or 5% Dextrose Injection	1 mL	Dilute to between 0.004 mg/mL and 0.02 mg/mL

Prograf (tacrolimus for injection) must be diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection to a concentration between 0.004 mg/mL and 0.02 mg/mL prior to use. Diluted infusion solution should be stored in glass or polyethylene containers and should be discarded after 24 hours. The diluted infusion solution should not be stored in a PVC container due to poor stability and the potential for extraction of phthalates. In situations where more dilute solutions are utilized (e.g., pediatric dosing, etc.), PVC-free tubing should likewise be used to minimize the potential for significant drug adsorption onto the tubing. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Due to the chemical instability of tacrolimus in alkaline media, Prograf injection should not be mixed or co-infused with solutions of pH 9 or greater (e.g., ganciclovir or acyclovir). Prograf injection is administered as a continuous intravenous infusion.

4.4 Administration

Prograf (tacrolimus for injection) – Intravenous Administration
Patients receiving Prograf intravenously (tacrolimus for injection) should be under continuous observation for at least the first 30 minutes following the start of the infusion and at frequent intervals thereafter. If signs or symptoms of anaphylaxis occur, the intravenous infusion should be stopped. An aqueous solution of epinephrine 1:1000 should be available at the bedside as well as a source of oxygen.

Prograf (tacrolimus immediate-release capsules, USP) – Oral Administration
Prograf (tacrolimus immediate-release capsules, USP) should be administered whole and should not be cut, crushed or chewed. Prograf can be administered with or without food; however, doses should be administered in a consistent manner, with doses spaced evenly throughout the day.

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

4.5 Missed Dose

Transplant and Rheumatoid Arthritis
If a dose is missed, contact your physician or pharmacist immediately.

5 OVERDOSE

Limited overdosage experience is available. Acute overdosages of up to 30 times the intended dose have been reported. All patients recovered with no sequelae. Acute overdosage has been followed by adverse reactions consistent with those listed in the Adverse Reactions section (see 8 Adverse Reactions), including mild elevations of renal function markers (creatinine), nausea, headache, hyperreflexia, oliguria, hypotension, tremor and elevations in liver enzymes. In one case, transient urticaria and lethargy were observed, and in another case, acute anuric renal insufficiency developed. Based on its high molecular weight, poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is anticipated that tacrolimus is not dialyzable to any significant extent; there is no experience with charcoal hemoperfusion. The oral use of activated charcoal has been reported in treating acute overdoses, but experience has not been sufficient to warrant recommending its use. General supportive measures and treatment of specific symptoms should be followed in all cases of overdosage.
In acute oral and intravenous toxicity studies, mortalities were seen at or above the following doses: in adult rats, 52X the recommended human oral dose: in immature rats, 16X the recommended oral dose, and in adult rats, 16X the recommended human intravenous dose (all based on body surface area corrections).

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION, AND PACKAGING

Table 3: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Capsules / 0.5 mg	croscarmellose sodium, ferric oxide, gelatin, hydroxypropylmethylcellulose 2910, lactose, magnesium stearate and titanium dioxide
oral	Capsules / 1 mg	croscarmellose sodium, gelatin, hydroxypropylmethylcellulose 2910, lactose, magnesium stearate and titanium dioxide
oral	Capsules / 5 mg	croscarmellose sodium, ferric oxide, gelatin, hydroxypropylmethylcellulose 2910, lactose, magnesium stearate and titanium dioxide
intravenous	Injection / 5 mg/mL	dehydrated alcohol, USP, 80% v/v and polyoxyl 60 hydrogenated castor oil (HCO-60), 200 mg

Prograf is also available as a sterile solution (tacrolimus for injection) containing the equivalent of 5 mg anhydrous tacrolimus in 1 mL for administration by intravenous infusion only. Each mL contains polyoxyl 60 hydrogenated castor oil (HCO-60), 200 mg, and dehydrated alcohol, USP, 80% v/v. Prograf for injection must be diluted to a concentration between 0.004 mg/mL and 0.02 mg/mL with 0.9% Sodium Chloride Injection or 5% Dextrose Injection before use. The diluted solution for infusion should be stored at 15-25°C in glass or polyethylene containers and should be discarded after 24 hours. The diluted solution for infusion should not be stored in a PVC container due to poor stability and the potential for extraction of phthalates. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Prograf (tacrolimus immediate-release capsules, USP) 0.5 mg
Oblong, light yellow, capsules imprinted with red "0.5 mg", on the capsule cap and “f 607" on the capsule body supplied in 100-count bottles or in blister packs of 100 capsules (10 capsules per card).

Prograf (tacrolimus immediate-release capsules, USP) 1 mg
Oblong, white, capsules imprinted with red "1 mg", on the capsule cap and “f 617" on the capsule body supplied in 100-count bottles or in blister packs of 100 capsules (10 capsules per card).

Prograf (tacrolimus immediate-release capsules, USP) 5 mg
Oblong, grayish/red, capsules imprinted with white "5 mg", on the capsule cap and “f 657" on the capsule body supplied in 100-count bottles or in blister packs of 100 capsules (10 capsules per card).

Prograf (tacrolimus for injection) 5 mg (for intravenous infusion)
Supplied as a sterile colourless solution in 1 mL ampoules containing the equivalent of 5 mg of anhydrous tacrolimus per mL, in boxes of 10 ampoules.

7 WARNINGS AND PRECAUTIONS

Please see the **Serious Warnings and Precautions Box** at the beginning of **PART 1: HEALTH PROFESSIONAL INFORMATION**.

General

Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P450 system (CYP3A). Since tacrolimus is metabolized mainly by the CYP3A enzyme systems, substances known to inhibit these enzymes may decrease the metabolism or increase bioavailability of tacrolimus with resultant increases in whole blood or plasma levels. Drugs known to induce these enzyme systems may result in an increased metabolism of tacrolimus or decreased bioavailability as indicated by decreased whole blood or plasma levels. Monitoring of blood levels and appropriate dosage adjustments in transplant patients are essential when such drugs are used concomitantly (see **4 DOSAGE AND ADMINISTRATION**, **4.2 Recommended Dose and Dose Adjustment**, and **9 DRUG INTERACTIONS**).

Prograf contains lactose and is not recommended for patients with rare hereditary disease of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

For Transplant Patients

Patients receiving Prograf for injection should be under continuous observation for at least the first 30 minutes following the start of the infusion and at frequent intervals thereafter. If signs or symptoms of anaphylaxis occur, the infusion should be stopped. An aqueous solution of epinephrine 1:1000 should be available at the bedside as well as a source of oxygen.

Prograf, when given orally, is a twice-a-day formulation of tacrolimus. 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.

Switching of Prograf (immediate-release formulation) to Advagraf (extended-release formulation) should be done under supervision of a transplant specialist. Inadvertent, unintentional or unsupervised switching of Prograf to Advagraf formulations of tacrolimus is unsafe. This can lead to graft rejection or increased incidence of side effects, including under- or over-immunosuppression, due to clinically relevant differences in systemic exposure to tacrolimus. Patients should be maintained on a single formulation of tacrolimus with the corresponding daily dosing regimen; alterations in formulation or regimen should only take place under the close supervision of a transplant specialist (see 4 Dosage and Administration).

Following conversion to any alternative formulation, therapeutic drug monitoring must be performed and dose adjustments made to ensure that systemic exposure to tacrolimus is maintained.

Carcinogenesis and Genotoxicity

An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants. The most common forms of neoplasms are non-Hodgkin's lymphomas and carcinomas of the skin and Kaposi’s sarcoma. As with other immunosuppressive therapies, the risk of developing lymphomas and other malignancies, particularly of the skin or Kaposi’s sarcoma, may be higher in Prograf recipients than in the normal, healthy population. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

Lymphoproliferative disorders associated with Epstein-Barr virus infection have been seen. It has been reported that reduction or discontinuation of immunosuppression may cause the lesions to regress (see 16 Non-Clinical Toxicology).

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

Cardiovascular

Hypertension is a common side effect of Prograf (tacrolimus) therapy (see 8 Adverse Reactions). Mild or moderate hypertension is more frequently reported than severe hypertension. The incidence of hypertension decreases over time. 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 Prograf-associated hypertension, care should be taken since interference with tacrolimus metabolism may require a dosage reduction in the

transplant patient (see 9 Drug Interactions). Hypertension and hyperkalemia have also been noted in patients with rheumatoid arthritis. Tacrolimus should be discontinued in patients in whom hypertension and hyperkalemia cannot be controlled.

Heart failure, myocardial hypertrophy and arrhythmia have been reported in association with the administration of Prograf. Myocardial hypertrophy is generally manifested by echocardiographically demonstrated concentric increases in left ventricular posterior wall and interventricular septum thickness. Hypertrophy has been observed in infants, children and adults. This condition appears reversible in most cases following dose reduction or discontinuance of therapy. In a group of 20 transplant patients with pre- and post-treatment echocardiograms who showed evidence of myocardial hypertrophy, mean tacrolimus whole blood concentrations during the period prior to diagnosis of myocardial hypertrophy ranged from 11 to 53 ng/mL in infants (N=10) age 0.4 to 2 years, 4 - 46 ng/mL in children (N=7) age 2 - 15 years and 11 - 24 ng/mL in adults (N=3) age 37 - 53 years.

Tacrolimus may prolong the QT interval and may cause *Torsades de pointes*. Caution should be exercised in patients with known risk factors for QT prolongation (including, but not limited to, congenital or acquired QT prolongation and concomitant medications known to prolong the QT interval or known to increase tacrolimus exposure) (see 9 Drug Interactions).

Driving and Operating Machinery

Tacrolimus may cause visual and neurological disturbances. No studies have been performed on the effects of tacrolimus on the ability to drive and use machines.

Gastrointestinal

Gastrointestinal perforation has been reported in patients treated with tacrolimus, although all cases were considered a complication of transplant surgery or were accompanied by infection, diverticulum, or malignant neoplasm. As gastrointestinal perforation may be serious or life-threatening, appropriate medical/surgical management should be instituted promptly (see 8 Adverse Reactions).

Hematologic

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. A mechanism for tacrolimus-induced PRCA has not been elucidated. All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease or concomitant medications associated with PRCA. If PRCA is diagnosed, discontinuation of tacrolimus should be considered.

Thrombotic microangiopathy (TMA) (including hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP))
Concurrent use of tacrolimus and mTOR inhibitors may contribute to the risk of thrombotic microangiopathies (TMA) including hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP).

Hepatic/Biliary/Pancreatic

The use of Prograf in liver transplant recipients experiencing post-transplant hepatic impairment may be associated with increased risk of developing renal insufficiency related to high whole blood levels of tacrolimus. These patients should be monitored closely and dose adjustments should be considered.

Some evidence suggests that the use of lower doses may be warranted in these patients (see 4 Dosage and Administration).

Prograf was shown to cause new onset diabetes mellitus in clinical trials of kidney, liver, and heart transplantation. New onset diabetes after transplantation may be reversible in some patients. Black and Hispanic kidney transplant patients are at an increased risk. Blood glucose concentrations should be monitored closely in patients using Prograf (see 8 Adverse Reactions).

Hyperglycemia, elevations in HbA_{1c}, and overt diabetes have also been noted in rheumatoid arthritis patients treated with tacrolimus. Tacrolimus should be discontinued in patients in whom blood sugars cannot be controlled.

Immune

A lymphoproliferative disorder (LPD) related to Epstein-Barr Virus (EBV) infection has been reported in immunosuppressed organ transplant recipients. The risk of LPD appears greatest in young children who are at risk for primary EBV infection while immunosuppressed, or who are switched to Prograf following long-term immunosuppression therapy. Experience on combining Prograf with immunosuppressive drugs other than adrenal corticosteroids, azathioprine and mycophenolate mofetil is limited because of the potency of Prograf and the risk of over immunosuppression and such combinations are not recommended.

Immunosuppressed patients are at increased risk of developing bacterial, viral, fungal, and protozoal infections, including infection reactivation (e.g. Hepatitis B reactivation) and opportunistic infections, including activation of latent viral infections. These include BK virus-associated nephropathy and JC virus-associated progressive multifocal leukoencephalopathy (PML) which have been observed in patients receiving tacrolimus. These infections are often related to a high 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.

Cytomegalovirus (CMV) Infections
CMV is the most frequent opportunistic infection reported with tacrolimus. CMV seronegative transplant patients who receive an organ from a CMV seropositive donor disease are at higher risk of developing CMV viremia and CMV disease.

A few patients receiving Prograf injection have experienced anaphylactic reactions. Although the exact cause of these reactions is not known, other drugs with castor oil derivatives in the formulation have been associated with anaphylaxis in a small percentage of patients. Because of this potential risk of anaphylaxis, Prograf injection should be reserved for patients who are unable to take Prograf capsules.

Monitoring and Laboratory Tests

Serum creatinine, potassium and fasting glucose should be assessed regularly. Routine monitoring of metabolic and hematologic systems should be performed as clinically warranted.

Blood Level Monitoring in Transplant Patients

Monitoring of tacrolimus blood levels in conjunction with other laboratory and clinical parameters is considered an essential aid to transplant patient management. During the immediate post-operative

period, trough blood concentrations should be measured every 1-3 days. Tacrolimus doses are usually reduced in the post-transplant period. In patients with hepatic or renal dysfunction, or in those receiving or discontinuing concomitant interacting medications, more intensive monitoring may be required, since tacrolimus clearance may be affected under each of these circumstances. More frequent monitoring may also be required in patients early after transplantation since it is at this time patients experience the highest risk of rejection. Blood concentration monitoring is not a replacement for renal and liver function monitoring and tissue biopsies. Following discharge from the hospital, the frequency of patient monitoring will decrease with time post-transplant.

Although there is a lack of direct correlation between tacrolimus levels and drug efficacy, data from Phase II and III studies of kidney and liver transplant patients has shown an increasing incidence of adverse events with increasing trough blood concentrations. Most stable patients are maintained with 12 hours trough whole blood levels of 5 to 20 ng/mL. Long-term post-transplant patients often are maintained at the low end of this target range.

Two methods are available for the assay of tacrolimus: 1) microparticle enzyme immunoassay (MEIA) and 2) enzyme-linked immunosorbent assay (ELISA). Both methods use the same monoclonal antibody for the tacrolimus parent compound. Whole blood is the matrix of choice and specimens should be collected into tubes containing ethylene diamine tetraacetic acid (EDTA) anti-coagulant. Heparin anti-coagulation is not recommended because of the tendency to form clots on storage. Samples which are not analyzed immediately should be stored in a refrigerator and assayed within 3 days; if samples are to be kept longer, they should be deep frozen at -20°C for up to 12 months.

Kidney Transplantation

Data from the U.S. and European Phase III studies indicate that trough concentrations of tacrolimus in whole blood, as measured by IMx®, were most variable during the first week of dosing. During the first three months, 80% of the patients maintained trough concentrations between 7 - 20 ng/mL, and then between 5 - 15 ng/mL, through one year.

The relative risk of toxicity is increased with higher trough concentrations. Therefore, monitoring of whole blood trough concentrations is recommended to assist in the clinical evaluation of toxicity.

Liver Transplantation

Data from the U.S. clinical trial show that tacrolimus whole blood concentrations, as measured by ELISA, were most variable during the first week post-transplantation. After this early period, the median trough blood concentrations, measured at intervals from the second week to one year post-transplantation, ranged from 9.8 ng/mL to 19.4 ng/mL.

Heart Transplantation

Data from a European Phase III study indicates that trough concentrations of tacrolimus in whole blood, as measured by IMx®, were most variable during the first week of dosing. From 1 week to 3 months, 80% of patients maintained trough concentrations between 8 - 20 ng/mL and, from 3 months through 18 months, 80% of patients maintained trough concentrations between 6 - 18 ng/mL.

The relative risk of toxicity is increased with higher trough concentrations. Therefore, monitoring of whole blood trough concentrations is recommended to assist in the clinical evaluation of toxicity.

Blood Level Monitoring in Rheumatoid Arthritis Patients

Prograf used in the treatment of rheumatoid arthritis patients, has resulted in a lower incidence rate of adverse events than previously seen in transplant patients. Trough blood levels of tacrolimus in this patient population have been demonstrated to be very close to the lower limit of quantitation in assays used to evaluate tacrolimus levels. The lower incidence rates of adverse events, as well as the lower levels of tacrolimus detected in rheumatoid arthritis patients, may be due to the lower daily dose of Prograf administered to this patient population. Consequently, monitoring tacrolimus trough levels in rheumatoid arthritis patients has not proven to be the most effective approach of managing this patient population. Management of these patients has proven to be effective based on the incidence of adverse events and monitoring serum creatinine levels. Current data further supports the fact that nephrotoxicity associated with Prograf is predictable and can be managed through the careful monitoring of serum creatinine, adjustments of concomitant medications, and if necessary, withdrawal of due to the treatment. Since Prograf can impair renal function, a reliable baseline level of serum creatinine should be established by at least two measurements prior to treatment. Serum creatinine should be monitored every 2 weeks during the first month of therapy and every four weeks for the next three months, then quarterly thereafter.

If serum creatinine is increased by more than 40% above baseline, the serum creatinine should be repeated in one week. If the repeated serum creatinine remains increased by more than 40% from baseline, dosing of Prograf should be interrupted for 14 days and the serum creatinine measurement should again be repeated. If the serum creatinine returns to a value less than a 40% increase from baseline, dosing with Prograf may be resumed. If the serum creatinine remains elevated by more than 40% from baseline, Prograf should be discontinued. These recommendations apply even if the patient's values still lie within the laboratory normal.

Neurologic

Prograf may cause neurotoxicity, particularly when used at high doses.

Neurotoxicity, including tremor, headache, and other changes in motor function, mental status and sensory function were reported in approximately 55% of liver transplant recipients in the two randomized studies. Tremor occurred more often in Prograf-treated kidney transplant patients in the U.S. and European studies (54 and 35%, respectively), and heart transplant patients (15%) compared with cyclosporine-treated patients. The incidence of other neurological events in the two treatment groups in both kidney studies and heart transplant patients was similar. Tremor and headache have been associated with high whole blood concentrations of tacrolimus and may respond to dosage adjustment. Seizures have occurred in adult and pediatric patients receiving Prograf. Coma and delirium also have been associated with high plasma concentrations of tacrolimus.
Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES). Symptoms indicating PRES include headache, altered mental status, seizures and visual disturbances. Diagnosis should be confirmed by radiological procedure (e.g., MRI). If PRES is suspected or diagnosed, blood pressure and seizure control and immediate discontinuation of immunosuppression is advised. Most patients completely recover after appropriate measures are taken.

Renal

Prograf may cause nephrotoxicity, and the likelihood increases with higher blood levels.

Nephrotoxicity has been noted in approximately 52% and 57% of kidney transplantation patients and in 40% and 36% of liver transplantation patients receiving Prograf in the U.S. and European randomized trials, respectively, and in 59% of heart transplantation patients in a European randomized trial (see 8 Adverse Reactions). 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 9 Drug Interaction). When concurrent use of tacrolimus with other known nephrotoxic drugs is required, monitor renal function and tacrolimus blood concentrations frequently, and dose adjustments of both tacrolimus and/or concomitant medications should be considered upon initiation, throughout concurrent treatment and at discontinuation of such concomitant drugs. **In particular, to avoid excess nephrotoxicity, when switching patients from a cyclosporine-based regimen to a Prograf-based regimen, cyclosporine should be discontinued at least 24 hours prior to initiating Prograf. Prograf dosing may be further delayed in the presence of elevated cyclosporine levels (see 9 Drug Interaction). When switching from tacrolimus to cyclosporine, tacrolimus should be discontinued for at least 24 hours before initiating the other medication.**

For patients with renal insufficiency, some evidence suggests that the use of lower doses may be warranted (see 10 Clinical Pharmacology and 4 Dosage and Administration).

Mild to severe hyperkalemia was reported in 31% and 21% of kidney transplant patients and in 45% and 13% of liver transplant recipients treated with Prograf in the U.S. and European randomized trials, respectively, and in 8% of heart transplant recipients in a European randomized trial and may require treatment (see 8 Adverse Reactions). **Serum potassium levels should be monitored. Potassium-sparing diuretics should not be used and high intake of potassium should be avoided during Prograf therapy (see 7 Warnings and Precautions, Monitoring and Laboratory Tests).**

Hyperkalemia has also been noted in patients with rheumatoid arthritis. Tacrolimus should be discontinued in patients in whom hypertension and hyperkalemia cannot be controlled. The adverse events associated with Prograf treatment in rheumatoid arthritis patients occurred at a lower rate of incidence than seen in transplant patients receiving Prograf. The majority of adverse events were mild or moderate in intensity, of limited duration and did not result in discontinuation of the study drug.

Reproductive Health

- **Fertility**

In reproduction studies in rats and rabbits, adverse effects on the fetus were observed mainly at dose levels that were toxic to dams. However, in female rats dosed during organogenesis, embryo toxicity (expressed as reduced pup weights) was seen at a dose, which was one-third of the maternally toxic dose. At this same dose, when administered prior to mating and during gestation, tacrolimus was associated with adverse effects on female reproductive parameters and embryolethality. This dose was equivalent to 0.5X the clinical dose (see 7 Warnings and Precautions).

7.1 Special Populations

7.1.1 Pregnancy

Prograf should not be used during pregnancy unless the potential benefit to the mother outweighs potential risk to the fetus. There are no adequate and well-controlled studies in pregnant women. Tacrolimus is transferred across the placenta and infants exposed to tacrolimus *in utero* may be at risk of prematurity, birth defects/congenital anomalies, low birth weight, and fetal distress. The use of tacrolimus during pregnancy has been associated with preterm delivery, neonatal hyperkalemia and renal dysfunction.

Tacrolimus may increase hyperglycemia in pregnant women with diabetes (including gestational diabetes). Monitor maternal blood glucose levels regularly.

Tacrolimus may exacerbate hypertension in pregnant women and increase pre-eclampsia. Monitor and control blood pressure. Females and males of reproductive potential should consider the use of appropriate contraception prior to starting treatment with tacrolimus.

Tacrolimus at oral doses of 0.32 and 1.0 mg/kg during organogenesis in rabbits, was associated with maternal toxicity as well as an increase in incidence of abortions; these doses are equivalent to 0.33X and 1.0X (based on body surface area corrections) the recommended clinical dose (0.3 mg/kg). At the higher dose only, an increased incidence of malformations and developmental variations was also seen. Tacrolimus, at oral doses of 3.2 mg/kg during organogenesis in rats, was associated with maternal toxicity and caused an increase in late resorptions, decreased numbers of live births, and decreased pup weight and viability.

Tacrolimus, given orally at 1.0 and 3.2 mg/kg (equivalent to 0.5X and 1.5X), the recommended clinical dose based on body surface area corrections to pregnant rats after organogenesis and during lactation, was associated with reduced pup weights.

Tacrolimus, given orally at 1.0 mg/kg (0.5X the recommended clinical dose based on body surface area corrections) to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with adverse effects on female reproduction and embryolethality. Effects on female reproductive function (parturition) and embryo lethal effects were indicated by a higher rate of pre-implantation loss and increased numbers of undelivered and nonviable pups. When given at 3.2 mg/kg (1.5X the recommended clinical dose based on body surface area correction), tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on estrous cycles, parturition, pup viability and pup malformations. Toxicities to parental rats were indicated by tremors and circling, as well as reduced weight gains and food consumption in males, and reduced food consumption during gestation and lactation in females. Adverse effects on reproductive parameters included: 1) increased copulatory intervals, 2) increased pre- and post-implantation loss of fetuses (resulting in smaller litter sizes), and 3) decreased numbers of dams delivering. No reduction in male or female fertility was evident. Adverse effects seen in pups were markedly reduced viability and a slight increase in the incidence of malformation (3 pups from 3 dams).

In experience reported by the University of Pittsburgh, eleven female transplant patients maintained on tacrolimus therapy throughout pregnancy delivered twelve babies, with one patient conceiving twice. These patients received tacrolimus from week one to 20 months prior to conception. Ten of the

pregnancies were successful, four with C-sections. The neonates showed no growth retardation or congenital anomalies. Hyperkalemia was observed in the majority of babies, but resolved within 24-48 hours without adverse effects. Two babies (both premature 22 and 24 weeks) died shortly after birth. One pregnancy was complicated by diabetes, hypertension and proteinuria, the other by CMV infection requiring ganciclovir therapy. Additional information includes a report of one newborn who had temporary anuria associated with high cord blood tacrolimus concentration, however, renal function was normal within one week. Another reference reports on the successful pregnancy (normal healthy male) in a 28 year-old female with bolus steroids and increased doses of tacrolimus for liver graft rejection. In this case, the cord blood plasma concentration was approximately one half that noted in maternal plasma.

A post-authorization safety study analyzed 2,905 pregnancies from the Transplant Pregnancy Registry International (TPRI), assessing outcomes of pregnancies in women treated with regimens containing tacrolimus (number of pregnancies = 1299) or other immunosuppressants (number of pregnancies = 1606). The study results did not indicate an increased risk of major malformations. There was a trend towards a higher prevalence of spontaneous abortion among women treated with tacrolimus compared with alternative immunosuppressants. Among kidney transplant patients, there was also a trend towards a higher prevalence of pre-eclampsia in women treated with tacrolimus. Among kidney and liver transplant patients exposed to tacrolimus, 45%-55% of their live births were premature, with 75%-85% having a normal birth weight for gestational age. Similar results were observed for other immunosuppressants.

7.1.2 Breastfeeding

Tacrolimus is excreted in human milk. The effects of tacrolimus on the breastfed infant, or on milk production have not been assessed. As detrimental effects on the newborn cannot be excluded, women should not breastfeed while receiving tacrolimus.

7.1.3 Pediatrics

Heart failure, cardiomegaly and increased thickness of the myocardium have been reported in patients taking Prograf. Patients at risk for these effects are primarily children younger than 5 years undergoing liver “rescue”, small bowel or multivisceral transplantation with trough whole blood tacrolimus levels exceeding 25 ng/mL. Also, these patients at risk often have experienced fluid overload, renal and/or hepatic dysfunction, hypertension and are receiving large doses of corticosteroids and other concomitant medications. Cardiovascular function for such patients should be carefully monitored. In addition, tacrolimus trough whole blood levels should be maintained below 25 ng/mL. If cardiac abnormalities develop, dose reduction or discontinuation of Prograf should be considered in cases where the perceived risk to the patient outweighs the benefit.

The two randomized active-controlled trials of Prograf in primary liver transplantation included 56 pediatric patients. Thirty-one patients were randomized to Prograf and 25 to cyclosporine-based therapies. Additionally, a minimum of 120 pediatric patients (median age 22.5 months) who underwent 122 liver transplants were studied in an uncontrolled published trial of tacrolimus in living related donor liver transplantation. Pediatric patients generally required higher doses of Prograf to maintain blood trough concentrations of tacrolimus similar to adult patients (see 4 Dosage and Administration). This is

thought to be a result of age-related differences in the oxidative capacity of the cytochrome P450 enzyme system (CYP3A) used to metabolize tacrolimus.

7.1.4 Geriatrics

No formal studies have been performed to evaluate the effect of Prograf specifically in the geriatric patient population.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Kidney Transplantation
The most common adverse reactions reported were infection, tremor, hypertension, decreased renal function, constipation, diarrhea, headache, abdominal pain and insomnia. Many of these adverse reactions were mild and responded to a reduction in dosage. Insulin-dependent post-transplant diabetes mellitus (PTDM) was related to increased whole blood trough concentrations of tacrolimus and higher doses of corticosteroids. The median time to onset of PTDM was 68 days.

Liver Transplantation
The principal adverse reactions of Prograf (tacrolimus) are tremor, headache, diarrhea, hypertension, nausea, and renal dysfunction. These occur with oral and intravenous administration of Prograf and may respond to a reduction in dosing. Diarrhea was sometimes associated with other gastrointestinal complaints such as nausea and vomiting.
Hyperkalemia and hypomagnesemia have occurred in patients receiving Prograf therapy. Hyperglycemia has been noted in many patients; some may require insulin therapy.

Heart Transplantation
The more common adverse reactions in Prograf-treated heart transplant recipients were kidney function abnormal, hypertension, diabetes mellitus, CMV infection, tremor, hyperglycemia, leukopenia, infection, and hyperlipemia.

Rheumatoid Arthritis
The adverse events associated with Prograf treatment in rheumatoid arthritis patients occurred at a lower rate of incidence than seen in transplant patients receiving Prograf. The majority of adverse events were mild or moderate in intensity, of limited duration and did not result in discontinuation of the study drug.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Kidney Transplantation

The incidence of adverse events was determined in two randomized Phase III comparative kidney transplant studies involving 508 patients receiving Prograf and 352 patients receiving cyclosporine.

Adverse events that occurred in ≥ 15% of Prograf-treated patients (combined study results) are presented below for the two controlled trials in kidney transplantation:

Table 4: Kidney transplantation: Treatment-Emergent Adverse Events Occurring in ≥ 15% of Prograf-treated Patients

Body System	U.S. STUDY		EUROPEAN STUDY	
	Prograf N=205 %	CBIR** N=207 %	Prograf N=303 %	CBIR** N=145 %
Nervous System				
Tremor*	54	34	35	12
Headache*	44	38	21	14
Insomnia	32	30	24	26
Gastrointestinal				
Diarrhea	44	41	22	10
Nausea	38	36	17	16
Constipation	35	43	31	35
Vomiting	29	23	13	8
Dyspepsia	28	20	16	13
Cardiovascular				
Hypertension*	50	52	37	39
Urogenital				
Creatinine increased*	45	42	35	21
Metabolic and Nutritional				
Hypophosphatemia	49	53	3	5
Hypomagnesemia	34	17	4	1
Hyperkalemia*	31	32	21	16
Diabetes mellitus*	24	9	12	2
Hyperglycemia*	22	16	16	7
Hemic and Lymphatic				
Anemia	30	24	18	17
Leukopenia	15	17	17	15
Body as a Whole				
Infection	45	49	76	75
Peripheral edema	36	48	16	16
Asthenia	34	30	7	4
Abdominal pain	33	31	27	23
Pain	32	30	21	23
Fever	29	29	8	9
Respiratory System				
Dyspnea	22	18	12	11
Musculoskeletal				
Arthralgia	25	24	9	10

* See Warnings and Precautions

** Cyclosporine-based immunosuppressive regimen.

Tacrolimus has been studied in combination with azathioprine and steroids (triple therapy) in recipients of kidney transplants. In a Phase II European trial, tacrolimus triple therapy was administered to 31 adults receiving deceased donor kidney transplants. Within six weeks post-transplant, there were no deaths or graft losses. Six patients (19.4%) experienced acute rejection, with one patient experiencing corticosteroid-resistant rejection. Three patients (9.7%) developed transient hyperglycemia, but no patient required long-term therapy for diabetes. Other adverse events reported frequently included infections (51.6%), minor neurological disorders (54.8%), and hypertension (48.8%) (Transpl Int 1995; 8:86-90). The University of Pittsburgh has studied double therapy (tacrolimus and steroids) compared to triple therapy in 204 adult recipients of kidney transplants between August 1991 and October 1992. (Clin Transplantation 1994; 8:508-515). The one year actuarial patient and graft survival of double therapy were 95 and 90% versus 91 and 82% for triple therapy (p=NS). The incidence of rejection was significantly lower with triple therapy in deceased donor recipients (39% versus 58%) but not significantly different in recipients from living related donors. New onset diabetes was seen in 20.2% of double therapy patients versus 7.7% of triple therapy patients. A U.S. Phase II trial studied 92 adult recipients of deceased donor kidney transplants randomized to three target whole blood concentration ranges of tacrolimus. All patients received antilymphoblast globulin induction with azathioprine and steroids followed by tacrolimus triple therapy initiated within 2 weeks post-transplant. With follow-up to six weeks post-transplant, there were no patient deaths, and one graft loss. The incidence of rejection was 14% combining all tacrolimus treatment groups. Adverse events requiring dose reduction were significantly associated with target tacrolimus blood concentrations (36%-62%).

Data on the safety and efficacy of tacrolimus in combination with immunosuppressants other than steroids in liver transplant patients is more limited. In the European multicentre liver transplant study, many patients received azathioprine or ATG/ALG when tacrolimus therapy was withheld. Seven patients received azathioprine in combination with tacrolimus and steroids. Of these 7 patients, one died and one lost their graft in the first year post-transplant.

Liver Transplantation

The incidence of adverse events reported in two randomized comparative liver transplant trials was determined in 514 patients receiving tacrolimus and steroids and 515 patients receiving a cyclosporine-based regimen (CBIR). The proportion of patients reporting more than one adverse event was 99.8% in the tacrolimus group and 99.6% in the CBIR group. Precautions must be taken when comparing the incidence of adverse events in the U.S. study to that in the European Study. The 12 month post-transplant information from the U.S. study and from the European study is presented below. The two studies included different patient populations and patients were treated with immunosuppressive regimens of differing intensities. Adverse events reported in ≥ 15% of tacrolimus patients (combined study results) are presented below for the two controlled trials in liver transplantation.

Table 5: Liver Transplantation: Treatment-Emergent Adverse Events Occurring in ≥ 15% of Prograf-treated Patients

Body System	U.S. STUDY		EUROPEAN STUDY	
	Prograf N=250 %	CBIR* N=250 %	Prograf N=264 %	CBIR* N=265 %
Nervous System				
Headache	64	60	37	26
Tremor	56	46	48	32
Insomnia	64	68	32	23
Paresthesia	40	30	17	17
Gastrointestinal				
Diarrhea	72	47	37	27
Nausea	46	37	32	27
Constipation	24	27	23	21
LFT Abnormal	36	30	6	5
Anorexia	34	24	7	5
Vomiting	27	15	14	11
Cardiovascular				
Hypertension	47	56	38	43
Urogenital				
Kidney Function Abnormal	40	27	36	23
Creatinine Increased	39	25	24	19
Hyperkalemia	45	26	13	9
Hypokalemia	29	34	13	16
BUN Increased	30	22	12	9
Urinary Tract Infection	16	18	21	19
Oliguria	18	15	19	12
Metabolic and Nutritional				
Hyperglycemia	47	38	33	22
Hypomagnesemia	48	45	16	9
Peripheral Edema	26	26	12	14
Hemic and Lymphatic				
Anemia	47	38	5	1
Leukocytosis	32	26	8	8
Thrombocytopenia	24	20	14	19
Body as a Whole				
Abdominal pain	59	54	29	22
Pain	63	57	24	22
Fever	48	56	19	22
Asthenia	52	48	11	7
Back Pain	30	29	17	17
Ascites	27	22	7	8

Body System	U.S. STUDY		EUROPEAN STUDY	
	Prograf N=250 %	CBIR* N=250 %	Prograf N=264 %	CBIR* N=265 %
Respiratory System				
Pleural Effusion	30	32	36	35
Atelectasis	28	30	5	4
Dyspnea	29	23	5	4
Skin and Appendages				
Pruritus	36	20	15	7
Rash	24	19	10	4

* Cyclosporine-based immunosuppressive regimen.

Heart Transplantation

The more common adverse reactions in Prograf-treated heart transplant recipients were kidney function abnormal, hypertension, diabetes mellitus, CMV infection, tremor, hyperglycemia, leukopenia, infection, and hyperlipemia.

Adverse events in heart transplant patients in the European trial are presented below:

Table 6: Heart Transplantation: Treatment-Emergent Adverse Events Occurring in ≥ 15% of Prograf-Treated Patients

COSTART Body System COSTART Term	Prograf N=157 %	CBIR N=157 %
Cardiovascular System		
Hypertension	62	69
Pericardial effusion	15	14
Body as a Whole		
CMV Infection	32	30
Infection	24	21
Metabolic and Nutritional Disorders		
Hyperlipemia	18	27
Diabetes Mellitus	26	16
Hyperglycemia	23	17
Hemic and Lymphatic System		
Leukopenia	48	39
Anemia	50	36
Urogenital System		
Kidney Function Abnormal	56	57
Urinary Tract Infection	16	12
Respiratory System		
Bronchitis	17	18
Nervous System		
Tremor	15	6

The incidence of hyperlipidemia or hypercholesterolemia as an adverse event at any time during the 18 month study was significantly lower in the tacrolimus group (45/157, 28.7%) than in the cyclosporine group (63/157, 40.1%) (p = 0.043, Fisher's exact test).

In the US study, mean serum creatinine levels at 1 year post-transplant were significantly lower in the tacrolimus/MMF group compared with those in either the cyclosporine/MMF group (p = 0.002, one-way ANOVA) or the tacrolimus/sirolimus group (p = 0.020, one-way ANOVA).

Rheumatoid Arthritis

In a long-term study of rheumatoid arthritis patients receiving Prograf treatment, the adverse events seen in this patient population were similar in nature to those previously reported for patients receiving liver or kidney transplants. In this study, as well as two other studies, the incidence of treatment-emergent adverse events seen in the rheumatoid arthritis patient, has a lower incidence of occurrence than seen in the transplant patient.

A summary of treatment-emergent adverse events experienced by at least 5% of patients in any treatment group is presented in the following tables.

Table 7: Summary of Common Treatment-Emergent Adverse Events (≥ 5%) in Rheumatoid Arthritis Patients

Body System	Phase II Study FK506RA-001			
	Placebo N=71 %	Prograf 1 mg N=69 %	Prograf 3 mg N=64 %	Prograf 5 mg N=64 %
Body as a Whole				
Flu Syndrome	19.7	26.1	20.3	15.6
Accidental Injury	1.4	10.1	3.1	7.8
Abdominal Pain	4.2	7.2	9.4	9.4
Asthenia	4.2	2.9	4.7	6.3
Allergic Reaction	2.8	5.8	6.3	1.6
Infection	2.8	1.4	6.3	1.6
Digestive System				
Diarrhea	11.3	11.6	15.6	28.1
Nausea	5.6	15.9	18.8	14.1
Dyspepsia	7.0	17.4	20.3	9.4
Vomiting	1.4	7.2	6.3	6.3
Gastroenteritis	1.4	4.3	7.8	7.8
Nervous System				
Headache	11.3	10.1	20.3	15.6
Tremor	0	4.3	3.1	21.9
Paresthesia	1.4	2.9	3.1	9.4
Anxiety	1.4	1.4	1.6	10.9

Body System	Phase II Study FK506RA-001			
	Placebo N=71 %	Prograf 1 mg N=69 %	Prograf 3 mg N=64 %	Prograf 5 mg N=64 %
Cardiovascular				
Hypertension	4.2	5.8	3.1	4.7
Migraine	2.8	1.4	6.3	3.1
Vasodilatation	0	2.9	1.6	6.3
Respiratory System				
Pharyngitis	2.8	10.1	3.1	3.1
Sinusitis	0	4.3	7.8	3.1
Dyspnea	0	5.8	0	1.6
Metabolic and Nutritional Disorders				
Creatinine Increased	0	2.9	3.1	6.3
Musculoskeletal System				
Arthralgia	5.6	5.8	4.7	4.7
Urogenital System				
Urinary Tract Infection	1.4	0	12.5	9.4

Table 8: Phase III Studies: Summary of Common Treatment-Emergent Adverse Events (≥ 5%) in Rheumatoid Arthritis Patients

Body System	Study 98-0-049			Study 98-0-51
	Placebo N=157 %	Prograf 2 mg N=154 %	Prograf 3 mg N=153 %	Prograf 3 mg N=896 %
Body as a Whole				
Flu Syndrome	16.6	16.2	16.3	26.2
Accidental Injury	5.1	7.8	6.5	8.7
Abdominal Pain	4.5	6.5	7.8	13.5
Asthenia	3.2	4.5	8.5	8.5
Back Pain	2.5	3.2	4.6	6.4
Insomnia	5.1	3.9	2.6	4.2
Digestive System				
Diarrhea	5.1	13.0	13.7	19.9
Nausea	6.4	11.7	10.5	14.6
Dyspepsia	3.2	11.0	6.5	13.1
Vomiting	1.3	2.6	5.2	6.6
Nervous System				
Headache	8.9	8.4	9.2	15.1
Dizziness	3.8	4.5	7.2	7.1
Tremor	1.9	4.5	8.5	10.5
Cardiovascular				
Hypertension	4.5	5.8	7.8	8.5

Body System	Study 98-0-049			Study 98-0-51
	Placebo N=157 %	Prograf 2 mg N=154 %	Prograf 3 mg N=153 %	Prograf 3 mg N=896 %
Respiratory System				
Pharyngitis	2.5	6.5	2.0	5.5
Sinusitis	3.2	4.5	3.9	6.0
Skin and Appendages				
Rash	6.4	7.1	3.3	6.8
Metabolic and Nutritional Disorders				
Creatinine Increased	1.9	1.9	6.5	6.7
Musculoskeletal System				
Cramps	0	2.6	5.2	5.6
Urogenital System				
Urinary Tract Infection	2.5	3.2	4.6	5.9

The overall incidence of treatment-emergent adverse events for any treatment group for the three studies (RA-001, 049, and 051) ranged from 72.0% to 90.6%. In the placebo-controlled studies (RA-001 and 049), the overall incidence of treatment-emergent adverse events for the tacrolimus-treated groups was significantly different from placebo. In the tacrolimus-treated groups, the most common adverse events seen across the three studies were flu syndrome, diarrhea, nausea, abdominal pain, dyspepsia, and tremor.

In the case of gastrointestinal events, the incidence of diarrhea in the tacrolimus-treated groups in the three studies varied from 13.0% to 28.1%, with incidence increasing with dose. Tacrolimus 5 mg/day in the RA-001 study elicited the highest incidence of diarrhea (28.1%); the next highest incidence of diarrhea was 19.9% in the 3 mg/day group in the 051 study. The incidences of diarrhea in the tacrolimus 5 mg/day group in the RA-001 study, and in the 2 mg and 3 mg groups in the 049 study were significantly different from placebo. Nausea was seen in the tacrolimus-treated groups with incidences of 10.5% to 18.8%. Only the incidence of nausea in the tacrolimus 3 mg/day group in the RA-001 study was significantly different from placebo, and the incidence did not increase with an increasing dose. Dyspepsia was observed in the tacrolimus-treated groups with incidences of 6.5% to 20.3%. In the three studies, the incidence of dyspepsia in patients taking 3 mg tacrolimus/day were 6.5% (049), 13.1% (051), and 20.3% (RA-001). The incidences of dyspepsia in the 2 mg tacrolimus/day group in the 049 study and in the tacrolimus 3 mg/day group in the RA-001 study were significantly different from placebo. No increase in incidence was seen with increasing dose in any study. Abdominal pain was reported in the tacrolimus-treated groups with incidences of 6.5% to 13.5%. There was no increase in incidence with increasing doses, and there was no significant difference from placebo in either placebo-controlled study.

The incidence of vasodilatation in the tacrolimus-treated groups varied from 1.6% to 6.3%. There was an increased incidence of vasodilatation with higher doses of tacrolimus. The incidences of vasodilatation in the tacrolimus 3 mg/day group in the 049 study and in the tacrolimus 5 mg/day group in the RA-001 study were significantly different from placebo.

Tremor occurred in the tacrolimus-treated groups with incidences of 3.1% to 21.9%. The incidence of tremor increased with an increasing dose, and in the tacrolimus 5 mg/day group in the RA-001 study, the incidence of tremor (21.9%) was more than twice the incidence of tremor seen with tacrolimus 3 mg/day in any of the three studies. The incidences of tremor in the tacrolimus 3 mg/day group in the 049 study and in the tacrolimus 5 mg/day group in the RA-001 study were significantly different from placebo. Paresthesia was seen in the tacrolimus-treated groups with incidences of 2.6% to 9.4%. The incidence of paresthesia increased with increasing dose, and in the tacrolimus 5 mg/day group in the RA-001 study, the incidence of paresthesia (9.4%) was more than twice the incidence of tremor seen with tacrolimus 3 mg/day in any of the three studies. The incidence of paresthesia in the tacrolimus 5 mg/day group in the RA-001 study was significantly different from placebo.

The incidence of urinary tract infections in the tacrolimus-treated groups varied from 3.2% to 12.5%. The incidence of urinary tract infection in the tacrolimus 3 mg/day group in the RA-001 study was significantly different from placebo; however, the incidence did not increase with increasing doses. The incidence of flu-like syndrome in the tacrolimus-treated groups ranged from 15.6% to 26.2%. There was no increase in incidence with larger doses, and no difference from placebo in any tacrolimus-treated group. The incidence of other infections was between 1.6% and 3.3% in the tacrolimus-treated groups. Increasing dose did not influence the incidence of infection, and there was no difference seen from placebo.

Comparisons of patient subpopulations were performed on data from patients in the 051 study, all of whom received tacrolimus 3 mg/day. In general, the incidence of adverse events was similar in patients < 65 years of age and ≥ 65 years of age, in patients with and without hypertension, in patients with and without hyperlipidemia, and in patients with and without diabetes.

A total of 213 patients (23.8%) were at least 65 years of age at study entry. The overall incidence of adverse events for patients ≥ 65 years of age (86.9%) was similar to that for patients < 65 years of age (88.7%). There were no notable differences between patients ≥ 65 years of age and those < 65 years of age for the incidence of any specific adverse events. The more common adverse events occurring in at least 10% of patients ≥ 65 years of age were flu syndrome (18.3%), diarrhea (16.9%), tremor (15.0%), nausea (13.6%), headache (12.7%), accidental injury (12.2%), hypertension (12.2%), dyspepsia (11.7%), and abdominal pain (11.3%). For patients < 65 years of age, the more common adverse events occurring in at least 10% of patients were flu syndrome (28.7%), diarrhea (20.8%), headache (15.8%), nausea (14.9%), abdominal pain (14.2%), and dyspepsia (13.5%). The incidences of tremor, accidental injury, and hypertension among these patients were 9.1%, 7.6%, and 7.3%, respectively.

Three hundred fifty patients (39.1%) had a history of hypertension at the time they entered the study. The overall incidence of adverse events for patients with a history of hypertension (91.1%) was similar to that for patients without a history of hypertension (86.4%). Among adverse events reported for at least 5% of patients with a history of hypertension, the incidences of bronchitis (6.9%) and peripheral edema (6.0%) were more than twice the incidences (3.1% and 2.4%, respectively) reported for patients without a history of hypertension. The more common adverse events occurring in at least 10% of patients with a history of hypertension were flu syndrome (26.9%), diarrhea (18.3%), nausea (15.7%), headache (13.4%), dyspepsia (13.1%), tremor (13.1%), abdominal pain (13.1%), and hypertension (11.7%). For patients without a history of hypertension, the more common adverse events occurring in at least 10% of patients were flu syndrome (25.8%), diarrhea (20.9%), headache (16.1%), nausea (13.9%), abdominal

pain (13.7%), and dyspepsia (13.0%). The incidences of tremor and hypertension among these patients were 8.8% and 6.4%, respectively.

A total of 271 patients (30.2%) had a history of hyperlipidemia at the time they entered the study. The overall incidence of adverse events for patients with a history of hyperlipidemia (92.6%) was similar to that for patients without a history of hyperlipidemia (86.4%). There were no notable differences between patients with a history of hyperlipidemia and those without a history of hyperlipidemia for the incidence of any specific adverse events. The more common adverse events occurring in at least 10% of patients with a history of hyperlipidemia were flu syndrome (26.2%), diarrhea (18.1%), nausea (15.9%), dyspepsia (14.0%), headache (12.9%), tremor (12.2%), abdominal pain (11.8%), and asthenia (10.3%). For patients without a history of hyperlipidemia, the more common adverse events occurring in at least 10% of patients were flu syndrome (26.2%), diarrhea (20.6%), headache (16.0%), abdominal pain (14.2%), nausea (14.1%), and dyspepsia (12.6%). The incidences of tremor and asthenia among these patients were 9.8% and 7.7%, respectively. Hypercholesterolemia and hyperlipemia were reported as adverse events in 3.0% and 2.2%, respectively, of patients with a history of hyperlipidemia, and in 1.4% and 1.0%, respectively, of patients without a history of hyperlipidemia.

Seventy-five patients (8.4%) had a history of diabetes at the time of study entry. The overall incidence of adverse events for patients with a history of diabetes (89.3%) was similar to that for patients without a history of diabetes (88.2%). Among adverse events reported for at least 5% of patients with a history of diabetes, the incidences of urinary tract infection (13.3%), hyperglycemia (9.3%), and infection (8.0%) were more than twice the incidences (5.2%, 1.8%, and 2.9%, respectively) reported for patients without a history of diabetes, and the incidence of headache (6.7%) in patients with a history of diabetes was less than half the incidence (15.8%) reported for patients without a history of diabetes. The more common adverse events occurring in at least 10% of patients with a history of diabetes were flu syndrome (26.7%), diarrhea (18.7%), tremor (17.3%), dyspepsia (16.0%), urinary tract infection (13.3%), nausea (13.3%), and hypertension (12.0%). The incidences of headache and abdominal pain among these patients were 6.7% and 8.0% respectively. For patients without a history of diabetes, the more common adverse events occurring in at least 10% of patients were flu syndrome (26.2%), diarrhea (20.0%), headache (15.8%), nausea (14.7%), abdominal pain (14.0%), and dyspepsia (12.8%). The incidences of tremor and urinary tract infection among these patients were 9.9% and 5.2%, respectively.

In some Rheumatoid Arthritis patients, an increase in serum creatinine levels has been detected. In the long-term safety study (98-0-051), in which patients were treated with Prograf for up to 18 months, 65.5% of all patients who had increases in serum creatinine ≥ 30% to < 40% above baseline had levels return to baseline during the study. For the remaining patients, creatinine levels either did not return to baseline or no documentation of follow-up levels was available. Patients with increases in serum creatinine levels ≥ 40% above baseline, had their levels return to baseline in 56.3% of all patients. These included patients who continued study drug therapy and patients who discontinued study drug therapy during the recovery period. For those patients whose creatinine levels returned to baseline, the median time to return to baseline creatinine levels was 40.5 days for patients with ≥ 30% to < 40% increase from baseline and 32.0 days for patients with ≥ 40% increases from baseline.

In Study FK506RA-001, patients who experienced an increase from baseline in serum creatinine levels of ≥ 30% and < 40%, 50% of the patients in the placebo group, 80% of patients in the 1 mg Prograf treatment group, 89% in the 3 mg Prograf treatment group and 78% of patients in the 5 mg Prograf treatment group experienced a return to baseline serum creatinine levels within 56 days for

placebo-treated patients, 33 days for patients treated with 1 mg Prograf, 29 days for those treated with 3 mg and 57 days for those treated with 5 mg.

In those patients experiencing a serum creatinine increase of ≥ 40% above baseline, 50% of placebo-treated patients, 20% of the 1 mg treated patients, 75% of the patients treated with 3 mg Prograf and 31% of patients treated with 5 mg Prograf experienced a subsequent return to baseline creatinine levels. The duration of time for serum creatinine levels to return to baseline for this patient population occurred sooner than those patients experiencing a serum creatinine increase of ≥ 30% and < 40%. Patients treated with placebo demonstrated a return to baseline of serum creatinine levels within 28 days, an average of 6 days for patients treated with 1 mg, 20 days for those treated with 3 mg and 38 days for those treated with 5 mg. There were however, eight of nine patients with elevated creatinine levels (> 40%) who discontinued the study. These patients had creatinine values return to below a 40% increase from baseline and within normal limits (0.7 - 1.4 mg/dL) post discontinuation, with one patient lost to follow-up.

In study 98-0-049, of those patients who experienced an increase from baseline in creatinine of ≥ 30% to < 40%, 63.6% of these patients in the placebo treatment group, 50.0% of patients in the 2 mg Prograf treatment group, and 77.8% of patients in the 3 mg Prograf treatment group, experienced a documented subsequent return to baseline creatinine values, within 36 days for placebo-treated patients, 43 days for 2 mg treated patients and 41 days for 3 mg patients treated with Prograf. For those patients with a ≥ 40% increase from baseline, 33.3% of patients in the placebo treatment group, 53.3% of patients in the 2 mg Prograf treatment group, and 45.5% of patients in the 3 mg Prograf treatment group experienced a documented subsequent return to baseline creatinine values. Serum creatinine levels in this patient population returned to baseline levels sooner than patients who experienced an increase from baseline of ≥ 30% to < 40%. Patients with a serum creatinine increase > 40% demonstrated a return to baseline at 20 days for placebo-treated patients, 33 days for patients treated with 2 mg and 38 days for those patients treated with 3 mg Prograf per day. The remaining patients either had creatinine levels that did not return to baseline during the follow-up period or were not monitored for return to baseline values.

For 88.5% (139/157) of placebo-treated patients, 87.0% (134/154) of patients treated with 2mg/day Prograf and 86.3% (132/153) of patients treated with 3 mg/day Prograf, creatinine levels were within the normal range at baseline, and remained within the normal range throughout the study. In total, four patients – all treated with 3 mg Prograf – discontinued treatment as a result of a reported adverse event of increased serum creatinine.

Table 9: Number of Patients with at Least a 30% Baseline Increase in Serum Creatinine that Returned to Baseline

Evaluated Study Groups	Increase in Serum Creatinine Levels Above Baseline	
	≥ 30% to < 40%††	**≥ 40%††**
Study 98-0-051		
Combined *De Novo*† (n=685)	46/78 (59.0%)	90/177 (50.8%)
2 mg‡ (n=103)	8/11 (72.7%)	20/37 (54.1%)
3 mg* (n=108)	20/24 (83.3%)	37/47 (78.7%)

Evaluated Study Groups	Increase in Serum Creatinine Levels Above Baseline	
	≥ 30% to < 40%††	**≥ 40%††**
Total (n=896)	74/113 (65.5%)	147/261 (56.3%)
Study FK506RA-001		
Placebo (n=71)	1/2 (50%)	2/4 (50%)
1 mg (n=69)	4/5 (80%)	1/5 (20%)
3 mg (n=64)	8/9 (88.9%)	9/12 (75%)
5 mg (n=64)	7/9 (77.8%)	4/13 (30.8%)
Study 98-0-049		
Placebo (n=157)	7/11 (63.6%)	5/15 (33.3%)
2 mg (n=154)	4/8 (50%)	16/30 (53.3%)
3 mg (n=153)	7/9 (77.8%)	20/44 (45.5%)

Patient base: Full analysis set; all patients who received at least one dose of the study drug in study 98-0-051.
†All *de novo* patients for study 98-0-051, all patients from study FK506RA-001, and all placebo rollover patients from study 98-0-049.
‡All 2 mg tacrolimus rollover patients from study 98-0-049.
††Percent increase from baseline during treatment. A patient could have been represented in both percentage increase groups if their creatinine increased, returned to baseline levels, and subsequently increased into the other percentage increase group.
*All 3 mg tacrolimus rollover patients from study 98-0-049.

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse events were reported in either liver, kidney, and/or heart transplant recipients who were treated with tacrolimus in clinical trials.

Body as a Whole: abdomen enlarged, abscess, accidental injury, allergic reaction, back pain, cellulitis, chills, fall, feeling abnormal, flu syndrome, generalized edema, hernia, mobility decreased, peritonitis, photosensitivity reaction, sepsis, temperature intolerance, ulcer, pain;

Cardiovascular: abnormal ECG, angina pectoris, arrhythmia, atrial fibrillation, atrial flutter, bradycardia, cardiac fibrillation, cardiopulmonary failure, cardiovascular disorder, chest pain, congestive heart failure, deep thrombophlebitis, echocardiogram abnormal, electrocardiogram QRS complex abnormal, electrocardiogram ST segment abnormal, heart rate decreased, heart failure, hemorrhage, hypotension, postural hypotension, peripheral vascular disorder, phlebitis, syncope, tachycardia, thrombosis, vasodilatation;

Endocrine System: (see 7 Warnings and Precautions) diabetes mellitus, Cushing's Syndrome;

Gastrointestinal: anorexia, cholangitis, cholestatic jaundice, dyspepsia, duodenitis, dysphagia, esophagitis, flatulence, gastritis, gastrointestinal hemorrhage, gastroesophagitis, GGT increase, GI disorder, GI perforation, granulomatous liver disease, hepatitis, ileus, increased appetite, jaundice, liver damage, liver function test abnormal, esophagitis ulcerative, oral moniliasis, pancreatic pseudocyst, rectal disorder, stomatitis;

Hemic/Lymphatic: coagulation disorder, ecchymosis, febrile neutropenia, hematocrit increased, hemoglobin abnormal, hypochromic anemia, leukopenia, prothrombin decreased, leukocytosis, polycythemia, serum iron decreased, thrombocytopenia;

Metabolic/Nutritional: acidosis, alkaline phosphatase increased, alkalosis, AST (SGOT) increased, ALT (SGPT) increased, bicarbonate decreased, bilirubinemia, BUN increased, dehydration, edema, GGT increased, gout, healing abnormal, hypercalcemia, hypercholesterolemia, hyperlipemia, hypertriglyceridemia, hyperphosphatemia, hyperuricemia, hypocalcemia, hypervolemia, hypoglycemia, hypokalemia, hypophosphatemia, hyponatremia, hypoproteinemia, lactic dehydrogenase increase, weight gain;

Musculoskeletal: arthralgia, muscle spasms, generalized spasm, joint disorder, leg cramps, myalgia, myasthenia, osteoporosis, pain in extremity including Calcineurin-Inhibitor Induced Pain Syndrome (CIPS);

Nervous System: (see 7 Warnings and Precautions) abnormal dreams, agitation, amnesia, anxiety, confusion, crying, convulsion, depression, dizziness, elevated mood, emotional lability, encephalopathy, hemorrhagic stroke, hallucinations, hypertonia, incoordination, monoparesis, myoclonus, nerve compression, nervousness, neuralgia, neuropathy, paralysis flaccid, paresthesia, psychomotor skills impaired, psychosis, quadriparesis, somnolence, thinking abnormal, vertigo, writing impaired;

Respiratory System: asthma, bronchitis, cough increased, emphysema, hiccups, lung disorder, lung function decreased, pharyngitis, pneumothorax, pneumonia, pulmonary edema, respiratory disorder, rhinitis, sinusitis, voice alteration;

Skin & Appendages: acne, alopecia, exfoliative dermatitis, fungal dermatitis, herpes simplex, herpes zoster, hirsutism, pruritus, rash, neoplasm skin benign, skin discolouration, skin disorder, skin ulcer, sweating;

Special Senses: abnormal vision, amblyopia, ear pain, otitis media, tinnitus;

Urogenital: (see 7 Warnings and Precautions) acute kidney failure, albuminuria, BK nephropathy, bladder spasms, cystitis, dysuria, hematuria, hydronephrosis, kidney failure, kidney tubular necrosis, nocturia, oliguria, pyuria, toxic nephropathy, urge incontinence, urinary frequency, urinary tract infection, urinary incontinence, urinary retention, vaginitis;

The following nervous system adverse events were also reported at a frequency (< 3%): acute brain syndrome (0.2%), coma (2.1%), delirium (1.2%), dysarthria (0.4%), dystonia (0.4%), encephalopathy (2.5%), flaccid paralysis (0.4%), hemiplegia (0.8%), nystagmus (0.8%), paralysis (0.4%) and stupor (0.2%).

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

Refer to 7 Warnings and Precautions (Hepatic, Renal, and Monitoring and Laboratory Tests).

8.5 Post-Market Adverse Reactions

The following adverse events have been reported from worldwide marketing experience with tacrolimus. Because these events are reported voluntarily from a population of uncertain size, are associated with concomitant diseases and multiple drug therapies and surgical procedures, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these events in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) frequency of the reporting, or (3) strength of causal connection to the drug:

Cardiac Disorders: cardiac arrhythmia, cardiac arrest, congestive cardiomyopathy, electrocardiogram T wave abnormal, flushing, myocardial infarction, myocardial ischemia, QT prolongation with or without *Torsades de pointes*, venous thrombosis deep limb, ventricular extrasystoles, ventricular fibrillation;

Ear and Labyrinth Disorders: Hearing loss including deafness;

Endocrine Disorders: Hypothyroidism;

Gastrointestinal Disorders: colitis, enterocolitis, gastrointestinal obstruction, gastrooesophageal reflux disease, hepatocellular injury, impaired gastric emptying, liver fatty, Mikulicz's syndrome, mouth ulceration, pancreatitis hemorrhagic, pancreatitis necrotizing, stomach ulcer;

Hepatobiliary Disorders: bile duct stenosis, cholestasis of pregnancy, hepatic cytolysis, hepatic necrosis, hepatotoxicity, venoocclusive liver disease;

Blood and Lymphatic System Disorders: agranulocytosis, disseminated intravascular coagulation, eosinophilia, febrile neutropenia, hemolytic anemia, hemolytic-uremic syndrome, neutropenia, pancytopenia, pure red cell aplasia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, thrombotic microangiopathy;

Infections and Infestations: eczema infected, Escherichia;

Investigations: blood urea increased, drug level below therapeutic, drug level fluctuating, immunosuppressant drug level decreased, platelet count increased, transaminases increased, weight decreased;

Injury, Poisoning and Procedural Complications**:** drug dispensing error, drug prescribing error, maternal exposure during pregnancy, medication error, primary graft dysfunction;

Metabolism and Nutritional Disorder: amylase increased, hyperammonaemia, ketoacidosis;

Musculoskeletal and Connective Tissue Disorders: immunoglobulin G4 related sclerosing disease, muscular weakness;

General Disorders and Administration Site Conditions: disease recurrence, drug effect delayed, drug effect increased, drug ineffective, drug interaction, drug intolerance, fatigue, feeling of body temperature change, feeling jittery, multi-organ failure, thirst;

Neoplasms benign, malignant and unspecified (including cysts and polyps): breast cancer, haematological malignancy, hepatic neoplasm malignant, Kaposi's sarcoma, lung neoplasm malignant, pharyngeal cancer stage unspecified;

Nervous system Disorders: aphasia, balance disorder, brachial plexopathy, carpal tunnel syndrome, cerebral infarction, cerebrovascular accident, hemiparesis, incoherent, leukoencephalopathy, mutism, neurotoxicity, paraesthesia, peripheral nerve lesion, posterior reversible encephalopathy syndrome (PRES), progressive multifocal leukoencephalopathy (PML), quadriplegia, speech disorder, polyneuropathy, neuropathy peripheral, peripheral sensory neuropathy, mononeuropathy multiplex;

Psychiatric Disorders: intentional drug misuse, mental disorder;

Respiratory, Thoracic and Mediastinal Disorders: acute respiratory distress syndrome, interstitial lung disease (predominantly in rheumatoid arthritis), lung infiltration, respiratory distress, respiratory failure;

Skin and Subcutaneous Tissue Disorders: dermatosis, Stevens-Johnson syndrome, toxic epidermal necrolysis;

Eye Disorders: blindness, blindness cortical, diplopia, eyelid edema, optic neuropathy, photophobia;

Renal and Urinary Disorders: acute renal failure, cystitis hemorrhagic, glycosuria, micturition disorder, renal failure chronic;

Vascular Disorders: flushing, hot flush;

There have been rare spontaneous reports of myocardial hypertrophy associated with clinically manifested ventricular dysfunction in patients receiving Prograf therapy (see 7 Warnings and Precautions).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P450 system (CYP3A). Tacrolimus dose reductions and prolongation of dosing interval may be required in order to maintain similar tacrolimus exposure when co-administered with strong CYP3A4 inhibitor. Drugs known to induce these enzyme systems may result in an increased metabolism of tacrolimus or decreased bioavailability as indicated by decreased whole blood or plasma concentrations, thereby potentially requiring dose increases in order to maintain similar tacrolimus exposure when co-administered with strong CYP3A4 inducers (Refer to Table 10). Close monitoring of tacrolimus blood levels, renal function and other side effects (including ECG monitoring for QT prolongation) is strongly recommended when administered with strong CYP3A4 inhibitors (see **4 DOSAGE AND**

ADMINISTRATION, **4.2 Recommended Dose and Dose Adjustment**, and **7 WARNINGS AND PRECAUTIONS**, **General**).

9.3 Drug-Behaviour Interactions

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

9.4 Drug-Drug Interactions

Drug Interactions Potentially Affecting Renal Function

Due to the potential for additive or synergistic impairment of renal function, care should be taken when administering Prograf with drugs that may be associated with renal dysfunction. These include, and are not limited to, aminoglycosides, amphotericin B, ganciclovir, acyclovir and cisplatin. NSAIDs may interact with Prograf causing deteriorations in blood pressure (BP) control and serum creatinine levels. The half-life of cyclosporine has been shown to increase when tacrolimus is given simultaneously. Initial clinical experience with Prograf and cyclosporine resulted in additive/synergistic nephrotoxicity when both agents were co-administered. For these reasons, the combined administration of cyclosporine and tacrolimus is not recommended and care should be taken when administering tacrolimus to patients who have previously received cyclosporine. Patients switched from cyclosporine to Prograf should receive the first Prograf dose no sooner than 24 hours after the last cyclosporine dose. Dosing may be further delayed in the presence of elevated cyclosporine levels.

Drug Interactions Potentially Affecting Tacrolimus Blood Concentrations

Since tacrolimus is metabolized mainly by the cytochrome P450 3A enzyme systems, substances known to inhibit these enzymes may decrease the metabolism or increase bioavailability of tacrolimus with resultant increases in whole blood or plasma levels. Drugs known to induce these enzyme systems may result in an increased metabolism of tacrolimus or decreased bioavailability as indicated by decreased whole blood or plasma levels.

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

Monitoring of blood levels and appropriate dosage adjustments in transplant patients are essential when such drugs (Table 10) are used concomitantly with Prograf.

Table 10: Established or Potential Drug-Drug Interactions

Concomitant Drug Class: Drug Name	Reference	Effect on Concentration of Prograf	Comment
Antacid: magnesium-aluminium-hydroxide	CT	↑ Prograf	In a single-dose crossover study in healthy volunteers, co-administration of tacrolimus and magnesium-aluminium-hydroxide resulted in a 21% increase in the mean tacrolimus AUC and a 10% decrease in the mean tacrolimus C_{max} relative to tacrolimus administration alone.
Anti-Arrhythmic Agent: amiodarone[†]	T	↑ Prograf	The concomitant use of Prograf with amiodarone may lead to increased levels of tacrolimus and/or a potential pharmacodynamic interaction based on displacement of amiodarone from its plasma protein binding site. [†]When co-administered with amiodarone dose, adjustment may be required in most patients.
Azole antifungals: ketoconazole[†]	CT	↑ Prograf	In a study of 24 healthy male volunteers, co-administration of two 2 mg Prograf doses with ketoconazole (400 mg/day) increased the mean AUC_{inf} and C_{max} of tacrolimus by 723% and 250%, respectively. In a study of 6 normal volunteers, a significant increase in tacrolimus oral bioavailability (14 ± 5% vs 30 ± 8%) was observed with concomitant administration of ketoconazole (200 mg), a strong CYP3A4 and P-glycoprotein inhibitor. The apparent clearance of oral tacrolimus during ketoconazole administration was significantly decreased compared to tacrolimus alone (0.430 + 0.129 L/hr/kg vs. 0.148 + 0.043 L/hr/kg). Overall, clearance of IV tacrolimus was not significantly changed by ketoconazole co-administration, although it was highly variable between patients. [†]When co-administered with ketoconazole, a dose adjustment of tacrolimus is required in most patients.

Concomitant Drug Class: Drug Name	Reference	Effect on Concentration of Prograf	Comment
Azole antifungals, cont'd: clotrimazole fluconazole† itraconazole† voriconazole†	T	↑ Prograf	The concomitant use of Prograf with azole antifungals that are strong or moderate CYP3A4 and P-glycoprotein inhibitors (e.g., itraconazole, fluconazole, voriconazole) might lead to an increased Prograf concentration. †When co-administered with fluconazole, itraconazole and voriconazole, a dose adjustment of tacrolimus is required in most patients.
Calcium channel blockers: diltiazem nicardipine nifedipine verapamil	T	↑ Prograf	Co-administration of substrates and/or inhibitors of CYP3A4 and P-glycoprotein with Prograf might increase blood concentrations of tacrolimus.
GI Prokinetic Agents: cisapride* metoclopramide	T	↑ Prograf	Co-administration of Prograf with substrates of CYP3A4 might increase blood concentrations of tacrolimus.
Macrolide antibiotics: erythromycin† clarithromycin‡ troleandomycin	T	↑ Prograf	Co-administration of Prograf with substrates and/or inhibitors of CYP3A4 and P-glycoprotein might increase blood concentrations of tacrolimus. ‡ Cases have been reported in which a sharp rise in tacrolimus levels occurred very rapidly, as early as within 1-3 days after co-administration with clarithromycin despite an immediate reduction of tacrolimus dose. Early, within the first few days of co-administration, and frequent continued monitoring of tacrolimus whole blood trough levels within 1-3 days is strongly recommended when co-administered with strong CYP3A4 inhibitors. †When co-administered with erythromycin, a dose adjustment of tacrolimus is required in most patients.

Concomitant Drug Class: Drug Name	Reference	Effect on Concentration of Prograf	Comment
Proton pump inhibitor: lansoprazole omeprazole	T	↑ Prograf	Lansoprazole and omeprazole (CYP2C19 and CYP3A4 substrate, inhibitor) may potentially inhibit CYP3A4-mediated metabolism of tacrolimus and thereby substantially increase tacrolimus whole blood concentrations, especially in transplant patients who are intermediate or poor CYP2C19 metabolizers, as compared to those patients who are efficient CYP2C19 metabolizers.
Other drugs: bromocriptine cimetidine chloramphenicol cyclosporine danazol ethinyl estradiol methylprednisolone nefazodone	T	↑ Prograf	Co-administration of Prograf with substrates and/or inhibitors of CYP3A4 and P-glycoprotein might increase blood concentrations of tacrolimus.
Protease Inhibitors: boceprevir nelfinavir ritonavir saquinavir telaprevir	CT	↑ Prograf	Interaction studies with drugs used in HIV/HCV therapy have not been conducted. However, care should be exercised when drugs that are metabolized by CYP3A4 (for example, but not limited to boceprevir, nelfinavir, ritonavir, saquinavir, telaprevir) are administered concomitantly with tacrolimus. In a single dose study in 9 healthy volunteers, co-administration of tacrolimus (0.5 mg single dose) with telaprevir (750 mg TID for 13 days) increased tacrolimus dose-normalized C_{max} by 9.3-fold and AUC by 70-fold. In a single dose study in 12 subjects, co-administration of tacrolimus (0.5 mg single dose) with boceprevir (800 mg three times daily for 11 days) increased tacrolimus C_{max} by 9.9-fold and AUC by 17-fold compared to tacrolimus alone. Based on a clinical study of 5 liver transplant recipients, co-administration of tacrolimus (administration as Prograf [immediate-release formulation]) with nelfinavir increased blood concentrations of tacrolimus significantly and, as a result, a reduction in the tacrolimus dose by an average of 16-fold was needed to maintain

Concomitant Drug Class: Drug Name	Reference	Effect on Concentration of Prograf	Comment
			mean trough tacrolimus blood concentrations of 9.7 ng/mL. Thus, frequent monitoring of tacrolimus blood concentrations and appropriate dosage adjustments are essential when used concomitantly with protease inhibitors.
Cytomegalovirus (CMV) antivirals: letermovir	CT	↑ Prograf	Co-administration of Prograf with letermovir may result in clinically relevant increases in the plasma concentrations of Prograf. Monitor blood concentrations and if needed make appropriate dosage adjustments when letermovir is used concomitantly with tacrolimus.
Anticonvulsants: carbamazepine phenobarbital phenytoin[†]	T	↓ Prograf	Co-administration of Prograf with inducers of CYP3A4 and P-glycoprotein might decrease blood concentrations of tacrolimus. [†]When co-administered with phenytoin, a dose adjustment of tacrolimus is required in most patients.
Anti-Infectives: rifampicin[†]	CT	↓ Prograf	In a study of 28 healthy male volunteers, co-administration of two 5 mg Prograf doses with rifampicin (600 mg/day) decreased mean AUC_{inf} and C_{max} of tacrolimus by 62% and 24%, respectively. In a study of 6 normal volunteers, a significant decrease in tacrolimus oral bioavailability (14 ± 6% vs 7 ± 3%) was observed with concomitant administration of rifampicin (600 mg), a strong CYP3A4 and P-glycoprotein inducer. In addition, there was a significant increase in tacrolimus clearance (0.036 ± 0.008 L/hr/kg vs. 0.053 ± 0.010 L/hr/kg) with concomitant rifampicin administration. In a study of 9 normal volunteers, concomitantly administered 10 mL doses of aluminum hydroxide or milk of magnesia antacids did not affect the rate and extent of absorption of orally administered tacrolimus, as indicated by C_{max}, T_{max} and AUC_{0-t}.

Concomitant Drug Class: Drug Name	Reference	Effect on Concentration of Prograf	Comment
			[†]When co-administered with rifampicin, a dose adjustment of tacrolimus is required in most patients.
Anti-infectives, cont'd: rifabutin	T	↓ Prograf	Co-administration of Prograf with inducers of CYP3A4 and P-glycoprotein might decrease blood concentrations of tacrolimus.
Anti-infectives, cont'd: caspofungin	T	↓ Prograf	Caspofungin reduced the blood AUC_{0-12} of tacrolimus by approximately 20%, peak blood concentration (C_{max}) by 16%, and 12-hour blood concentration (C_{12hr}) by 26% in healthy adult subjects when tacrolimus (2 doses of 0.1 mg/kg 12 hours apart) was administered on the 10^{th} day of CANCIDAS 70 mg daily, as compared to results from a control period in which tacrolimus was administered alone.
Calcineurin inhibitor: sirolimus	CT	↓ Prograf	Following 14 days co-administration of tacrolimus and sirolimus (2 mg/day or 5 mg/day; a substrate for both CYP3A4 and P-glycoprotein) in stable renal transplant patients, tacrolimus AUC and C_{min} decreased approximately 30% relative to tacrolimus alone. Mean tacrolimus AUC_{0-12} and C_{min} following co-administration of 1 mg/day of sirolimus decreased approximately 3% and 11%, respectively. The safety and efficacy of the use of tacrolimus with sirolimus has not been established.
Direct-acting antiviral (DAA): Sofosbuvir	T	↓ or ↑ Tacrolimus	The pharmacokinetics of tacrolimus may be impacted by changes in liver function during DAA therapy, related to clearance of HCV virus. Impact on tacrolimus concentration may vary depending on the combination of DAA drugs used. A close monitoring and potential dose adjustment of tacrolimus is warranted to ensure continued efficacy and safety.
Herbal preparation: St. John's wort	T	↓ Prograf	St. John's wort (*Hypericum perforatum*) induces CYP3A4 and P-glycoprotein. Since tacrolimus is a substrate for CYP3A4, there is the potential that the use of St. John's wort in patients receiving Prograf could result in reduced tacrolimus levels.

Concomitant Drug Class: Drug Name	Reference	Effect on Concentration of Prograf	Comment
Schisandra sphenanthera extracts	T	↑ Prograf	Co-administration of Prograf with substrates and/or inhibitors of CYP3A4 and P-glycoprotein might increase blood concentrations of tacrolimus.
Cannabidiol	T	↑ Prograf	Co-administration of Prograf with cannabidiol might increase blood concentrations of tacrolimus. Monitor tacrolimus whole blood trough concentrations and adjust the Prograf dose if needed.

*No longer marketed in Canada CT = Clinical Trial T = Theoretical

Lack of Drug Interaction with Prograf

At a given mycophenolate mofetil (MMF) dose, mycophenolic acid (MPA) exposure is higher with Prograf co-administration than with cyclosporine co-administration due to the inhibitory action of cyclosporine on biliary excretion of MPA-glucuronide by MRP-2 and the resulting reduction in enterohepatic recirculation of MPA. As a result, exposure to MPA when mycophenolate mofetil is given in combination with cyclosporine is approximately 30-40% lower than that observed when given alone or with tacrolimus. No effect on enterohepatic MPA-glucuronide recirculation is exerted by tacrolimus; thus, clinicians should be aware that there is a potential for increased MPA exposure after crossover from cyclosporine to tacrolimus in patients concomitantly receiving MMF or mycophenolate sodium (MPS). Conversely, there is a potential for decreased MPA exposure after crossover from tacrolimus to cyclosporine in patients concomitantly receiving MMF or MPS. Therapeutic drug monitoring of MPA is recommended.

Prograf and Vaccinations

Immunosuppressants may affect vaccination. Therefore, during treatment with Prograf, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to: measles, mumps, rubella, oral polio, BCG, yellow fever and TY 21a typhoid.

9.5 Drug-Food Interactions

Grapefruit juice inhibits P450 3A-mediated metabolism and should be avoided.

9.6 Drug-Herb Interactions

St. John's wort (*Hypericum perforatum*) induces CYP3A4 and P-glycoprotein. Since tacrolimus is a substrate for CYP3A4, there is the potential that the use of St. John's wort in patients receiving Prograf could result in reduced tacrolimus levels.

Schisandra sphenanthera extracts inhibit CYP3A4 and P-glycoprotein and may increase blood concentrations of tacrolimus.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Tacrolimus, the active ingredient in Prograf, is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis.*

Tacrolimus prolongs the survival of the host and transplanted graft in animal transplant models of liver, kidney, heart, bone marrow, small bowel and pancreas, lung and trachea, skin, cornea and limb.

Tacrolimus has been demonstrated to suppress some humoral immunity and, to a greater extent, cell-mediated reactions such as allograft rejection, delayed type hypersensitivity, Freund's adjuvant arthritis, experimental allergic encephalomyelitis and graft-versus-host disease in several animal species.

Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. The minimum inhibitory tissue culture level of tacrolimus that prevents antigen stimulation of T-lymphocytes is 0.1 nM – 0.3 nM. Experimental evidence suggests that tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin and calcineurin is then formed and the phosphatase activity of calcineurin inhibited. This effect may prevent the generation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate the gene transcription for the formation of lymphokines (interleukin-2, gamma interferon). The net result is the inhibition of T-lymphocyte activation (i.e., immunosuppression).

10.2 Pharmacodynamics

See 10 CLINICAL PHARMACOLOGY, 10.1 Mechanism of Action

10.3 Pharmacokinetics

Tacrolimus activity is primarily due to the parent drug. After oral administration, absorption of tacrolimus into the systemic circulation from the gastrointestinal tract is incomplete and can be variable. Elimination of tacrolimus is via hepatic metabolism with a mean terminal elimination half-life of 18.8 hours in kidney transplant patients, 11.7 hours in liver transplant patients, 23.6 hours in heart transplant patients receiving a single intravenous dose of Prograf and 34.2 hours in healthy volunteers following intravenous administration. In rheumatoid arthritis patients, the administration of a single intravenous and oral dose of Prograf produced a mean terminal elimination half-life of 34.9 and 35.2 hrs respectively.

In transplant patients, the intersubject variability in tacrolimus pharmacokinetics has resulted in the need for the dosing regimen to be individualized. Dosing individualization can be achieved by therapeutic drug monitoring of tacrolimus blood concentrations and evaluation of clinical status (see 4 Dosage and Administration). Pharmacokinetic data indicate that whole blood concentrations rather than plasma concentrations serve as the more appropriate sampling compartment to describe tacrolimus pharmacokinetics.

Absorption

Absorption of tacrolimus from the gastrointestinal tract after oral administration is incomplete and can be variable. Mean (±S.D.) pharmacokinetic parameters of tacrolimus in whole blood after oral administration to volunteers in two studies are presented in the following table.

Table 11: Mean (±S.D.) Pharmacokinetic Parameters of Tacrolimus in Whole Blood after Oral Administration

Parameter	Bioequivalence Study		Pharmacokinetic Study
Age	19-53 yrs		19-50 yrs
Number	62	59	16
Dose	5 x 1 mg single dose	1 x 5 mg single dose	5 x 1 mg single dose
Absolute Bioavailability (%)	---	---	17.8 ± 5.0
C_{max} (ng/mL)	25.2 ± 9.7	26.5 ± 10.8	29.7 ± 7.2
T_{max} (hr)	1.2 ± 0.4	1.4 ± 0.6	1.6 ± 0.7
AUC_{0-t} (ng•hr/mL)	196 ± 93†	209 ± 97†	243 ± 73††
†AUC (0-72) †† AUC (0-120)			

The 1 mg and 5 mg dose strengths of tacrolimus capsules are bioequivalent as indicated in the table above.

Bioequivalence Study 0.5 mg Capsule

An open-label, four period, four sequence, randomized crossover study was done to determine the bioequivalence of the 0.5 mg Prograf capsule to the 1 mg Prograf capsule. In two periods of the study, a single dose of 6 x 0.5 mg capsules were consumed by healthy volunteers. In the two other periods of the study, 3 x 1 mg capsules were consumed in a single dose. The pharmaceutical parameters derived from this bioequivalence study are outlined in the table below.

Table 12: Bioequivalence of the 0.5 mg Prograf (tacrolimus) Capsule to the 1 mg Prograf (tacrolimus) Capsule in Healthy Volunteers: From Measured and Log Transformed Data, Uncorrected for Potency, Geometric Mean, Arithmetic Mean (CV %)

Parameter	Test (6 X 0.5 mg capsules)		Reference (3 x 1 mg capsules)		% Ratio of Geometric Means
	A1	A2	B1	B2	
AUC_T (ng•h/mL)	140 ± 52.4	122 ± 40.1	133 ± 53.9	125 ± 46.5	102.6
AUC_I (ng•h/mL)	168 ± 66.3	148 ± 50.4	160 ± 70.9	152 ± 62.1	102.9

Parameter	Test (6 X 0.5 mg capsules)		Reference (3 x 1 mg capsules)		% Ratio of Geometric Means
	A1	A2	B1	B2	
AUC_T (ng•h/mL)	140 ± 52.4	122 ± 40.1	133 ± 53.9	125 ± 46.5	102.6
C_{max} (ng/mL)	20.3 ± 6.94	18.7 ± 6.55	19.0 ± 6.91	18.7 ± 6.43	103.4
T_{max}*(h)	1.4 ± 0.61	1.3 ± 0.44	1.4 ± 0.51	1.5 ± 0.50	92.5
$T_{1/2}$*(h)	34.4 ± 9.12	35.4 ± 11.1	32.6 ± 7.86	35.8 ± 9.10	102.2

*Expressed as arithmetic mean (CV %) only. A1 and A2 refer to data from two different study periods for test drug. B1 and B2 refer to data from two different study periods for reference drug.

Table 13: Bioequivalence of the 0.5 mg Prograf (tacrolimus) Capsule to the 1 mg Prograf (tacrolimus) Capsule in Healthy Volunteers: Corrected for Potency, Geometric Mean

Parameter	Test	Reference	% Ratio of Geometric Means
AUC_T (ng•h/mL)	121.1[a]	116.3[a]	104.2
AUC_I (ng•h/mL)	145.5[a]	139.2[a]	104.5
C_{max} (ng/mL)	18.1[a]	17.3[a]	105.0

Potency corrections made using potencies of 100.8% for the 0.5 mg capsule and 102.3% for the 1.0 mg capsule.
[a]Values calculated using LS Means of log-transformed data.

In 26 kidney transplant patients, peak concentrations (C_{max}) were achieved at approximately 1-3 hours. The absorption half-life of tacrolimus in 17 liver transplant patients averaged 0.6 hours (S.D. 1.0 hour) with peak concentrations (C_{max}) in blood and plasma being achieved at approximately 1.5-3.5 hours. In rheumatoid arthritis patients, peak concentrations (C_{max}) were achieved within 1.3 hours. Mean (± S.D.) pharmacokinetic parameters of tacrolimus in whole blood after initial dose in adult kidney and liver transplant patients and in rheumatoid arthritis patients are presented in the table below:

Table 14: Mean (±S.D.) Pharmacokinetic Parameters of Tacrolimus in Whole Blood after Initial Dose in Adult Transplant and Rheumatoid Arthritis Patients

Population	N		Pharmacokinetic Parameters		
		Route (Dose)	C_{max} (ng/mL)	T_{max} (hr)	AUC (ng·hr/mL)
Kidney Transplant Patients	26	IV (0.02 mg/kg/12hr)	NA	NA	294§ ± 262
		PO (0.2 mg/kg/day)	19.2 ± 10.3	3.0	203§ ± 42
		PO (0.3 mg/kg/day)	24.2 ± 15.8	1.5	288§ ± 93
Liver Transplant Patients	17	IV (0.05 mg/kg/12hr)	NA	NA	NA
		PO (0.3 mg/kg/day)	68.5 ± 30.0	2.3 ± 1.5	519§ ± 179
Heart Transplant Patients	11	IV (0.01 mg/kg/day as a continuous infusion)	NA	NA	954¶±334
	11	PO (0.075 mg/kg/day)	24.9 ± 7.72	1.0	175†† ± 49.8
Rheumatoid Arthritis Patients	12	PO (3 X 1 mg single dose)	19.64 ± 6.32	1.3 ± 0.58	192.88 ± 86.42

PO: oral; IV: intravenous; NA: not available; §$AUC_{0\text{-}inf}$; ¶$AUC_{0\text{-}t}$;

††$AUC_{0\text{-}12}$

The absolute bioavailability of tacrolimus is approximately 17% in kidney transplant patients, 22% in adult liver transplant patients, 34% in pediatric liver transplant patients, and approximately 25% in rheumatoid arthritis patients. In healthy volunteers, the absolute bioavailability of tacrolimus was found to be approximately 18% (previous table).

Food Effects: The rate and extent of tacrolimus absorption is greatest under fasted conditions. The presence and composition of food decreased both the rate and extent of tacrolimus absorption when administered to healthy volunteers:

Table 15: Food Effects on the Rate and Extent of Tacrolimus Absorption in Healthy Volunteers

Parameter	Fasted (n=15)	High Carbohydrate* (n=15)	High Fat** (n=15)
C_{max} (ng/mL)	25.6 ± 11.4	9.0 ± 3.8	5.9 ± 2.3
T_{max} (hr)	1.4 ± 0.6	3.2 ± 1.1	6.5 ± 3.0
$AUC_{0\text{-}t}$ (ng•hr/mL)	233 ± 121†	168 ± 59†	147 ± 56†

* 668 kcal (4% fat; 85% carbohydrate) ** 848 kcal (46% fat, 39% carbohydrate) † AUC (0-96)

The effect was most pronounced with the high-fat meal: mean area under the curve (AUC_{0-96}) and C_{max} were decreased 37% and 77%, respectively; T_{max} was lengthened 5-fold. The high-carbohydrate meal decreased AUC_{0-96} and C_{max} by 28% and 65%, respectively.

The effect of food was also studied in 11 liver transplant patients. Prograf was administered in the fasted state or 15 minutes after a breakfast of known fat content (34% of 400 total calories). The results indicate that the presence of food reduces the absorption of tacrolimus in these patients (decrease in AUC and C_{max} and increase in T_{max}). The relative oral bioavailability (whole blood) was reduced by 27.0 (±18.2) % compared to administration in the fasting state.

In healthy volunteers, the time of the meal also affected tacrolimus bioavailability. Relative to the fasted state, there was little effect on tacrolimus bioavailability when administered one hour prior to a high-fat breakfast, whereas bioavailability (both extent and rate of absorption) was greatly reduced when the drug was administered immediately or 1.5 hours after the meal. When given immediately following the meal, C_{max} was reduced 71%, AUC_{0-96} was reduced by 39%, and T_{max} was delayed 1.6 hours relative to the fasting condition. When administered 1.5 hours following the meal, C_{max} was reduced 63%, AUC_{0-96} was reduced 39%, and T_{max} was delayed 1.4 hours relative to the fasted condition.

In fasted healthy volunteers given a single dose, the absorption of tacrolimus was proportional to dose; see table below.

Table 16: Absorption of Tacrolimus in Fasted Healthy Volunteers

Parameter	Dose		
	3 mg n = 18	**7 mg n = 18**	**10 mg n = 18**
C_{max} (ng/mL)	14.5 ± 5.8	31.2 ± 10.1	45.1 ±15.0
	14.5 ± 5.8*	13.4 ± 4.3*	13.5 ± 4.5*
T_{max} (hr)	1.4 ± 0.4	1.4 ± 0.5	1.3 ± 0.4
AUC_{0-96} (ng•hr/mL)	131 ± 77	303 ± 138	420 ± 166
	131 ± 77*	130 ± 59*	126 ± 50*

*Adjusted to 3 mg dose

Distribution

The apparent volume of distribution (based on whole blood concentrations) of tacrolimus is approximately 1.41, 1.91, 0.85 and 2.37 L/kg in kidney transplant patients, healthy volunteers, adult liver transplant patients and adult rheumatoid arthritis patients, respectively (refer to table below).

Table 17: Volume of Distribution and Clearance in Transplant and Rheumatoid Arthritis Patients

Parameter	Volunteers (n=8)	Kidney Transplant Patients (n=26)	Liver Transplant Patients (Adults, n=17)	Heart Transplant Patients (n=11)	Rheumatoid Arthritis Patients (Adults, n=12)
Mean IV Dose	0.025 mg/kg/4 hr	0.02 mg/kg/4 hr	0.05 mg/kg/12 hr	0.01 mg/kg/day as a continuous infusion	0.015 mg/kg/4 hr
V (L/kg)	1.91 ± 0.31	1.41 ± 0.66	0.85 ± 0.3	NA	2.37 ± 0.45
Cl (L/hr/kg)	0.040 ± 0.009	0.083 ± 0.050	0.053 ± 0.017	0.051 ± 0.015	0.049 ± 0.014

NA: not available

The plasma protein binding of tacrolimus is approximately 99% and is independent of concentration over a range of 5 - 50 ng/mL. Tacrolimus is bound to proteins, mainly albumin and alpha-1-acid glycoprotein, and has a high level of association with erythrocytes. The distribution of tacrolimus between whole blood and plasma depends on several factors, such as hematocrit, temperature at the time of plasma separation, drug concentration, and plasma protein concentration. In a U.S. study, the ratio of whole blood concentration to plasma concentration ranged from 12 to 67 (mean 35).

In 18 kidney transplant patients, tacrolimus trough concentrations from 3 to 30 ng/mL measured at 10-12 hours post dose (C_{min}), correlated well with the AUC_{0-12} (correlation coefficient 0.93). In 24 liver transplant patients over a concentration range of 10 to 60 ng/mL, the correlation coefficient was 0.94. In 25 heart transplant patients, the correlation coefficient was 0.89 after an oral dose of 0.075 or 0.15 mg/kg/day at steady-state.

Metabolism

Tacrolimus is extensively metabolized in the liver by the mixed-function oxidase systems, primarily the cytochrome P450-3A4 (CYP3A4) and the cytochrome P450-3A5 (CYP3A5) enzyme systems. A metabolic pathway leading to the formation of 8 possible metabolites has been proposed. Demethylation and hydroxylation were identified as the primary mechanisms of biotransformation *in vitro*. The major metabolite identified in incubations with human liver microsomes is 13-demethyl tacrolimus. In *in vitro* studies, a 31-demethyl metabolite has been reported to have the same activity as tacrolimus; the 13-demethyl, 15-demethyl and 15- and 31- double-demethylated metabolites were shown to retain an activity of less than 10%.

Elimination

The clearance of tacrolimus is 0.040, 0.083, 0.042 and 0.049 L/hr/kg in healthy volunteers, adult kidney transplant patients, adult liver transplant patients, and adult rheumatoid arthritis patients, respectively. In man, less than 1% of the dose administered is excreted unchanged in urine.

Human Studies

In vitro, several drugs have been shown to inhibit the metabolism of tacrolimus by human liver microsomes. Conversely, tacrolimus has been shown to inhibit the metabolism of other drugs (e.g.,

CyA). *In vivo*, the metabolism of tacrolimus is presumably by hepatic P4503A4. Therefore, there is a potential for a drug-drug interaction between tacrolimus and other drugs that are substrates for this P450 isozyme.

Five healthy volunteers received a single IV infusion of 0.03 mg/kg of tacrolimus. The mean (SD) pharmacokinetic parameters for whole blood concentrations were: half-life, 17.6 (4.6) h; volume of distribution, 0.63 (0.15) L/kg; and clearance, 0.032 (0.008) L/h/kg. The mean pharmacokinetic parameters for plasma concentrations were: half-life, 43.4 (14.7) h; volume of distribution, 16.9 (6.7) L/kg; and clearance, 0.43 (0.15) L/h/kg.

Table 18: Mean Pharmacokinetic Parameters for Tacrolimus Whole Blood Concentrations in Healthy Volunteers

Component	$T_{1/2}$ (h)	V_d (L)	V_d (L/kg)	Cl (L/h)	Cl (L/h/kg)
Blood	17.6	47.6	0.63	2.4	0.032
Plasma	43.4	1303	16.9	33.6	0.43

The administration of tacrolimus did not result in clinically significant immunosuppression in the subjects. Four of the 5 subjects experienced decreases in creatinine clearance that returned to normal within 2-9 days post-dose. The average creatinine clearance decreased from 110 mL/min at baseline to 90 mL/min between 12-48 hours post-dose. There were no clinically significant changes observed during 24-hour electrocardiogram monitoring.

The following pharmacokinetic parameters were calculated following the first IV dose of FK506 in kidney transplant patients: Elimination half-life ($T_{½}$), area under the concentration-time curve from 0 to 12 hours (AUC_{0-12}), area under the concentration-time curve from 0 to infinity ($AUC_{0-\infty}$), total body clearance (Cl), and volume of distribution at steady-state (V_{ss}).

Table 19: Mean Pharmacokinetic Parameters for Tacrolimus Whole Blood Concentrations following the Initial IV Dose of FK506 in Kidney Transplant Patients

Component	$T_{1/2}$ (h)	Cl (L/h/kg)	V_{ss} (L/kg)	AUC_{0-12} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)
Blood	8.04 ± 4.88	0.12 ± 0.05	1.0 ± 0.36	481.0 ± 129	755.0 ± 297
Plasma	6.86 ± 2.92	4.29 ± 2.1	29.2 ± 15.8	20.0 ± 19.5	25.3 ± 20.9

The following pharmacokinetic parameters were calculated following maintenance oral dosing with FK506 in kidney transplant patients: bioavailability (BA), time to maximum concentration (T_{max}), maximum blood/plasma concentration (C_{max}), plasma/blood concentration before dosing (C_{0h}), and plasma/blood concentration 12 hours after dosing (C_{12h}).

Table 20: Mean Pharmacokinetic Parameters for Tacrolimus Whole Blood Concentrations following the Maintenance Oral Dosing of FK506 in Kidney Transplant Patients

Component	BA (%)	T_{max} (h)	C_{max} (ng/mL)	C_{0h} (ng/mL)	C_{12h} (ng/mL)
Blood	20.0 ± 17.8	4.2 ± 2.9	44.0 ± 4.2	15.0 ± 10	16.0 ± 12
Plasma	17.3 ± 12.0	3.1 ± 2.4	1.4 ± 1.7	0.4 ± 0.1	0.4 ± 0.2

There were great individual differences among the IV and oral pharmacokinetic parameters. However, C_{0h} and C_{12h} in whole blood and plasma from each patient following oral dosing were almost identical. It was suggested that steady-state was obtained upon repeated dosing.

In a prospective, multicentre study, 37 kidney transplant patients received 0.075 mg/kg IV infused over 4 hours twice daily, and were converted to oral tacrolimus at a dose of 0.3 mg/kg/day in two divided doses when they were able to tolerate oral medication. The results of this study suggested that if the range of trough whole blood tacrolimus levels is maintained between 15 and 20 ng/mL, the incidence of adverse events is decreased. Maintaining optimal therapeutic levels may also decrease the incidence of rejection. Results suggested that tacrolimus is better monitored with whole blood than with plasma, and that patient's trough tacrolimus levels in whole blood be maintained at 20 ng/mL for the initial 2 weeks following transplantation, then decreased to trough blood levels of 15 ng/mL for the next 12 weeks.

In an open-labelled study to evaluate the effect of hepatic dysfunction on the pharmacokinetics of tacrolimus, patients with and without liver impairment received 0.15 mg/kg IV tacrolimus over 1 to 2 hours and 0.15 mg/kg oral tacrolimus. The effect of T-tube clamping on the oral absorption of tacrolimus at 0.15 mg/kg was studied in 5 liver transplant patients, who had a duct-to-duct biliary reconstruction with a T-tube stent. In patients with moderate to severe hepatic dysfunction, the elimination half-life of tacrolimus was increased and the total body clearance was decreased, resulting in higher daily trough plasma concentrations. The bioavailability increased following oral administration of tacrolimus to hepatically impaired patients. Bile did not alter the absorption of tacrolimus. Dosage adjustments may be necessary for patients with severe hepatic impairment, but not for those patients with mild impairment.

The clearance of tacrolimus is independent of renal function; less than 1% is recovered unchanged in the urine. However, reducing the dose of tacrolimus may be necessary with deterioration of renal function in order to reduce the potential nephrotoxic effects of the drug.

Studies showed that as the dose of tacrolimus increased, a dose-proportional increase in AUC and C_{max} resulted. However, a large interpatient variability was observed. Whole blood and plasma trough concentrations taken 10-12 hours after oral administration of tacrolimus (C_{min}) correlated well with the $AUC_{0\text{-}12h}$ r = 0.93-0.98, demonstrating that C_{min} is an accurate indicator of overall patient exposure to drug.

Children ≤ 12 years of age required approximately twice the adult IV and oral doses to attain similar tacrolimus plasma trough concentrations following liver transplantation.

Tacrolimus concentrations measured by EIA have been shown to correlate well with those determined by HDLC-MS assay specific for the parent compound, (r = 0.86 - 0.93), indicating that EIA provides a reliable measure of tacrolimus concentrations.

Special populations and conditions

- **Pediatrics**

A study in liver transplantation has been conducted in sixteen pediatric patients (age range: 0.7-13.2 years). A mean terminal elimination half-life of 11.5 hours was determined following an intravenous dose of 0.037 mg/kg/day in twelve patients; the volume of distribution was 2.6 L/kg, whereas clearance was 0.135 L/hr/kg. In nine patients receiving capsule formulation, a mean C_{max} of 48.4 ng/mL was attained at a mean T_{max} of 2.7 hours following an oral dose of 0.152 mg/kg as Prograf capsules. The AUC (0-72 hr) was 337 ng•hr/mL. The absolute bioavailability was 31%.

Whole blood trough concentrations from 31 pediatric patients (less than 12 years old) showed that pediatric patients need higher doses than adults to achieve similar tacrolimus trough concentrations, suggesting that the pharmacokinetic characteristics of tacrolimus are different in pediatric patients compared to adults (see 4 Dosage and Administration).

- **Geriatrics**

The pharmacokinetics of tacrolimus has not been established in the geriatric population.

- **Sex**

A formal study to evaluate the effect of gender on tacrolimus pharmacokinetics has not been conducted; however, there was no differences noted in dosing by gender in the kidney transplant trial. A retrospective comparison of pharmacokinetics in healthy volunteers, and in kidney and liver transplant patients, indicated no gender-based differences.

- **Ethnic origin**

A formal study to evaluate the pharmacokinetic disposition of tacrolimus in Black transplant patients has not been conducted; however, a retrospective comparison of Black and Caucasian kidney transplant patients indicated that Black patients required higher tacrolimus doses to attain similar trough concentrations (see 4 Dosage and Administration).

- **Hepatic Insufficiency**

Tacrolimus pharmacokinetics have been determined in six patients with mild hepatic dysfunction (mean Pugh score: 6.2) following single intravenous and oral administrations. The pharmacokinetic parameters obtained were as follows:

Table 21: Tacrolimus Pharmacokinetics in Patients with Mild Hepatic Impairment

Parameter (N = 6)	Dose and Route	
	7.7 mg P.O.	1.3 mg IV
Age Range (yrs)	52-63	
Absolute Bioavailability (%)	22.3 ± 11.4	-
C_{max} (ng/mL)	48.2 ± 17.9	-
T_{max} (hr)	1.5 ± 0.6	-
AUC_{0-72} (ng•hr/mL)	488 ± 320	367 ± 107
V (L/kg)	3.7 ± 4.7*	3.1 ± 1.6
Cl (L/hr/kg)	0.034 ± 0.019*	0.042 ± 0.020
$t_{1/2}$ (hr)	66.1 ± 44.8	60.6 ± 43.8

*Corrected for bioavailability

The disposition of tacrolimus in patients with mild hepatic dysfunction was not substantially different from that in normal volunteers (see previous tables). In general, tacrolimus elimination half-life was longer and volume of distribution larger in patients with mild hepatic dysfunction compared to normal volunteers. The clearance in both populations was similar and since tacrolimus is extensively metabolized at multiple sites, patients with mild hepatic dysfunction may not require lower maintenance doses of tacrolimus than patients with normal hepatic function.

Tacrolimus pharmacokinetics were studied in 6 patients with severe hepatic dysfunction (mean Pugh score: > 10). The mean clearance was substantially lower in patients with severe hepatic dysfunction, irrespective of the route of administration.

Table 22: Tacrolimus Pharmacokinetics in Patients with Severe Hepatic Impairment

Route, N	Dose	AUC ng•hr/mL (0-t)	$T_{1/2}$(hr)	V (L/kg)	Cl (L/hr/kg)
IV, N=6	0.02 mg/kg/4 hr IV (N=2)	762 (t=120 hr)	198 ± 158 Range: 81-436	-	-
	0.01 mg/kg/8 hr IV (N=4)	289 ± 117 (t=144 hr)		3.9 ± 1.0	0.017 ± 0.013
PO, N=5†	8 mg PO (N=1)	658 (t=120 hr)	119 ± 35 Range: 85-178	3.1 ± 3.4	0.016 ± 0.011
	5 mg PO (N=4)	533 ± 156 (t=144 hr)			
	4 mg PO (N=1)	-			

† 1 patient did not receive the PO dose.

- **Renal Insufficiency**

Tacrolimus pharmacokinetics following a single intravenous administration have been determined in 12 patients (7 not on dialysis and 5 on dialysis) prior to their kidney transplant. The pharmacokinetic parameters obtained are presented in the table below:

Table 23: Tacrolimus Pharmacokinetics in Patients with Renal Insufficiency

Serum Creatinine (mg/dL)	3.9 ± 1.6 (not on dialysis) 12.0 ± 2.4 (on dialysis)
Age range (yrs)	25-65
Route	IV
Dose (mg)	1.17 ± 0.28
AUC_{0-60} (ng•hr/mL)	393 ± 123
AUC_{0-inf} (ng•hr/mL)	499 ± 155
V (L/kg)	1.07 ± 0.20
Cl (L/hr/kg)	0.038 ± 0.014
$t_{1/2}$(hr)	26.3 ± 9.2

The disposition of tacrolimus in patients with renal dysfunction was not different from that in normal volunteers (see previous tables). The clearance was similar whereas volume of distribution was smaller and the mean terminal elimination half-life shorter than that of normal volunteers.

11 STORAGE, STABILITY, AND DISPOSAL

Prograf (tacrolimus immediate-release capsules, USP): Store and dispense at controlled room temperature, 15˚C - 30˚C.

Prograf (tacrolimus for injection): Store in the carton and protect from light. Dispense Prograf ampoules between 15˚C and 25˚C.

Prograf (tacrolimus for injection) must be diluted to a concentration between 0.004 mg/mL and 0.02 mg/mL with 0.9% Sodium Chloride Injection or 5% Dextrose Injection before use. The diluted infusion solution should be stored at 15 - 25˚C in glass or polyethylene containers and should be discarded after 24 hours. The diluted infusion solution should not be stored in a PVC container due to poor stability and the potential for extraction of phthalates. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

12 SPECIAL HANDLING INSTRUCTIONS

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

PART 2: SCIENTIFIC INFORMATION

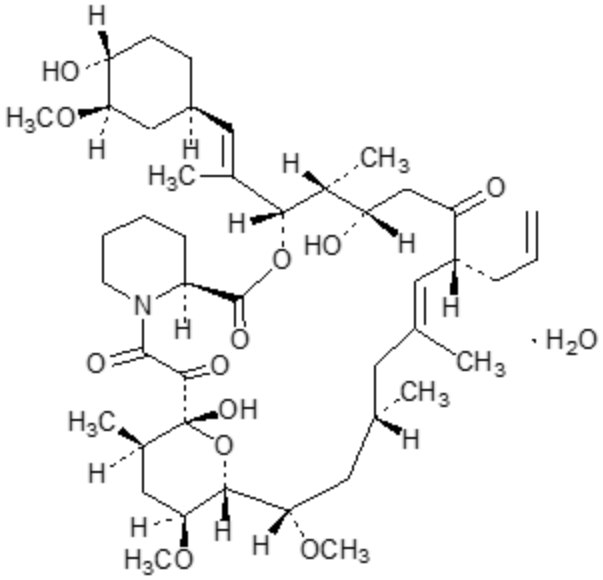
13 PHARMACEUTICAL INFORMATION

Non-proprietary name of the drug substance: tacrolimus

Chemical name: [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 and molecular mass: $C_{44}H_{69}NO_{12}\bullet H_2O$ and 822.03

Structural formula:



Physicochemical properties: Tacrolimus appears as white crystals or crystalline powder.

Solubility: It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform.

Melting Point: 124.9 - 126.8°C by thermal analysis.

Partition Coefficient: > 1000 (in n-octanol/water).

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Kidney Transplantation

Table 24: Summary of Patient Demographics for Prograf (tacrolimus) Kidney Transplantation Trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender	Race (Caucasian/ Black/Other)
93-0006 (U.S)	Randomized, multi-centre, open-label, comparative	0.2 mg/kg per day tacrolimus BID orally (IV dose is 20% of oral dose), 1 year	N = 205	43.4 ± 13.1 (9-71 years)	M = 123 F = 82	114/56/35
		Initial Dose: 10 mg/kg per day cyclosporine A BID orally (IV dose is 33% of oral dose), 1 year	N = 207	43.6 ± 12.4 (10-74 years)	M =129 F = 78	123/48/36
FG-02-02 (Europe)	Multicentre, open, parallel-group study, randomized	Initial dose 0.3 mg/kg per day BID to target whole blood trough concentrations of 10-20 ng/mL, oral, 1 year	N = 303	46.6 ± 13.5 (18-72 years)	M = 196 F = 107	300/1/2
		Initial dose 8.0 mg/kg per day to target blood level 100-300 ng/mL, oral, 1 year	N = 145	45.8 ± 12.5 (20-70 years)	M = 92 F = 53	143/0/2

Liver Transplantation

Table 25: Summary of Patient Demographics for Prograf (tacrolimus) Liver Transplantation Trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender	Race (Caucasian/ Black/Other)
FPC-FK506-7	Open-label, randomized, multicenter, active comparator, parallel study	Tacrolimus: 0.075 mg/kg then 0.15 mg/kg PO BID or 0.05 mg/kg IV BID, 360 days	N = 263	44.0	M = 136 F = 127	208/13/42
		CyA*: 1-2 mg/kg IV BID, 5 mg/kg PO, 360 days	N = 266	44.0	M = 140 F = 126	203/14/49

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender	Race (Caucasian/ Black/Other)
GHBA-157	Randomized, multicenter, active comparator, open-label, parallel study	0.075 mg/kg then 0.03-0.05 IV BID, 360 days	N = 270	45.7	M = 136 F = 134	260/2/8
		CyA*: 1-15 mg/kg/day, 360 days	N = 275	45.6	M = 158 F = 117	260/2/13
FPC-FK506-9	Open-label, multicenter, rescue use of FK506 (tacrolimus)	0.075 mg/kg then 0.15 mg/kg PO BID or 0.05 mg/kg IV BID, 360 days	N = 125	34.7	M = 56 F = 69	79/18/28

*CyA: Cyclosporine A

Heart Transplantation

Table 26: Summary of Patient Demographics for Prograf (tacrolimus) Heart Transplantation Trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N)	Mean age (Range)	Gender	Race (Caucasian/ Black/Other)
FG-506-05-02	Open-label, randomized, parallel-group study	Antibody induction therapy; azathioprine, corticosteroids and tacrolimus. Tacrolimus initial oral dose, 0.075 mg/kg/day. At ≤ 3 months post-transplant, tacrolimus blood trough concentrations between 10 - 20 ng/mL. At > 3 months post-transplant, tacrolimus blood trough concentrations at 15 ng/mL.	157	50.8 ± 11.0 (18 - 65)	Female: 30 Male: 127	153/1/3
		Antibody induction therapy; azathioprine, corticosteroids and cyclosporine. Cyclosporine microemulsion: Initial oral dose at	157	50.7 ± 9.9 (18 - 65)	Female: 28 Male: 129	151/4/2

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N)	Mean age (Range)	Gender	Race (Caucasian/ Black/Other)
		4-6 mg/kg/day. At ≤ 3 months post-transplant, cyclosporine blood trough concentrations between 200-350 ng/mL. At > 3 months post-transplant, cyclosporine blood trough concentrations between 100-200 ng/mL thereafter.				
20-01-003	Randomized, Prospective, Multi-center Comparison	Tacrolimus, MMF and steroid treatment therapy Tacrolimus: 2-4 mg/kg per day, in two divided oral doses, within 12 hours of transplant. Dosing was adjusted to achieve whole blood concentrations of 200-400ng/mL in the first 3 months and 100 to 300 ng/mL thereafter.	113	54.34 ± 10.9 (20 - 75)	M = 86 F = 21	95/9/3
		Cyclosporine, MMF and steroids Cyclosporine: 3 to 5 mg/kg per day, as two divided oral doses, within 12 hours of transplant. Dosing was adjusted to achieve whole blood concentrations of 200-400ng/mL in the first 3 months and 100 to 300 ng/mL thereafter.	117	51.89 ± 11.5 (22 - 72)	M = 84 F = 31	91/20/4

Rheumatoid Arthritis

Table 27: Summary of Patient Demographics for Prograf (tacrolimus) Clinical Trials in Rheumatoid Arthritis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender	Race (Caucasian/ Black/Other)
FK-506-RA-001	Randomized, double-blind parallel group	Placebo, 1, 3 or 5 mg tacrolimus as a single daily oral dose for 24 weeks	N = 268	52.0 ± 10.4	M = 59 F = 209	253/11/4
98-0-049	Randomized, double-blind parallel group	Placebo, 2 mg tacrolimus, or 3 mg tacrolimus as a single daily dose for 6 months	N = 464	55.8 ± 12.25	M = 38 F = 119	421/25/18
98-0-051	Open-label, long-term safety study	3 mg tacrolimus single daily oral dose for 12 months (roll-over from 98-0-049 in total patient received up to 18 months of treatment.)	N = 896	55.7 ± 11.84	M = 242 F = 654	835/36/25

14.2 Comparative Bioavailability Studies

Kidney Transplantation

The safety and efficacy of Prograf®-based immunosuppression following kidney transplantation was assessed in two, Phase III randomized, multicentre, non-blinded, prospective studies. The active control groups were treated with cyclosporine-based immunosuppression. These studies were designed to evaluate whether the two regimens were therapeutically equivalent for one-year patient and graft survival. Based on the results from these two studies, the Prograf-based regimen was found to be therapeutically equivalent to the cyclosporine-based regimen.

In one trial, (Study 93-0006), 412 kidney transplant patients were enrolled at 19 clinical sites in the United States; 205 patients were randomized to Prograf-based immunosuppression and 207 patients were randomized to cyclosporine-based immunosuppression. All patients received prophylactic induction therapy consisting of an antilymphocyte antibody preparation, corticosteroids and azathioprine. Prograf was initiated when renal function was stable as indicated by a serum creatinine ≤ 4 mg/dL (353.6 µmol/L). Prograf was initiated a median of 4 days after transplantation. Patients less than 6 years of age were excluded.

In the second trial, (Study FG-02-02), 448 kidney transplant patients were enrolled at 15 clinical sites in Europe; 303 patients were randomized to Prograf-based immunosuppression and 145 patients were randomized to cyclosporine-based immunosuppression. Prograf was initiated within 24 hours of transplantation and was administered with corticosteroids and azathioprine. Patients less than 18 years of age were excluded.

One-year patient and graft survival in the Prograf-based treatment groups were equivalent to those in the cyclosporine-based treatment groups. The overall one-year patient survival (Prograf and cyclosporine combined) was 96.1% in the U.S. study and 94.2% in the European study. The overall one-year graft survival was 89.6% in the U.S. study and 83.7% in the European study.

The two large, randomized clinical trials demonstrated that significantly fewer tacrolimus-treated patients (approximately 16% fewer) experienced an episode of acute rejection during the one-year treatment period compared with cyclosporine-treated patients ($p < 0.001$).

Significantly fewer tacrolimus-treated patients crossed over to cyclosporine therapy due to adverse events and acute rejection episodes compared to cyclosporine-treated patients transferring to tacrolimus therapy ($p = 0.007$). The majority of patients who crossed over from the cyclosporine therapy to tacrolimus therapy were due to rejection (n = 27). The majority of patients who crossed over from tacrolimus therapy to cyclosporine therapy were due to adverse reactions (n = 13) and rarely for rejection (n = 2). Of 27 cyclosporine-treated patients demonstrating acute rejection episodes and transferred to tacrolimus, 21 of these patient rejection episodes resolved (77.8%). Of the 2 tacrolimus patients transferred to cyclosporine due to acute rejection, one of the rejection episodes resolved.

An open-label, rescue study, 93-0003, assessed the effect of tacrolimus on 73 kidney transplant patients with biopsy-proven, corticosteroid-resistant acute rejection. Responses to tacrolimus therapy included improvement in 78% of patients, stabilization in 11% and progressive deterioration in 11%. Patient and graft survival one year-post conversion to tacrolimus was 93% and 75% respectively.

The use of Prograf-based immunosuppression in combination with mycophenolate mofetil or azathioprine was evaluated in a Phase IV, randomized, 3-arm, multicenter, non-blinded, prospective study. A total of 176 deceased donor kidney transplant recipients were randomized to one of three treatment groups; azathioprine, mycophenolate mofetil 1 gram per day or mycophenolate mofetil 2 grams per day in two divided doses. All patients received prophylactic induction therapy consisting of an antilymphocyte antibody preparation and corticosteroids. The respective one-year patient survival rates were 98.3%, 94.9% and 94.8% for the three treatment groups of azathioprine, mycophenolate mofetil 1 gram per day and mycophenolate mofetil 2 grams per day in two divided doses. Corresponding one year graft survival rates were 94.9%, 93.2% and 94.8%.

A long-term comparison study of tacrolimus (n = 205) and cyclosporine (n = 207) in kidney transplantation was conducted as a 5-year follow-up to study 93-0006. The study focused on the long-term impact of tacrolimus therapy. Patient and graft survival rates over the follow-up period were equivalent between tacrolimus and cyclosporine treatment arms (79.1% vs. 81.4% and 64.3% vs. 61.6%, respectively). The estimated graft half-life was 13.3 years for tacrolimus and 11.9 years for cyclosporine. However, the incidence of crossover from cyclosporine to tacrolimus was significantly greater than the crossover from tacrolimus to cyclosporine (27.5% vs. 9.3%).

Kidney function tests showed mean serum creatinine levels were higher among patients treated with cyclosporine than those treated with tacrolimus. Significantly fewer patients in the tacrolimus treatment arm developed serum creatinine levels >1.5 mg/dL (40.4% vs. 62.0%).

The risk of treatment failure (defined as the occurrence of graft loss or discontinuation of randomized drug) was significantly lower among patients treated with tacrolimus compared to those treated with cyclosporine (43.8% vs. 56.3%; $p = 0.008$). Graft failure due to rejection occurred more frequently

among cyclosporine-treated patients (22.1% vs. 17.0%). At 5 years, fewer patients receiving tacrolimus-based therapy were treated with antihypertensive and antihyperlipidemia medications. It was found that significantly fewer patients maintained on tacrolimus-based therapy developed hypercholesterolemia compared to those receiving cyclosporine (4.7% vs. 17.4%).

Liver Transplantation

The safety and efficacy of Prograf (tacrolimus) administered in combination with adrenal corticosteroids was compared with cyclosporine-based immunosuppressive regimens in two randomized, prospective, open-labelled, multicentre studies after orthotopic liver transplantation. In addition, the efficacy of Prograf as rescue therapy in patients with liver allograft rejection refractory to standard therapy was examined in an open-labelled, nonrandomized, multicentre, historically-controlled trial.

In one controlled trial, (Study FPC-FK506-7), 529 patients were randomized to receive immunosuppression with Prograf (N=263) or cyclosporine-based regimens (N=266). Patient survival was equivalent with Kaplan-Meier actuarial one-year estimates of 88% for both Prograf and cyclosporine-based regimens. Actuarial one-year graft survival estimates were 82% for the Prograf group and 79% for the cyclosporine-based group. The incidences of acute rejection (68% vs. 76%), steroid-resistant rejection requiring treatment with OKT3 (19% vs. 36%), and refractory rejection (3% vs. 15%) were lower in recipients of the Prograf regimen compared with cyclosporine-based regimens (see table below). Cumulative adrenal corticosteroid use was lower in the Prograf group; however, equivalent doses of corticosteroids were not mandated for induction or maintenance in the two arms of the study. Other measures of efficacy, such as liver function tests and Karnofsky scores, showed similar improvement over time in both groups.

Table 28: Results for the Liver Transplantation Study FPC-FK506-7

Efficacy Parameters	Prograf (%)	CBIR*(%)	95% Confidence Intervals (%)**
Actuarial One Year Patient Survival Estimates	88	88	-5, 7
Actuarial One Year Graft Survival Estimates	82	79	-5, 10
Incidence of Acute Rejection	68	76	-17, 1
Incidence of Steroid-Resistant Rejection Requiring Orthoclone OKT3 Treatment	19	36	-25, -8
Incidence of Refractory Rejection	3	15	-18, -6

* Cyclosporine-Based Immunosuppressive Regimens ** Prograf minus CBIR

In the second controlled study (Study GHBA-157), 545 patients were randomized to receive Prograf combined with adrenal corticosteroids (N=270) as a treatment for prevention of rejection of primary liver allograft patients, compared with cyclosporine-based therapy (N=275).

The estimated one-year Kaplan-Meier patient survival rates were 81% for the Prograf treatment group and 75% for the cyclosporine-based treatment group. One-year estimated Kaplan-Meier graft survival rates were 76% for the Prograf group and 70% for the cyclosporine-based group. The acute rejection rate was 42% for the Prograf group compared with 55% for the cyclosporine-based group. The incidence of refractory rejection was also less in the Prograf group (3%) compared with the cyclosporine-based

group (10%) (see table below). The cumulative amount of adrenal corticosteroids administered to patients in the Prograf group was less than in the cyclosporine-based group.

Table 29: Results for the Liver Transplantation Study GHBA-157

Efficacy Parameters	Prograf (%)	CBIR* (%)	95% Confidence Intervals (%)**
Actuarial One Year Patient Survival Estimates	81	75	-1, 13
Actuarial One Year Graft Survival Estimates	76	70	-1, 14
Incidence of Acute Rejection	42	54.7	-23, -4
Incidence of Refractory Rejection	2.6	9.2	-12, -3

* Cyclosporine-Based Immunosuppressive Regimens ** Prograf minus CBIR

In a non-randomized historically controlled trial (Study FPC-FK506-9), 125 patients previously treated with cyclosporine-based regimens with refractory acute or chronic liver allograft rejection were treated with Prograf plus adrenal corticosteroids as rescue therapy. Actuarial Kaplan-Meier estimates of survival at one year post-conversion to Prograf were 71% for patient survival and 56% for graft survival. Other measures of efficacy, such as clinical response scores, liver function test, and Karnofsky performance status showed improvement over time after conversion to Prograf.

Study 91-0045 was conducted in the United States to establish a safe and effective reduced dosage regimen for adult liver transplant patients. Patients were randomized to an initial low dose (0.15 mg/kg/day) or an initial high dose (0.30 mg/kg/day) of oral Prograf and all patients received the same initial dose of corticosteroids. Azathioprine was not allowed during the first 42 days of the study. Prograf doses were adjusted upward or downward in the event of rejection or toxicity, respectively. The mean dose in the higher group shifted downward while the mean dose in the lower group shifted upward over time. By study day 42, both groups were receiving similar Prograf doses (0.13 mg/kg/day). At one year post-transplant, patient results based on the two initial dosing groups were as follows:

Table 30: Results for the Liver Transplantation Study 91-0045

12 Month Results	Low Dose (n = 100)	High Dose (n = 98)
Patient Survival	91.9%	89.7%
Graft Survival	88.9%	85.6%
Acute Rejection	65.1%	49.7%
Mean Whole Blood Trough Levels of Tacrolimus	9.6 ng/mL (n=76)	10.6 ng/mL (n=67)

Two of 100 patients in the low dose group and 8 of 98 patients in the high dose group discontinued the study due to an adverse event during the first 6 weeks of therapy.

A long-term (5-year) comparison study of tacrolimus (n = 263) versus cyclosporine (n = 266) in primary liver transplantation was conducted in a 1-year randomized, multicenter trial (FPC-FK506-7) with a 4-year follow-up period.

The 5-year patient and graft survival rates were comparable among tacrolimus (79.0%, 71.8%) and cyclosporine (73.1%, 66.4%) treatment groups. However, patient half-life survival was significantly longer for tacrolimus-treated patients (25.1 ± 5.1 years vs. 15.2 ± 2.5 years), a similar trend occurred with graft half-life. Patient survival of hepatitis C-positive patients was also significantly longer with tacrolimus treatment (78.9% vs. 60.5%).

During the first year after transplant, patients in the tacrolimus group had a statistically significant lower incidence of acute rejection (68% vs. 76%) and steroid-resistant rejection (19% vs. 36%). There was no significant difference between treatment groups in the following years. The incidence of death or graft loss due to rejection was 3% in both treatment groups over the 5-year follow-up period. The incidence of malignancies, lymphoproliferative disorders, and late infections were low and comparable between treatment groups.

Heart Transplantation
Two open-label, randomized, comparative studies evaluated the safety and efficacy of Prograf-based and cyclosporine-based immunosuppression in primary orthotopic heart transplantation. In a Phase III study conducted in Europe, 314 patients received a regimen of antibody induction, corticosteroids and azathioprine in combination with Prograf or cyclosporine modified for 18 months. In the US study, all patients received corticosteroids in addition to Prograf plus mycophenolate (MMF) (113 patients) or cyclosporine modified plus MMF (117 patients) for 1 year.

In the European Phase III 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 cyclosporine group (treatment difference 2.4%; 95% CI: -4.0%, 8.9%). In the US study, patient and graft survival at 12 months was comparable between the treatment groups with 93.5% survival in the Prograf plus MMF group and 86.1% survival in the cyclosporine modified plus MMF group.

In the European Phase III study, the incidence of biopsy-verified acute rejection standardized grade ≥1B at 6 months post-transplantation was significantly lower (p = 0.029, Cochran-Mantel-Haenszel) in the tacrolimus group (54%) compared with the cyclosporine group (66.4%) based on blinded central assessments. The incidence of biopsy-verified acute rejection standardized grade ≥3A at 6 months post-transplantation was significantly lower with tacrolimus-based immunosuppression (29.3%) compared with cyclosporine-based immunosuppression (42%; p = 0.018, chi-square) based on blinded central assessments. The incidence of biopsy-verified acute rejection grade ≥3A with hemodynamic compromise was similar (Prograf: 0.6% vs cyclosporine modified 0%; treatment difference 0.6%; 95% CI: -0.6%, 1.9%).

In the US comparative study, biopsy-verified acute rejection grade ≥3A and biopsy-verified acute rejection grade ≥3A with hemodynamic compromise at 1 year were similar between the treatment groups (Prograf/MMF: 24.3% and 3.7%; cyclosporine/MMF: 35.7% and 7.8%).

Rheumatoid Arthritis

Safety and efficacy of Prograf-based treatment in rheumatoid arthritis patients was evaluated in one Phase II study and two Phase III studies.

The results for the Phase II study, FK506RA-001 and a Phase III study, 98-0-049, depicting the ACR response rates and change from baseline to the end of treatment for individual component scores are depicted below:

Table 31: ACR Response Rates and Change from Baseline to End of Treatment for Individual Component Scores

Variable	FK506RA-001[1]				98-0-049[1]		
	Placebo	1 mg	3 mg	5 mg	Placebo	2 mg	3 mg
ACR20 Response Rate	15.5%	29.9%#	34.4%*	50.0%***	13.4%	21.4%#	32.0%***
ACR20 Success Rate	11.3%	29.0%#	23.4%#	40.6%***	10.2%	18.8%*	26.8%***
ACR50 Response Rate	1.4%	14.5%*	17.2%*	14.1%*	4.5%	11.7%	11.8%*
ACR70 Response Rate	NA	NA	NA	NA	0.6%	5.2%*	3.3%
Swollen Joint Count[2] (LS Mean)	-1.8	-3.8	-5.4*	-6.8**	-1.47	-4.02*	-5.3***
Tender Joint Count[2] (LS Mean)	-0.9	-6.3*	-7.9**	-12.9***	-1.87	-3.09	-7.25***
Patient's Assessment of Pain[2]	-5.4	-11.4	-16.2*	-23.7***	-2.13	-11.3**	-10.6**
Patient's Global Assessment of Disease Activity[2] (mm)	-3.4	-11.0	-13.5#	-21.1***	2.5	-7.2**	-6.6**
Physician's Global Assessment of Disease Activity[2] (mm)	-10.2	-13.4	-18.5#	-27.8***	-9.0	-15.8*	-18.2**
Patient's Assessment of Physical Function (MHAQ)[2]	0.0	-0.1	-0.3*	-0.4***	0.09	-0.13***	-0.03*
CRP[2] (mg/dL)	0.5	-0.3#	-0.8**	-1.7***	0.01	-0.8**	-0.6*
ESR[2] (mm/hr)	5.1	-4.0*	-4.3*	-11.4*	2.6	-4.3**	-8.6

[1]Patients who were randomized and received at least one dose of study medication.
[2]Mean change from baseline. ACR20, ACR50 and ACR70: ≥ 20%, ≥ 50% and ≥ 70%, respectively, improvement in tender or painful joint count and swollen joint count and ≥ 20%, ≥ 50% and ≥ 70% respectively, improvement in 3 of the 5 following parameters: patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function (based on the modified health assessment questionnaire), and an acute-phase reactant (erythrocyte sedimentation rate or C-reactive protein). LS Mean: Least square means are based on general linear model analysis with treatment group and DMARD strata included in the model. #p ≤ 0.10, *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001. NA: not available

Phase II Study

In the randomized, double-blind, placebo-controlled study (Study FK-506-RA-001), patients intolerant or resistant to methotrexate were enrolled and were also being treated with corticosteroids, such as prednisone or its equivalent and/or nonsteroidal anti-inflammatory drugs (NSAIDS) and/or analgesics. Patients were randomized to receive one of the following oral doses of study medication capsules: 1 mg FK506, 3 mg FK506, 5 mg FK506 or placebo once a day, for 6 months.

The primary and secondary efficacy endpoints evaluated in this patient population included the ACR20, 50 and 70 responses, as defined by the American College of Rheumatology, for improvement assessment in rheumatoid arthritis at the end of treatment. These criteria are based in corresponding increases of 20, 50 or 70% improvement in tender or painful joint counts and swollen joint counts and a 20%, 50% or 70% improvement in 3 of 5 of the following parameters: patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function (based on the modified health assessment questionnaire), and an acute-phase reactant (ESR or C-reactive protein (CRP)).

The ACR20 response rate at the end of treatment was higher in all 3 dose groups: 29.0% (1 mg), 34.4% (3 mg), 50.0% (5 mg) compared to placebo (15.5%). The response rates in the 3 mg and 5 mg groups were statistically significantly higher than placebo (p = 0.013 and < 0.001, respectively), while the rate for the 1 mg group was not statistically significant (p = 0.058). A difference in ACR20 response rates between placebo and active dose groups was first observed at Week 8, with substantial increases seen in the proportion of patients in the 5 mg group who achieved ACR20 responses during Weeks 12 and 16.

While there were no differences in swollen and tender joint counts in all 3 dose groups at baseline, there was a definite dose response, with the greatest improvement occurring in the 5 mg dose group. Improvement in swollen joint count was significantly higher in the 3 mg and 5 mg groups than in the placebo group (p = 0.029 and 0.002, respectively). Improvement in tender joint counts was significantly greater for the 1, 3 and 5 mg dose groups versus placebo (p = 0.022, 0.004 and < 0.001, respectively).

There was a statistically significant linear dose relationship over the 4 groups with respect to ACR20 at the end of treatment (p < 0.001), swollen joint counts at end of treatment (p = 0.001) and tender joint counts at the end of treatment (p < 0.001). The primary efficacy measure indicated a dose response among the Prograf groups, with statistically significantly greater efficacy at the 3 and 5 mg dose levels versus placebo for all primary measures.

Phase III Studies

In a randomized, double-blind, placebo-controlled study (Study 98-0-049), 465 patients who were concomitantly using prednisone (or its equivalent) and/or NSAIDS and had previously demonstrated resistance or intolerance to one or more disease-modifying antirheumatic drugs (DMARDS), were enrolled to receive either placebo, 2 mg/day or 3 mg/day Prograf, for a duration of 6 months.

Patients treated with Prograf generally experienced notable improvements in the ACR components of tender or painful joint counts, swollen joint counts as well as the physician's global assessment while experiencing either no change or a slight improvement in the other ACR components. The median time required for the first ACR20 response to be detected in the tacrolimus dose group (2 mg/day and 3 mg/day) was approximately 8 weeks and was achieved by approximately 42% of the patient population.

The ACR20 response rate at the end of treatment for the full analysis set was significantly greater in the 2 mg and 3 mg tacrolimus treatment groups as well as the combined treatment groups compared with placebo. The differences between the ACR20 response rates at the end of treatment for the 2 mg tacrolimus treatment group and the placebo treatment group were not statistically significant ($p = 0.0595$), while that for the 3 mg tacrolimus treatment group and placebo were statistically significant ($p = 0.0001$). The ACR20 response at the end of treatment demonstrated a dose-response relationship.

Based on the median percent change from baseline to the end of treatment, patients in the 2 mg and 3 mg tacrolimus treatment groups also generally experienced notable improvements in tender or painful joint counts, 10.5% (2 mg) and 30.0% (3 mg) versus 2.2% (placebo) as well as improvements in the swollen joint counts 16.7% (2 mg) and 30.0% (3 mg) versus 5.9% (placebo). With the exception of tender or painful joint counts for the 2 mg tacrolimus treatment group, statistically significantly greater improvements from baseline to the end of treatment in each of the ACR component scores were observed in the 2 mg tacrolimus treatment group, the 3 mg tacrolimus treatment group and the combined tacrolimus treatment group as compared to placebo.

Among DMARD intolerant patients (those patients unable to continue on methotrexate therapy as determined by documented adverse events as judged by the investigator), significantly greater proportions of patients in the combined 2 mg and 3 mg tacrolimus treatment groups achieved ACR20 and ACR50 responses at the end of treatment compared with patients in the placebo treatment group. Among DMARD resistant patients (a patient on 15 mg/wk or more of methotrexate for at least 8 weeks who still presented with active disease), the proportion of patients achieving an ACR20 response at the end of treatment was not significantly different for the 2 mg tacrolimus treatment group or the combined tacrolimus treatment group compared with the placebo treatment group. However, a significantly greater proportion of DMARD resistant patients treated with 3 mg tacrolimus achieved an ACR20 response at the end of treatment compared with placebo. Among tacrolimus-treated patients, ACR20, 50 and 70 response rates at the end of treatment were greater for DMARD intolerant patients compared with DMARD resistant patients.

In the long-term safety study, (Study 98-0-051), an extension of study 98-0-049, patients were treated for a 12 to 18 month duration. These patients demonstrated continued improvement in the ACR20 response rates with an overall response rate at the end of treatment of 37.6%. Approximately 30% of patients experienced an ACR20 response within 3 months of receiving Prograf treatment. The ACR20 response rate was higher among patients who had previously received tacrolimus therapy in 98-0-049,

at 45.5% (96/211) than among *de novo* patients enrolled in this study 35.2% (241/685), thereby indicating that those patients receiving a longer duration of treatment experienced a greater rate of response. Two of the greatest improvements in the median percent change from baseline were the ACR component scores at the end of treatment observed for swollen joint counts (47.5%) and tender or painful joint counts (50.0%).

15 MICROBIOLOGY

Not Applicable.

16 NON-CLINICAL TOXICOLOGY

Animal Studies
The primary mechanism of rejection following transplantation involves activation of T-lymphocytes and the subsequent formation of factors such as interleukin-2 (IL-2). Tacrolimus inhibits the activation of T-lymphocytes in both animals and humans, especially the activation that is calcium-dependent. The minimum inhibitory tissue culture level of tacrolimus that prevents antigen stimulation of T-lymphocytes is 0.1 nM - 0.3 nM. Tacrolimus interferes with the formation of active transcription factor NF-AT (nuclear factor of activated T-cells) and inhibits the formation of lymphokines such as IL-2, IL-3, IL-4, and interferon-γ. The net result is immunosuppression.

Tacrolimus significantly prolonged host survival and/or graft viability in animal transplant models involving the liver, kidney, heart, small bowel, lung, pancreas, pancreatic islet, bone marrow, skin, limb, cornea, and trachea. A dose range of 0.1 to 1 mg/kg/day PO or IM was used in most studies in various dosing regimens: pre- and post-surgery, short- and long-term administration.

At intravenous doses of 0.32 to 3.2 mg/kg, and at oral doses of 3.2 to 32 mg/kg, tacrolimus showed little effect on general activity and the central nervous system; little or no effect on somatic and autonomic nervous systems and smooth muscle.

Most of the effects shown by IV tacrolimus in dogs and cats were also shown by the tacrolimus-placebo IV formulation. Intravenous tacrolimus at ≥ 0.1 mg/kg increased the respiration rate in dogs only; blood pressure was decreased by IV tacrolimus at ≥ 0.1 mg/kg in dogs, to a lesser extent at 3.2 mg/kg in cats, and by PO tacrolimus at 32 mg/kg in rats; heart rate was decreased by IV tacrolimus at ≥ 0.1 mg/kg in dogs, at ≥ 0.32 mg/kg in cats, at 3.2 mg/kg in rats, and by PO tacrolimus at 10 and 32 mg/kg in rats; blood flow in femoral artery of dogs was decreased by IV tacrolimus at ≥ 0.1 mg/kg; carotid artery blood flow was increased at 3.2 mg/kg IV in cats.

Intravenous tacrolimus at ≥ 1.0 mg/kg increased pilocarpine-induced salivary secretion in rabbits and decreased gastric fluid secretion in rats; and, at 3.2 mg/kg, increased accumulation of intestinal fluid and slightly inhibited gastrointestinal transit rate in rats. Intravenous tacrolimus did not affect bile secretion nor produce irritation to gastric mucosa in rats. Gastrointestinal transit rate and accumulation of intestinal fluid in rats were not affected by PO tacrolimus. Bleeding time in mice and prothrombin time and activated partial thromboplastin time in rats were not affected by IV or PO tacrolimus. Tacrolimus did not affect ADP- or collagen-induced aggregation of rabbit platelets, or produce hemolysis in rabbit blood. Oral tacrolimus at 32 mg/kg slightly increased urine volume and Na+ excretion, but not excretion

of K+, Cl-, or uric acid, in rats; IV tacrolimus at 3.2 mg/kg had no effect. Oral tacrolimus had no effect on carrageenin-induced paw edema in rats.

When ^{14}C-tacrolimus was dosed orally to pregnant or lactating rats, trace amounts of tacrolimus were found in fetal liver and in breast milk, respectively.

When ^{14}C-tacrolimus was administered to rats, either intravenously or orally, total recovery of radioactivity in urine and feces was over 95%. Trace amounts of unchanged tacrolimus, as well as small amounts of numerous metabolites, were detected in urine, feces, and bile, indicating that the drug is extensively metabolized. *In vitro* studies identified the main metabolite as 13-demethylated-tacrolimus in animals and humans.

Acute Toxicology

Table 32: Acute Toxicology Studies of Tacrolimus in Rats and Baboon

Species	No./ Group (M/F)	Route	Dose Range (mg/kg)	Overt Signs of Toxicology	LD_{50} (mg/kg)
Rat, Sprague-Dawley	5/5	Gavage	32-320	Tremor, ptosis, salivation, hyperreactivity, decreased spontaneous motility	134 (M) 194 (F)
	5/5	IV	10-100	Bloody urine, prone position, ptosis, hyperreactivity, salivation, decreased motility	57.0 (M) 23.6 (F)
Rat, Sprague-Dawley (21 days old)	5/5	Gavage	10-320	Hyperreactivity, salivation, decreased motility	70 (M) 32-100 (F)
Baboon	1/1	Gavage	5-250	Huddled posture, emesis	ND*
	1/1	IV	2-50	Debility and exhaustion: 1 of 2	ND*

*Not determined

Subchronic and Chronic Toxicity

Both rats and baboons showed a similar toxicologic profile following oral or intravenous administration of tacrolimus. Toxicity following intravenous administration was evident at lower doses than after oral administration for both rats and baboons. Toxicity was seen at lower doses in rats than in baboons. The primary target organs of toxicity were the kidney, pancreatic islets of Langerhans and exocrine pancreas, spleen, thymus, gastrointestinal tract, and lymph nodes. In addition, decreases in erythrocyte parameters were seen. Effects such as atrophy of the spleen, lymph nodes, and thymus may be a reflection of the immunosuppressant actions of tacrolimus. In rats, chronic oral administration of tacrolimus at high doses resulted in changes in sex organs and glaucoma/eye changes.

Rats receiving oral doses greater than 1 mg/kg/day for two and 13 weeks experienced decreased body weight gain, hypersalivation, hematology changes, elevated BUN, atrophy of the thymus and kidney, mineralization of the kidney, vacuolation of the islets of Langerhans, lenticular opacity and

degeneration, and prostate contraction. In a 52-week study, the no-observable effect level was 0.15 mg/kg/day PO.

A 4-week oral toxicity study of tacrolimus in immature rats showed a similar toxicological profile; however, the severity of the changes noted appeared to be increased relative to mature animals. The no-observable effect level in immature rats was 0.32 mg/kg/day PO.

Rats receiving intravenous doses showed a dose-dependent decrease in weight gain. Micropathological changes were similar to those seen after oral administration of higher doses, and consisted of thymic, lymph node, and splenic atrophy, vacuolation of the pancreatic islets, reduced colloid and contraction of the prostate and seminal vesicles, uterine wall narrowing, and corticomedullary mineralization in the kidney. The no-observable effect level was 0.032 mg/kg/day IV.

Baboons receiving 10 mg/kg/day PO for 4 weeks, showed body weight loss, quiet behaviour, huddled behaviour, pelleted feces, and piloerection. There were no abnormal laboratory findings or lesions.

In a 13-week oral study, body weight gain increased after the first 4 weeks in a manner parallel to that of controls. There were incidences of drowsiness and 4 huddled and/or unnatural posture. Histopathological examination indicated atrophy of the thymus and spleen. The no-observable effect level was 1 mg/kg/day PO.

A second 13-week oral study additionally produced intermittent tremors, unsteadiness, gingivitis, and emesis. There was a slight reduction in packed cell volume and hemoglobin, and a slight increase in clotting time in the high-dosage group animals. Elevations in BUN and blood glucose levels and a reduction in serum cholesterol concentration were dose related. There were increased levels of total reducing substances and glucose, and significant reductions in absolute thymus and pancreas weight in both dosage groups. There were dose-related pathological changes in the thymus (atrophy), spleen (atrophy), lymph nodes (atrophy), pancreas (exocrine cell degranulation or increased eosinophilic islet cells), intestinal tract (lymphoid infiltration, ulceration), and kidneys (interstitial inflammation).

Oral administration to baboons for 52 weeks at doses of 0, 1, 3.2, or 10 mg/kg/day resulted in an initial decreased weight gain, increase in urinary glucose and reducing substances, and pathological changes in the thymus, lymph nodes, and pancreas. The no-observable effect level was 1 mg/kg/day PO.

IV administration of tacrolimus to baboons for 4 weeks at doses of 0.5, 1, or 2 mg/kg/day resulted in overt signs of toxicity in all animals. Body weight gain was reduced and animals displayed quiet behavior, huddled posture, sleepiness, and piloerection. One out of 3 female animals at 2 mg/kg was sacrificed because of overt toxicity. BUN and serum potassium were elevated in animals dosed at 1 and 2 mg/kg. Glucose and total reducing substances were present in urine samples from one animal in each of the treatment groups. Pathological changes were noted in the thymus (atrophy), lymph nodes (atrophy), spleen (atrophy), and pancreatic islets (angiectasis of islets).

Carcinogenicity

No evidence of genotoxicity was seen in bacterial (*Salmonella* and *E. coli*) or in mammalian (Chinese hamster lung-derived cells) *in vitro* assays of mutagenicity. Tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes in either the *in vitro* CHO/HGRPT assay of mutagenicity or in the *in vivo* clastogenicity assays performed in mice.

An 80 week study in mice administered tacrolimus at oral doses of 0.3, 1.0 and 3.0 mg/kg/day showed no evidence of tumorigenicity. The 104 week studies in rats administered tacrolimus at oral doses of 0.2, 0.5, 1.25, 2.5 and 5.0 mg/kg/day demonstrated no evidence of tumorigenicity.

The carcinogenicity potential of FK506 has been evaluated in mice and rats. Mice (56/sex) were administered FK506 as a dietary admix at doses of 0 (control), 0 (placebo), 0.3, 1 and 3 mg/kg/day. There was no evidence of any tumorigenic potential of FK506 in this study. Signs of toxicity were evident in the form of reduced bodyweight gain in both sexes receiving 3.0 mg/kg/day and for males receiving 1 mg/kg/day. For males receiving 3.0 mg/kg/day, there was a reduction in the efficiency of food utilization. An increase in mortality for males at 3.0 mg/kg/day was accompanied by pathological findings of minimal adipose tissue and fur staining, evidence of dysfunctional testes/epididymides, prostate glands and seminal vesicles. Males and females at 3.0 mg/kg/day also demonstrated reduced islets of Langerhans and increased basophilia and cellularity of islets. The no-effect level was considered to be 0.3 mg/kg/day in both sexes. In addition, 1 mg/kg/day was a no-effect level for females only.

Rats (55/sex/group) were administered FK506 as a dietary admix at doses of 0 (basal diet), 0 (placebo), 0.2, 0.5 and 1.25 mg/kg/day. There was no evidence of any tumorigenic potential for FK506 in this study, nor were there any FK506 administration-related effects on factors contributory to death. Evidence of toxicity were reduced body weight gain in both sexes at 1.25 mg/kg/day and in males at 0.5 mg/kg/day. The non-toxic dose level in the study was 0.2 mg/kg/day for males and 0.5 mg/kg/day for females.

FK506 was administered to rats as a dietary admix in the supplementary study, at doses of 0 (placebo) to 50/sex, and 2.5 mg/kg/day (100/sex). In the absence of clear toxicity, at the end of week 26, the FK506-treated group was divided into two groups (50/sex/group). One group received a dose of 2.5 mg/kg/day whereas the dose in the other group was increased to 5.0 mg/kg/day. There was no evidence of tumorigenic potential at either dose level. Evidence of toxicity were dose-related mortality rates, reduced body weight gain and histopathological changes; toxicity was more pronounced in males. There was no non-toxic dose in this study.

Reproductive and developmental toxicity

The reproductive toxicity of tacrolimus was evaluated in Segment 1 (rats), Segment 2 (rats and rabbits) and Segment 3 (rats) studies. The results of these studies are summarized below in Table 33.

Table 33: Reproductive and Developmental Toxicity Studies of Orally Administered Tacrolimus

Study	Oral Dose (mg/kg/day)		Major Findings	
			Parental	F_1 Offspring
Segment 1, Rat	0.32		No observable effect	No observable effect
	1		Incomplete delivery	No observable effect
	3.2		↓Body weight with ↓food consumption	Some lethality; ↓Implantation ↑Post-implantation loss

Study	Oral Dose (mg/kg/day)		Major Findings	
			Parental	F_1 Offspring
			↓Male copulatory index ↑Copulatory interval Incomplete delivery ↑Female diestrus period	↓Embryo/offspring viability
Segment 2, Rat	0.32		No observable effect	No observable effect
	1		No observable effect	↓Fetal body weight
	3.2		Some lethality; ↓Body weight with ↓food consumption	↓Fetal body weight ↑Post-implantation loss ↓Offspring viability ↑Skeletal variations
Segment 2, Rabbit	0.1		↓Body weight	No observable effect
	0.32		↓Body weight Abortions	↑Developmental variations
	1		↓Body weight Abortions	↑Developmental variations ↑Post-implantation loss ↓Viable fetuses ↑Morphological variations
Segment 3, Rat	0.32, 1		No observable effect	No observable effect
	3.2		↓Body weight	↓Body weight

Tacrolimus subcutaneously administered to male rats at doses of 2 or 3 mg/kg/day (1.6 to 6.4 times the clinical dose range based on body surface area) resulted in a dose-related decrease in sperm count.

Special toxicology

The toxicity of tacrolimus degradation products and a dosage form excipient were studied for antigenicity, effects on morphology and function of pancreas, and local irritation in several species. The acute IV toxicity of known heat- and light-degradation products of tacrolimus, a tacrolimus tautomer, related compounds, and a tacrolimus metabolite was assessed in mice. The acute toxicity of these compounds was not greater than that of tacrolimus as bulk drug or as the IV formulation.

Antigenicity studies produced no antibody formation in mice, and no skin reactions, sensitization, or delayed hypersensitivity reactions.

Tacrolimus produced a reversible, dose-dependent, pancreatic islet cell toxicity in rats; there were no effects on pancreatic exocrine function.

The irritation potential of the IV formulation of tacrolimus was similar to that of 0.425% acetic acid.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

TRANSPLANTATION

PrPROGRAF®

tacrolimus for injection

tacrolimus immediate-release capsules, USP

This Patient Medication Information is written for the person who will be taking **PROGRAF**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **PROGRAF**, talk to a healthcare professional.

Serious warnings and precautions box

- Prograf may increase your chances of getting serious infection and some kinds of cancer.
- Prograf should only be prescribed by doctors with experience in the use of immunosuppressive (anti-rejection) drugs and the management of organ transplants.

What PROGRAF is used for:

- Prograf is used to help prevent organ rejection.
- It is used in patients who have received a kidney, a liver transplant or a heart transplant.
- It is used along with other medicines.
- Prograf is the brand name for tacrolimus immediate-release capsules.

How PROGRAF works:

Your immune system is your body's defence system. Immunity is the way your body protects itself from infections and other foreign material. When you receive a transplant, your immune system recognizes the transplanted organ as foreign and will try to reject it. Prograf is an anti-rejection drug that helps your body accept your transplanted organ.

The ingredients in PROGRAF are:

Medicinal ingredients: tacrolimus

Non-medicinal ingredients:

Prograf immediate-release capsules contain croscarmellose sodium, hydroxypropylmethylcellulose 2910, lactose and magnesium stearate. The 1 mg capsule shell also contains gelatin and titanium dioxide and the 0.5 mg and 5 mg capsule shells also contain gelatin, titanium dioxide and ferric oxide.

Prograf injection contains polyoxyl 60 hydrogenated castor oil and dehydrated alcohol.

PROGRAF comes in the following dosage form(s):

Prograf is available in 0.5 mg, 1 mg and 5 mg immediate-release capsules.

Prograf solution for injection is available as a 5 mg / mL solution.

Do not use PROGRAF if:

- you are allergic to tacrolimus.
- you are allergic to any of the other ingredients in this medication or to a component of the container.
- you are allergic to castor oil which is in the Prograf solution for injection only.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PROGRAF. Talk about any health conditions or problems you may have, including if you:

- have heart problems including congenital or acquired QT prolongation.
- have or have had kidney problems.
- have a rare hereditary disease of galactose intolerance, such as the Lapp lactase deficiency or glucose-galactose malabsorption, because Prograf capsules contain lactose.
- are taking a diuretic.
- were previously taking cyclosporine to protect your organ.

Other warnings you should know about:

Allergic reactions (injection):

- Prograf injection can cause serious allergic reactions. These may be caused by the castor oil which is part of the Prograf solution for injection. Do not use Prograf solution for injection if you are allergic to castor oil. Tell your doctor if you are allergic to castor oil.

Vaccinations and other medicines:

- Prograf is often given with other medications. Make sure you know if you are to stop, or continue, other immunosuppressive drugs you had been taking.
- Talk to your doctor if you have had or are planning to have any vaccinations including live vaccines. The vaccination may not work as well as it should or may result in serious side effects.
- You should avoid taking too much potassium while you are taking Prograf. Talk to your doctor if you are not sure if your potassium intake is high.

New onset diabetes:

- Prograf may cause new onset diabetes in kidney transplant patients. Your doctor may order tests to monitor your blood glucose levels.

General:

- Be sure that you are taking the correct dose and correct formulation of tacrolimus (Prograf, immediate-release capsules) prescribed by your doctor.

Pregnancy:

- Tell your doctor if you are pregnant, think you might be pregnant, are planning to become pregnant, or father a child while taking Prograf. Prograf can cause abnormalities and malformations in an unborn baby. You should not use Prograf if you are pregnant unless advised by your doctor. It is not known if it will harm your unborn baby.
  You should use a reliable method of birth control before, during your treatment and for 6 weeks after stopping your treatment with Prograf. A study was done on pregnant women with organ transplants who took tacrolimus or similar drugs. Results did not show a higher risk of major birth defects with tacrolimus. It showed that women who took tacrolimus had more miscarriages than those taking similar drugs. Those with kidney transplants taking tacrolimus tended to have more pre-eclampsia. This condition causes or worsens high blood pressure and a lot of protein in the urine.

Breastfeeding:

- Tell your doctor if you are breastfeeding or planning to breastfeed your baby. Prograf can pass into your breast milk. It is not known if this can harm your baby. You should not breastfeed your baby while you are taking Prograf.

Skin protection:

- Prograf may increase your chances of getting some kinds of cancer including skin cancer. You must protect your skin from sunlight and UV light. Wear protective clothing and use a sunscreen with a high sun protection factor (SPF 30 or higher) while you are taking Prograf.

Driving and using machines:

- Prograf may cause vision and nervous system problems. Wait until you know how Prograf affects you before driving or using machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines. Tell all health professionals you see that you are taking Prograf.

The following may [also] interact with PROGRAF:

- Antacids: magnesium aluminum hydrochloride
- Medicines used to treat irregular heart rhythm such as amiodarone
- Medicines used for fungal infections such as clotrimazole, fluconazole, ketoconazole, itraconazole, voriconazole
- Medicines used to treat circulation and heart problems such as diltiazem, nicardipine, nifedipine, verapamil
- Medicines used to treat stomach disorders such as cisapride, metoclopramide, lansoprazole, omeprazole
- Medicines used for bacterial infections such as erythromycin, clarithromycin, troleandomycin
- Other drugs such as bromocriptine, cimetidine, chloramphenicol, cyclosporine, danazol, ethinyl estradiol, methylprednisolone, nefazodone
- Medicines used to treat HIV infection such as ritonavir, nelfinavir, and saquinavir
- Medicines used to treat HCV infection such as sofosbuvir, telaprevir and boceprevir
- Cytomegalovirus (CMV) antiviral medicines such as letermovir

- Anticonvulsant medicines used to control seizure such as carbamazepine, phenobarbital, phenytoin
- Anti-infective medicines used to treat tuberculosis such as rifampin, rifabutin, caspofungin
- Sirolimus, a medicine used to avoid rejection of the kidney transplant
- Potassium sparing diuretics such as amiloride, triamterene, or spironolactone
- St. John's wort (*Hypericum perforatum*), an herbal product used for depression
- *Schisandra sphenanthera* extracts, an herbal product with various uses
- Grapefruits or grapefruit juice
- Cannabidiol (used for the treatment of seizures and other conditions).

How to take PROGRAF:

Prograf® – Capsules:

- Take Prograf exactly as your doctor has told you to. Your doctor will tell you when and how many times a day to take Prograf.
- Try to take your doses at the same time every day. This will help keep the same amount of Prograf in your body so it can continue to protect your transplanted organ.
- Space your doses of Prograf as evenly as you can throughout the day. For example, if you take Prograf twice a day, doses should be 12 hours apart. Ask your transplant nurse or pharmacist about a dosing schedule that best fits your lifestyle.
- Prograf may be taken with or without food, but it is best to be consistent. Once you decide when you are going to take it in relation to food, do it the same way each time.
- Swallow the capsules whole. Do not cut, crush, or chew the Prograf capsule.
- Avoid contact of your skin or mucous membranes with the tacrolimus powder inside the Prograf capsule. If such contact occurs, wash the skin and eyes.

Make sure that you receive the same tacrolimus medicine every time you collect your prescription. If the appearance of Prograf is not the same as usual, if dosage instructions have changed or if the brand name has changed, speak to your doctor or pharmacist as soon as possible to make sure that you have the right medicine. Serious side effects can occur if you do not take the exact tacrolimus medication that you are supposed to take. You need to be taking the exact tacrolimus medicine prescribed to you by your doctor to ensure that your organ is protected.

Prograf® – Solution for Injection:

- If you are receiving the Prograf solution for injection, it will be given to you by your doctor.
- Your doctor will make sure that Prograf is prepared correctly before it is given to you.
- It will be infused into your vein.
- Follow all instructions given to you by your doctor.

Usual dose:

Your doctor will give you specific instructions about how much Prograf you should take each day. Your doctor has decided the dose you should take based on your medical condition and response to the drug. **It is very important to take the exact amount of Prograf that your doctor has told you.**

Blood tests are one of the ways your doctor decides how much Prograf you need. Based on these tests and your response to Prograf, your doctor may change your dose from time to time. **Do not change your dose on your own.**

Overdose:

If you think you, or a person you are caring for, have taken too much PROGRAF, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

Missing even a few doses of Prograf may cause your body to reject your transplanted organ. That is why it is very important to take each dose as your doctor prescribed. If you have trouble remembering doses, or if you are not sure how to take them, talk to your doctor. Be sure to discuss any concerns you have about taking Prograf as prescribed.

If you do miss a dose of Prograf, do not try to catch up on your own and take a missed dose. Instead, call your doctor or pharmacist right away for advice. Ask your doctor ahead of time what to do about missed doses.

Never allow your medication to run out between refills. Be sure to take enough medication with you when you will be away from home for a long period of time.

Possible side effects from using PROGRAF:

These are not all the possible side effects you may feel when taking Prograf®. If you experience any side effects not listed here, contact your healthcare professional.

Common side effects may include:

- Anxiety
- Constipation
- Diarrhea
- Edema (swelling) of the legs and arms
- Headache
- Insomnia
- Tremor (shaking), especially of the hands

Prograf can cause abnormal blood test results. Your doctor may perform blood tests and will interpret the results.

Like other medicines, Prograf may cause side effects in some people. If you think that you are having side effects, talk to your doctor right away. **DO NOT stop taking Prograf on your own.**

It is important to regularly tell your doctor how you are feeling and if you have developed any new symptoms while taking Prograf.

Serious side effects and what to do about them

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Very common			
Anemia (decreased red blood cells): dizziness, fainting, fatigue, feeling unwell, lack of energy, pale skin, pale stool, rapid heartbeat, shortness of breath, weakness		✓	
Diabetes (high blood sugar): blurred vision, confusion, drowsiness, frequent urination, fruity smell on your breath, increased thirst and hunger, loss of appetite, nausea, stomach pain or vomiting		✓	
Hypertension (high blood pressure): usually without symptoms but can appear as altered vision, dizziness, fainting, headache, head feeling "light", tinnitus (buzzing or hissing in the ears), vertigo		✓	
Infections of urinary tract: frequent urination, pain or burning sensation when urinating, pain or pressure in lower back or abdomen, urine not looking or smelling normal		✓	
Leukopenia (decreased white blood cells): aches, fatigue, fever, infections, mouth ulcers, pains and flu-like symptoms, sweating		✓	
Liver problem: back pain, yellowing of the skin or eyes		✓	
Kidney problem: back and abdominal pain, change in the colour of urine (pale or dark), less urine produced, pain or discomfort when urinating, swelling of the legs and ankles		✓	
Common			
Infections of upper respiratory tract (sinus, nose, throat): common cold symptoms, cough, facial pain		✓	

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
or pressure, fever, headache, nasal congestion, runny or stuffy nose, sneezing, sore throat			
Infections: chills, fatigue, feeling unwell, fever, sore throat		✓	
Electrolyte disturbance (high/low blood levels of calcium, magnesium and/or phosphate): dehydration, diarrhea, eating disorders, vomiting		✓	
Uncommon			
Thrombotic microangiopathy: fever and bruising under the skin that may appear as red dots, with or without unexplained tiredness, confusion, yellowing of the skin or eyes, reduced urine output. When tacrolimus is taken together with sirolimus or everolimus, the risk of developing these symptoms may increase		✓	
Rare/Unknown			
Posterior encephalopathy syndrome (a nervous system disorder): change in mental state, coma, confusion, numbness and tingling, headache, seizures, vision changes		✓	
Heart problems: abnormal heart rhythms, chest pain, dizziness, fainting, low or no pulse, nausea, pain irradiating in the arm, neck or back, palpitations, short breath, sweating			✓
Gastrointestinal perforation (a hole in your stomach or bowels): chills or fever, nausea, severe abdominal pain, vomiting			✓
Respiratory distress: chest pain, difficulty to breathe, short breath			✓
Sepsis: confusion, fever, low body temperature, rapid breathing, rapid heart rate, swelling			✓

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Cancer: new or abnormal mole on the skin, patch on the skin that doesn't heal, or is itchy, bleeds or oozes, size or shape of an existing mole, skin ulcers (broken skin with an open wound), appearance of lumps in your breast or other areas of the body, a nagging cough or hoarseness, persistent and severe headaches, swollen lymph nodes, a change in your bladder or bowel habits, skin changes such as new or changing discoloration, lesions or lumps.		✓	
Progressive multifocal leukoencephalopathy (PML) (rare brain infection): changes in thinking, clumsiness of limbs, confusion, disturbance of vision, progressive weakness on one side of the body, memory and orientation, personality changes		✓	
Pure red cell aplasia (PRCA) (bone marrow stops producing red cells): dizziness, fainting, fatigue, feeling unwell, pale skin, pale stools, rapid heartbeat, shortness of breath, weakness		✓	
Febrile Neutropenia (decrease in white blood cells): fever		✓	
Optic neuropathy (problem with the nerves in your eye): change or loss of vision		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store Prograf capsules at room temperature (15°C – 30°C).

Store Prograf solution for injection between 15°C and 25°C.

Keep out of reach and sight of children.

If you want more information about PROGRAF:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (Drug Product Database: Access the database); the manufacturer's website http://www.astellas.ca/; or by calling 1-888-338-1824.

This leaflet was prepared by Astellas Pharma Canada, Inc.

Date of Authorization: 2025-12-17

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

RHEUMATOID ARTHRITIS

PrPROGRAF®

tacrolimus immediate-release capsules, USP

This Patient Medication Information is written for the person who will be taking **PROGRAF**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **PROGRAF**, talk to a healthcare professional.

Serious warnings and precautions box

- Prograf may increase your chances of getting serious infection and some kinds of cancer.
- Prograf should only be prescribed by doctors with experience in the use of immunosuppressive (anti-rejection) drugs and the management of organ transplants.

What PROGRAF is used for:

- Prograf is used to treat rheumatoid arthritis (RA) in adult patients.
- It is used in patients whose RA could not be treated with other medicines, called disease modifying anti-rheumatic drugs (DMARDs).
- It is used alone or in combination with other medicines.

How PROGRAF works:

A normal immune system leaves healthy body tissues alone. In people with rheumatoid arthritis, the immune system attacks normal body tissues causing damage and inflammation, especially in the tissues of your joints.
The way tacrolimus works in rheumatoid arthritis is not known. Approximately 8 weeks of treatment with Prograf may be required before any significant improvement is seen in your symptoms of rheumatoid arthritis.

The ingredients in PROGRAF are:

Medicinal ingredients: tacrolimus

Non-medicinal ingredients: Prograf immediate-release capsules contain croscarmellose sodium, hydroxypropylmethylcellulose 2910, lactose and magnesium stearate. The 1 mg capsule shell also contains gelatin and titanium dioxide and the 0.5 mg and 5 mg capsule shells also contain gelatin, titanium dioxide and ferric oxide.

PROGRAF comes in the following dosage form(s):

Prograf is available in 0.5 mg, 1 mg and 5 mg immediate-release capsules.

Do not use PROGRAF if:

- you are allergic to tacrolimus.
- you are allergic to any of the other ingredients in this medication or to a component of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PROGRAF. Talk about any health conditions or problems you may have, including if you:

- have heart problems including congenital or acquired QT prolongation.
- have or have had kidney problems.
- have a rare hereditary disease of galactose intolerance, such as the Lapp lactase deficiency or glucose-galactose malabsorption, because Prograf capsules contain lactose.
- are taking a diuretic.
- were previously taking cyclosporine to protect your organ.

Other warnings you should know about:

Vaccinations and other medicines:

- Prograf is often given with other medications. Make sure you know if you are to stop, or continue, other drugs you had been taking.
- Talk to your doctor if you have had or are planning to have any vaccinations including live vaccines. The vaccination may not work as well as it should or may result in serious side effects.

Pregnancy:

- Tell your doctor if you are pregnant, think you might be pregnant, are planning to become pregnant, or father a child while taking Prograf. Prograf can cause abnormalities and malformations in an unborn baby. You should not use Prograf if you are pregnant unless advised by your doctor. It is not known if it will harm your unborn baby. You must use a reliable method of birth control before, during your treatment and for 6 weeks after stopping your treatment with Prograf. A study was done on pregnant women with organ transplants who took tacrolimus or similar drugs. Results did not show a higher risk of major birth defects with tacrolimus. It showed that women who took tacrolimus had more miscarriages than those taking similar drugs. Those with kidney transplants taking tacrolimus tended to have more pre-eclampsia. This condition causes or worsens high blood pressure and a lot of protein in the urine.

Breastfeeding:

- Tell your doctor if you are breastfeeding or planning to breastfeed your baby. Prograf can pass into your breast milk. It is not known if this can harm your baby. You should not breastfeed your baby while you are taking Prograf.

Skin protection:

- Prograf may increase your chances of getting some kinds of cancer including skin cancer. You must protect your skin from sunlight and UV light. Wear protective clothing and use a sunscreen with a high sun protection factor (SPF 30 or higher) while you are taking Prograf.

Driving and using machines:

- Prograf may cause vision and nervous system problems. Wait until you know how Prograf affects you before driving or using machines.

General:

- Be sure that you are taking the correct dose and correct formulation of tacrolimus (Prograf, immediate-release capsules) prescribed by your doctor.
- Tell all doctors you see that you are taking Prograf.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may [also] interact with PROGRAF:

- Antacids: magnesium aluminum hydrochloride
- Medicines used to treat irregular heart rhythm such as amiodarone
- Medicines used for fungal infections such as clotrimazole, fluconazole, ketoconazole, itraconazole, voriconazole
- Medicines used to treat circulation and heart problems such as diltiazem, nicardipine, nifedipine, verapamil
- Medicines used to treat stomach disorders such as cisapride, metoclopramide, lansoprazole, omeprazole
- Medicines used for bacterial infections such as erythromycin, clarithromycin, troleandomycin
- Other drugs such as bromocriptine, cimetidine, chloramphenicol, cyclosporine, danazol, ethinyl estradiol, methylprednisolone, nefazodone
- Medicines used to treat HIV infection such as ritonavir, nelfinavir, and saquinavir
- Medicines used to treat HCV infection such as sofosbuvir, telaprevir and boceprevir
- Cytomegalovirus (CMV) antiviral medicines such as letermovir
- Anticonvulsant medicines used to control seizure such as carbamazepine, phenobarbital, phenytoin
- Anti-infective medicines used to treat tuberculosis such as rifampin, rifabutin, caspofungin
- Sirolimus, a medicine used to avoid rejection of the kidney transplant
- Potassium sparing diuretics such as amiloride, triamterene, or spironolactone
- St. John's wort (*Hypericum perforatum*), an herbal product used for depression
- *Schisandra sphenanthera* extracts, an herbal product with various uses
- Grapefruits or grapefruit juice
- Cannabidiol (used for the treatment of seizures and other conditions).

How to take PROGRAF:

Prograf may be taken with or without food, but it is best to be consistent. Once you decide when you are going to take it in relation to food, do it the same way each time.

Swallow the capsules whole. Do not cut, crush, or chew the Prograf capsule.

Avoid contact of your skin or mucous membranes with the tacrolimus powder inside the Prograf capsule. If such contact occurs, wash the skin and eyes.

Try to take your doses at the same time every day.

Usual dose:

Your doctor will decide the dosage. The usual adult dosage is 3 mg taken once daily.

Make sure that you receive the same tacrolimus medicine every time you collect your prescription. If the appearance of Prograf is not the same as usual, speak to your doctor or pharmacist as soon as possible to make sure that you have the right medicine.

Overdose:

If you think you, or a person you are caring for, have taken too much PROGRAF, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you do miss a dose of Prograf, skip this dose and take the next one at the regular scheduled time; do not take twice your dose. Call your doctor or pharmacist right away for advice. It is also a good idea to ask your doctor ahead of time what to do about missed doses.

Do not allow your medication to run out between refills. Be sure to take enough medication with you when you will be away from home for a long extended period of time.

Possible side effects from using PROGRAF:

These are not all the possible side effects you may feel when taking Prograf®. If you experience any side effects not listed here, contact your healthcare professional.

Common side effects may include:

- Anxiety
- Constipation
- Diarrhea
- Edema (swelling) of the legs and arms
- Headache
- Insomnia
- Tremor (shaking), especially of the hands

Prograf can cause abnormal blood test results. Your doctor may perform blood tests and will interpret the results.

Like other medicines, Prograf may cause side effects in some people. If you think that you are having side effects, talk to your doctor right away.

It is important to regularly tell your doctor how you are feeling and if you have developed any new symptoms while taking Prograf.

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Very common			
Anemia (decreased red blood cells): dizziness, fainting, fatigue, feeling unwell, lack of energy, pale skin, pale stool, rapid heartbeat, shortness of breath, weakness		✓	
Diabetes (high blood sugar): blurred vision, confusion, drowsiness, frequent urination, fruity smell on your breath, increased thirst and hunger, loss of appetite, nausea, stomach pain or vomiting		✓	
Hypertension (high blood pressure): usually without symptoms but can appear as altered vision, dizziness, fainting, headache, head feeling “light”, tinnitus (buzzing or hissing in the ears), vertigo		✓	
Infections of urinary tract: frequent urination, pain or burning sensation when urinating, pain or pressure in lower back or abdomen, urine not looking or smelling normal		✓	
Leukopenia (decreased white blood cells): aches, fatigue, fever, infections, mouth ulcers, pains and flu-like symptoms, sweating		✓	
Liver problem: back pain, yellowing of the skin or eyes		✓	
Kidney problem: back and abdominal pain, change in the colour of urine (pale or dark), less urine produced, pain or discomfort when urinating, swelling of the legs and ankles		✓	
Common			
Infections of upper respiratory tract (sinus, nose, throat): common cold symptoms, cough, facial pain or pressure, fever, headache, nasal		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
congestion, runny or stuffy nose, sneezing, sore throat			
Infections: chills, fatigue, feeling unwell, fever, sore throat		✓	
Electrolyte disturbance (high/low blood levels of calcium, magnesium and/or phosphate): dehydration, diarrhea, eating disorders, vomiting		✓	
Uncommon			
Thrombotic microangiopathy: fever and bruising under the skin that may appear as red dots, with or without unexplained tiredness, confusion, yellowing of the skin or eyes, reduced urine output. When tacrolimus is taken together with sirolimus or everolimus, the risk of developing these symptoms may increase		✓	
Rare			
Posterior encephalopathy syndrome (a nervous system disorder): change in mental state, coma, confusion, numbness and tingling, headache, seizures, vision changes		✓	
Heart problems: abnormal heart rhythms, chest pain, dizziness, fainting, low or no pulse, nausea, pain irradiating in the arm, neck or back, palpitations, short breath, sweating			✓
Gastrointestinal perforation (a hole in your stomach or bowels): chills or fever, nausea, severe abdominal pain, vomiting			✓
Respiratory distress: chest pain, difficulty to breathe, short breath			✓
Sepsis: confusion, fever, low body temperature, rapid breathing, rapid heart rate, swelling			✓

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Cancer: new or abnormal mole on the skin, patch on the skin that doesn't heal, or is itchy, bleeds or oozes, size or shape of an existing mole, skin ulcers (broken skin with an open wound), appearance of lumps in your breast or other areas of the body, a nagging cough or hoarseness, persistent and severe headaches, swollen lymph nodes, a change in your bladder or bowel habits, skin changes such as new or changing discoloration, lesions or lumps.		✓	
Progressive multifocal leukoencephalopathy (PML) (rare brain infection): changes in thinking, clumsiness of limbs, confusion, disturbance of vision, progressive weakness on one side of the body, memory and orientation, personality changes		✓	
Pure red cell aplasia (PRCA) (bone marrow stops producing red cells): dizziness, fainting, fatigue, feeling unwell, pale skin, pale stools, rapid heartbeat, shortness of breath, weakness		✓	
Febrile Neutropenia (decrease in white blood cells): fever		✓	
Optic neuropathy (problem with the nerves in your eye): change or loss of vision		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store Prograf capsules at room temperature (15°C – 30°C).

Keep out of reach and sight of children.

If you want more information about PROGRAF:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (Drug Product Database: Access the database); the manufacturer's website http://www.astellas.ca/; or by calling 1-888-338-1824.

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