# Prograf®

tacrolimus capsules
tacrolimus injection (for intravenous infusion only)

**WARNING**
Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immuno-suppressive therapy and management of organ transplant patients should prescribe Prograf. For patients with lupus nephritis, this product should be prescribed by physicians experienced in lupus nephritis therapy. 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.

## 1 INDICATIONS AND USAGE

Prograf is indicated for the prophylaxis of organ rejection in patients receiving allogenic liver or kidney transplants. It is recommended that Prograf be used concomitantly with adrenal corticosteroids. Because of the risk of anaphylaxis Prograf injection should be reserved for patients unable to take Prograf capsules orally. In kidney transplant recipients, it is recommended that Prograf be used in conjunction with azathioprine or mycophenolate mofetil (MMF). The safety and efficacy of the use of Prograf with sirolimus has not been established (see CLINICAL STUDIES).
Prograf is indicated for Lupus nephritis (in a case where the effect of steroids is insufficient or administration of steroids is difficult because of their adverse reactions).
For lupus nephritis, the efficacy and safety of this product for patients in an acute phase with high disease activity has not been established.

## 2 DOSAGE AND ADMINISTRATION

***Prograf injection (tacrolimus injection)***
***For Intravenous Infusion Only***
**NOTE: Anaphylactic reactions have occurred with injectable containing castor oil derivatives. See WARNINGS.**

In patients unable to take oral Prograf capsules, therapy may be initiated with Prograf injection. The initial dose of Prograf should be administered no sooner than 6 hours after transplantation. The recommended starting dose of Prograf injection is 0.03-0.05 mg/kg/day as a continuous 24-hour intravenous infusion. 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 injection should be continued only until the patient can tolerate oral administration of Prograf capsules.

***Preparation for Administration/Stability***
Prograf 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. Tacrolimus is not compatible with PVC. Tubing, syringes and other equipment used to prepare or administer the tacrolimus products should not contain PVC. The diluted infusion solution stored in a PVC container decreased 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 absorption 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 pH9 or greater (e.g., ganciclovir or acyclovir).

***Prograf capsules (tacrolimus capsules)***
**Transplantation:**
**Summary of Initial Oral Dosage Recommendations and Observed Whole Blood Trough Concentrations**

| Patient Population | Recommended Initial Oral Dose[a] | Observed Whole Blood Trough Concentrations |
|---|---|---|
| Adult kidney transplant patients | | |
| In combination with azathioprine | 0.2 mg/kg/day | month 1-3: 7-20 ng/mL<br>month 4-12: 5-15 ng/mL |
| In combination with MMF/IL-2 receptor antagonist[b] | 0.1 mg/kg/day | month 1-12: 4-11 ng/mL |
| Adult liver transplant patients | 0.10-0.15 mg/kg/day | month 1-12: 5-20 ng/mL |
| Pediatric liver transplant patients | 0.15-0.20 mg/kg/day | month 1-12: 5-20 ng/mL |

a) Note: two divided doses, q12h.
b) In a second smaller study, the initial dose of tacrolimus was 0.15-0.2 mg/kg/day and observed tacrolimus concentrations were 6-16 ng/mL during month 1-3 and 5-12 ng/mL during month 4-12.

***Liver Transplantation***
It is recommended that patients initiate oral therapy with Prograf capsules if possible. If intravenous therapy is necessary, conversion from intravenous 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. The recommended starting oral dose of Prograf capsules is 0.10-0.15 mg/kg/day administered in two divided daily doses every 12 hours. Co-administered grapefruit juice has been reported to increase tacrolimus blood trough concentrations in liver transplant patients (see Drugs that May Alter Tacrolimus Concentrations).

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.

Dosage and typical tacrolimus whole blood trough concentrations are shown in the table above; blood concentration details are described in Therapeutic Drug Monitoring: *Liver Transplantation* below.

***Kidney Transplantation***
The recommended starting oral dose of Prograf administered every 12 hours in two divided doses is 0.2 mg/kg/day when used in combination with azathioprine or 0.1 mg/kg/day when used in combination with MMF and IL-2 receptor antagonist (see CLINICAL STUDIES). 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 $\leq$ 4 mg/dL). Black patients may

require higher doses to achieve comparable blood concentrations. Dosage and typical tacrolimus whole blood trough concentrations are shown in the table above; blood concentration details are described in Therapeutic Drug Monitoring: *Kidney Transplantation* below.
The data in kidney transplant patients indicate that the Black patients required a higher dose to attain comparable trough concentrations compared to Caucasian patients.

| **Time After Transplant** | **Caucasian (n = 114)** | | **Black (n = 56)** | |
|---|---|---|---|---|
| | **Dose (mg/kg)** | **Trough Level (ng/mL)** | **Dose (mg/kg)** | **Trough Level (ng/mL)** |
| Day 7 | 0.18 | 12.0 | 0.23 | 10.9 |
| Month 1 | 0.17 | 12.8 | 0.26 | 12.9 |
| Month 6 | 0.14 | 11.8 | 0.24 | 11.5 |
| Month 12 | 0.13 | 10.1 | 0.19 | 11.0 |

***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 should be initiated in pediatric patients at a starting intravenous 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 transplantation patients is limited.

***Patients with Hepatic or Renal Dysfunction***
Due to the reduced clearance and prolonged half-life, patients with severe hepatic impairment (Pugh ≥ 10) may require lower doses of Prograf. Close monitoring of blood concentrations is warranted.

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. Prograf therapy usually should be delayed up to 48 hours or longer in patients with post-operative oliguria.

***Conversion from One Immunosuppressive Regimen to Another***
Prograf should not be used simultaneously with cyclosporine. Prograf or cyclosporine should be discontinued at least 24 hours before initiating the other. In the presence of elevated Prograf or cyclosporine concentrations, dosing with the other drug usually should be further delayed.

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

The relative risks of toxicity and efficacy failure are related to tacrolimus whole blood trough concentrations. Therefore, monitoring of whole blood trough concentrations is recommended to assist in the clinical evaluation of toxicity and efficacy failure.

Two methods have been used for the assay of tacrolimus, a microparticle enzyme immunoassay (MEIA) and an ELISA. Both methods have the same monoclonal

antibody for tacrolimus. Comparison of the concentrations in published literature to patient concentrations using the current assays must be made with detailed knowledge of the assay methods and biological matrices employed. 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 at room temperature or in a refrigerator and assayed within 7 days; if samples are to be kept longer they should be deep frozen at -20$^{o}$C for up to 12 months.

***Liver Transplantation***
*Therapeutic Drug Monitoring*, 1995, Volume 17, Number 6 contains a consensus document and several position papers regarding the therapeutic monitoring of tacrolimus from the 1995 International Consensus Conference on Immunosuppressive Drugs. Refer to these manuscripts for further discussions of tacrolimus monitoring.

***Kidney Transplantation***
A clinical trial of Prograf in conjunction with MMF and basiliximab, approximately 80% of patients maintained tacrolimus whole trough blood concentrations between 6-16 ng/mL during month 1-3 and, then, between 5-12 ng/mL from month 4 through 1 year.

**Lupus nephritis:**
For adults, usually, a dose of 3 mg as tacrolimus is orally administered, once daily after supper.

In order to avoid development of adverse reactions in patients with lupus nephritis, it is recommended that the blood levels be monitored monthly for 3 months after the start of tacrolimus therapy; thereafter, the blood levels approximately 12 hours after the administration should be monitored periodically, and the dosage should be adjusted. If this product does not improve the clinical signs of nephritis, such as urinary protein excretion, or the immunological findings after continuous treatment for 2 months, the treatment with this product should be discontinued, or the patient should be switched to another product. If treatment with this product is sufficiently effective, it is recommended that the dose should be reduced to the lowest level possible that will still allow the effect to be maintained.

## 3 DOSAGE FORMS AND STRENGTHS

**Prograf capsules (tacrolimus capsules) 0.5 mg**
Oblong, light yellow, branded with red “0.5 mg” on the capsule cap and “ f 607” on the capsule body, containing 0.5 mg tacrolimus.

**Prograf capsules (tacrolimus capsules) 1 mg**
Oblong, white, branded with red “1 mg” on the capsule cap and “f 617” on the capsule body, containing the equivalent of 1 mg anhydrous tacrolimus.

**Prograf injection (tacrolimus injection) 5 mg (for intravenous infusion only)**
Sterile solution in 1-mL ampoules containing the equivalent of 5 mg of anhydrous tacrolimus per mL.

## 4 CONTRAINDICATIONS

Prograf is contraindicated in patients with a hypersensitivity to tacrolimus. Prograf injection is contraindicated in patients with a hypersensitivity to HCO-60 (polyoxyl 60 hydrogenated castor oil).

## 5 WARNINGS AND PRECAUTIONS

**WARNINGS:**

(See boxed WARNING)

**Post-Transplant Diabetes Mellitus**

Insulin-dependent post-transplant diabetes mellitus (PTDM) was reported in 20% of Prograf-treated kidney transplant patients without pre-transplant history of diabetes mellitus in the Phase III study (see Tables below). The median time to onset of PTDM was 68 days. Insulin dependence was reversible in 15% of these patients at one year and in 50% at two years post-transplant. Black and Hispanic kidney transplant patients were at an increased risk of development of PTDM.

Incidence of Post-transplant Diabetes Mellitus (PTDM)* and Insulin Use at 2 years in Kidney Transplant Recipients

| **Status of PTDM*** | **Prograf** | **CBIR** |
|---|---|---|
| Patients without pre-transplant history of diabetes mellitus | 151 | 151 |
| New onset PTDM*, 1st Year | 30/151 (20%) | 6/151 (4%) |
| Still insulin dependent at one year in those without prior history of diabetes | 25/151 (17%) | 5/151 (3%) |
| New onset PTDM* post 1 year | 1 | 0 |
| Patients with PTDM* at 2 years | 16/151 (11%) | 5/151 (3%) |

*use of insulin for 30 or more consecutive days, with < 5 day gap, without a prior history of insulin dependent diabetes mellitus or non-insulin dependent diabetes mellitus.

Development of Post-transplant Diabetes Mellitus (PTDM) by Race and by Treatment Group during First Year Post Kidney Transplantation

| **Patient Race** | **Prograf** | | **CBIR** | |
|---|---|---|---|---|
| | **No. of Patients at Risk** | **Patients Who Developed PTDM*** | **No. of Patients at Risk** | **Patients Who Developed PTDM*** |
| Black | 41 | 15 (37%) | 36 | 3 (8%) |
| Hispanic | 17 | 5 (29%) | 18 | 1 (6%) |
| Caucasian | 82 | 10 (12%) | 87 | 1 (1%) |
| Other | 11 | 0 (0%) | 10 | 1 (10%) |
| Total | 151 | 30 (20%) | 151 | 6 (4%) |

* use of insulin for 30 or more consecutive days, with < 5 day gap, without a prior history of insulin dependent diabetes mellitus or non-insulin dependent diabetes mellitus.

Insulin-dependent post-transplant diabetes mellitus was reported in 18% and 11% of Prograf-treated liver transplant patients and was reversible in 45% and 31% of these patients at one year post transplant, in the U.S. and European randomized studies, respectively (see Table below). Hyperglycemia was associated with the use of Prograf in 47% and 33% of liver transplant recipients in the U.S. and European randomized studies, respectively, and may require treatment (see ADVERSE REACTIONS).

Incidence of Post-transplant Diabetes Mellitus (PTDM)* and Insulin Use at One Year in Liver Transplant Recipients

| **Status of PTDM*** | **US Study** | | **European Study** | |
|---|---|---|---|---|
| | **Prograf** | **CBIR** | **Prograf** | **CBIR** |
| Patients at risk** | 239 | 236 | 239 | 249 |
| New Onset PTDM* | 42 (18%) | 30 (13%) | 26 (11%) | 12 (5%) |
| Patients still on insulin at 1 year | 23 (10%) | 19 (8%) | 18 (8%) | 6 (2%) |

*use of insulin for 30 or more consecutive days, with < 5 day gap, without a prior history of insulin dependent diabetes mellitus or non-insulin dependent diabetes mellitus.
****** Patients without pre-transplant history of diabetes mellitus.

**Nephrotoxicity**
Prograf can result in both acute and chronic renal function impairment in transplant patients due to its vasoconstrictive effect on renal vasculature, toxic tubulopathy and tubularinterstitial effects. Prograf can cause nephrotoxicity, particularly when used in high doses. Nephrotoxicity was reported in approximately 52% of kidney transplantation patients and in 40% and 36% of liver transplantation patients receiving Prograf in the U.S. and European randomized trials, respectively (see ADVERSE REACTIONS).
Acute renal impairment can result in high serum creatinine, hyperkalemia, decreased secretion of urea, hyperuricemia, and is usually reversible. Chronic renal impairment is characterized by progressive renal dysfunction, increased blood urea and proteinuria. Patients with impaired renal function should be monitored closely as the dosage of Prograf may need to be transiently reduced or discontinued. In patients with persistent elevations of serum creatinine who are unresponsive to dosage adjustments, consideration should be given to changing to another immunosuppressive therapy. Acute renal impairment without active intervention may progress to chronic renal impairment.
Concurrent use of Prograf with other known nephrotoxic drugs could result in potentiation of nephrotoxicity. When concurrent use of tacrolimus with other known nephrotoxic drugs is required, monitor renal function and tacrolimus blood concentrations frequently, and dose adjustments of both tacrolimus and/or concomitant medications should be considered upon initiation, throughout concurrent treatment and at discontinuation of such concomitant drugs. In particular, to avoid excess nephrotoxicity, Prograf should not be used simultaneously with cyclosporine. Prograf or cyclosporine should be discontinued at least 24 hours prior to initiating the other. In the presence of elevated Prograf or cyclosporine concentrations, dosing with the other drug usually should be further delayed (see DRUG INTERACTIONS).

**Hyperkalemia**
Mild to severe hyperkalemia was reported in 31% of kidney transplant recipients and in 45% and 13% of liver transplant recipients treated with Prograf in the U.S. and European randomized trials, respectively, and may require treatment (see ADVERSE REACTIONS). Serum potassium levels should be monitored and potassium-sparing diuretics should not be used during Prograf therapy (see PRECAUTIONS).

**Live vaccine**
As with other immunosuppressants, response to vaccination during treatment with tacrolimus may be less effective. The use of live attenuated vaccines should be avoided.

**Neurotoxicity**
Prograf can cause neurotoxicity, particularly when used in 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 (54%) compared to cyclosporine-treated patients. The incidence of other neurological events in kidney transplant patients was similar in the two treatment groups (see ADVERSE REACTIONS). 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 (see ADVERSE REACTIONS). 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, visual disturbances and hypertension. Diagnosis may be confirmed by radiological procedure. If PRES is suspected or diagnosed, blood pressure control should be maintained and immediate reduction of immunosuppression is advised. This syndrome is characterized by reversal of symptoms upon reduction or discontinuation of immunosuppression.

**Malignancy and Lymphoproliferative Disorders**
As in patients receiving other immunosuppressants, patients receiving Prograf are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immuno-suppression rather than to the use of any specific agent. 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. Because of the danger of over-suppression of the immune system which can increase susceptibility to infection, combination immunosuppressant therapy should be used with caution.

**Latent Viral Infections**
Immunosuppressed patients are at increased risk for opportunistic infections, including latent viral infections. These include BK virus associated nephropathy, JC virus associated progressive multifocal leukoencephalopathy, and CMV infection that have been observed in patients receiving tacrolimus. These infections may lead to serious, including fatal, outcomes.

**Anaphylactic Reactions**
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.

Patients receiving Prograf 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 should be available at the bedside as well as a source of oxygen.

**Pure Red Cell Aplasia**
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 Prograf should be considered.

**Use with CYP3A4 Inhibitors and Inducers Including Those That Prolong QT**
Co-administration with strong CYP3A4-inhibitors (e.g., telaprevir, boceprevir, ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin) and strong inducers (e.g., rifampin, rifabutin) is not recommended without adjustments in the dosing regimen of tacrolimus and subsequent close monitoring of tacrolimus whole blood trough concentrations and tacrolimus-associated adverse reactions.

Early and frequent continued monitoring of tacrolimus blood levels within the first few days of co-administration, as well as monitoring for renal function, for QT prolongation with ECG, and for other side effects is strongly recommended when co-administered with CYP3A4 inhibitors (see DRUG INTERACTIONS). Use of tacrolimus with amiodarone has been reported to result in increased tacrolimus whole blood concentrations with or without concurrent QT prolongation.

**Use with herbal preparation**
Herbal preparations containing St. John's wort (*Hypericum perforatum*) should be avoided when taking tacrolimus due to the risk of interactions that lead to decrease in blood concentrations of tacrolimus and reduced clinical effect of tacrolimus (see DRUG INTERACTIONS).

**PRECAUTIONS:**
**Hypertension**
Hypertension is a common adverse effect of Prograf therapy (see ADVERSE REACTIONS). Mild or moderate hypertension is more frequently reported than severe hypertension. 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 (see DRUG INTERACTIONS).

**Myocardial Hypertrophy**
Myocardial hypertrophy has been reported in association with the administration of Prograf, and 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 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 to 46 ng/mL in children (N = 7, age 2 to 15 years) and 11 to 24 ng/mL in adults (N = 3, age 37 to 53 years).

In patients who develop renal failure or clinical manifestations of ventricular dysfunction while receiving Prograf therapy, echocardiographic evaluation should be considered. If myocardial hypertrophy is diagnosed, dosage reduction or discontinuation of Prograf should be considered.

**Gastrointestinal perforation**
Gastrointestinal perforation has been reported in patients treated with tacrolimus, although all cases were considered a complication of transplant surgery or accompanied by infection, diverticulum, or malignant neoplasm. As gastrointestinal

perforation is a medically important event that may lead to a life-threatening or serious condition, adequate treatments including surgery should be considered immediately after a suspect symptom occurs.

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

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

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

Patients with lupus nephritis are more likely to suffer from hyperlipidemia or hypertension, etc., which are considered to be risk factors for the development of the coronary artery disease associated with systemic erythematosus, the underlying disease, patients being treated with Prograf should also receive appropriate therapy for these corollary diseases.

In patients with lupus nephritis, creatinine clearance decreased after 28 weeks of treatment. There are only a few results from clinical trials in patients with lupus nephritis lasting longer than 28 weeks, and therefore the long-term safety of this product has not been established.

**Information for Patients**
Patients should be informed of the need for repeated appropriate laboratory tests while they are receiving Prograf. They should be given complete dosage instructions, advised of the potential risks during pregnancy, and informed of the increased risk of neoplasia. Patients should be informed that changes in dosage should not be undertaken without first consulting their physician.

Patients should be informed that Prograf can cause diabetes mellitus and should be advised of the need to see their physician if they develop frequent urination, increased thirst or hunger.

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 a sunscreen with a high protection factor.

**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.

**Others**
Medication errors, including inadvertent, unintentional or unsupervised substitution of immediate- or prolonged-release tacrolimus formulations, have been observed. This has led to serious adverse reactions, including graft rejection, or other adverse reactions 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.

The combined administration of cyclosporine and tacrolimus should be avoided and care should be taken when administering tacrolimus to patients who have previously received cyclosporine.

## 6 ADVERSE REACTIONS

***Liver Transplantation***

The principal adverse reactions of Prograf are tremor, headache, diarrhea, hypertension, nausea, and abnormal renal function. 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 (see WARNINGS).

The incidence of adverse events was determined in two randomized comparative liver transplant trials among 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 also included different patient populations and patients were treated with immunosuppressive regimens of differing intensities. Adverse events reported in ≥ 15% in tacrolimus patients (combined study results) are presented below for the two controlled trials in liver transplantation:

**Liver Transplantation: Adverse Events Occurring in ≥ 15% of Prograf-Treated Patients**

| | U.S. STUDY (%) | | EUROPEAN STUDY (%) | |
|---|---|---|---|---|
| | Prograf N = 250 | CBIR N = 250 | Prograf N = 264 | CBIR N = 265 |
| **Nervous System** | | | | |
| Headache (see WARNINGS) | 64 | 60 | 37 | 26 |
| Tremor (see WARNINGS) | 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 (see PRECAUTIONS) | 47 | 56 | 38 | 43 |
| **Urogenital** | | | | |
| Kidney Function Abnormal (see WARNINGS) | 40 | 27 | 36 | 23 |
| Creatinine (see WARNINGS) | 39 | 25 | 24 | 19 |
| BUN Increased (see WARNINGS) | 30 | 22 | 12 | 9 |
| Urinary Tract Infection | 16 | 18 | 21 | 19 |
| Oliguria | 18 | 15 | 19 | 12 |
| **Metabolic and Nutritional** | | | | |
| Hyperkalemia (see WARNINGS) | 45 | 26 | 13 | 9 |
| Hypokalemia | 29 | 34 | 13 | 16 |
| Hyperglycemia (see WARNINGS) | 47 | 38 | 33 | 22 |
| Hypomagnesemia | 48 | 45 | 16 | 9 |
| **Hemic and Lymphatic** | | | | |
| Anemia | 47 | 38 | 5 | 1 |
| Leukocytosis | 32 | 26 | 8 | 8 |
| Thrombocytopenia | 24 | 20 | 14 | 19 |
| **Miscellaneous** | | | | |
| 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 |
| Peripheral Edema | 26 | 26 | 12 | 14 |
| **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 |

Less frequently observed adverse reactions in both liver transplantation and kidney transplantation patients are described under the subsection **Less Frequently Reported Adverse Reactions** below.

***Kidney Transplantation***

The most common adverse reactions reported were infection, tremor, hypertension, decreased renal function, constipation, diarrhea, headache, abdominal pain and insomnia.

Adverse events that occurred in ≥ 15% of kidney transplant patients treated with Prograf in conjunction with azathioprine are presented below:

**Kidney Transplantation: Adverse Events Occurring in ≥ 15% of Patients Treated with Prograf in conjunction with azathioprine**

| | **Prograf N = 205** (%) | **CBIR N = 207** (%) |
|---|---|---|
| **Nervous System** | | |
| Tremor (see WARNINGS) | 54 | 34 |
| Headache (see WARNINGS) | 44 | 38 |
| Insomnia | 32 | 30 |
| Paresthesia | 23 | 16 |
| Dizziness | 19 | 16 |
| **Gastrointestinal** | | |
| Diarrhea | 44 | 41 |
| Nausea | 38 | 36 |
| Constipation | 35 | 43 |
| Vomiting | 29 | 23 |
| Dyspepsia | 28 | 20 |
| **Cardiovascular** | | |
| Hypertension (see PRECAUTIONS) | 50 | 52 |
| Chest pain | 19 | 13 |
| **Urogenital** | | |
| Creatinine increased (see WARNINGS) | 45 | 42 |
| Urinary tract infection | 34 | 35 |
| **Metabolic and Nutritional** | | |
| Hypophosphatemia | 49 | 53 |
| Hypomagnesemia | 34 | 17 |
| Hyperlipidemia | 31 | 38 |
| Hyperkalemia (see WARNINGS) | 31 | 32 |
| Diabetes mellitus (see WARNINGS) | 24 | 9 |
| Hypokalemia | 22 | 25 |
| Hyperglycemia (see WARNINGS) | 22 | 16 |
| Edema | 18 | 19 |
| **Hemic and Lymphatic** | | |
| Anemia | 30 | 24 |
| Leukopenia | 15 | 17 |
| **Miscellaneous** | | |
| Infection | 45 | 49 |
| Peripheral edema | 36 | 48 |
| Asthenia | 34 | 30 |
| Abdominal pain | 33 | 31 |
| Pain | 32 | 30 |
| Fever | 29 | 29 |
| Back pain | 24 | 20 |
| **Respiratory System** | | |
| Dyspnea | 22 | 18 |
| Cough increased | 18 | 15 |
| **Musculoskeletal** | | |
| Arthralgia | 25 | 24 |

| | | |
|---|---|---|
| **Skin** | | |
| Rash | 17 | 12 |
| Pruritus | 15 | 7 |

Adverse events that occurred in ≥ 10% of kidney transplant patients treated with Prograf in conjunction with MMF in Study 1* are presented below:

**Kidney Transplantation: Adverse Events Occurring in ≥ 10% of Prograf - Treated Patients**

| | **Prograf (Group C) (N = 403)** | **Cyclosporine (Group A) (N = 384)** | **Cyclosporine (Group B) (N = 408)** |
|---|---|---|---|
| Anemia | 17% | 19% | 17% |
| Leukopenia | 13% | 10% | 10% |
| Diarrhea | 25% | 16% | 13% |
| Edema peripheral | 11% | 12% | 13% |
| Urinary tract infection | 24% | 28% | 24% |
| Hyperlipidemia | 10% | 15% | 13% |
| Hypertension (see PRECAUTIONS) | 13% | 14% | 12% |

*Study 1 was conducted entirely outside of the United States. Such studies often report a lower incidence of adverse events in comparison to US studies.

Adverse events that occurred in ≥ 15% of kidney transplant patients treated with Prograf in conjunction with MMF in Study 2 are presented below:

**Kidney Transplantation: Adverse Events Occurring in ≥ 15% of Prograf - Treated Patients**

| | **Prograf N = 212** (%) | **Cyclosporine N = 212** (%) |
|---|---|---|
| **Gastrointestinal** | | |
| Diarrhea | 44 | 26 |
| Nausea | 39 | 47 |
| Constipation | 36 | 41 |
| Vomiting | 26 | 25 |
| Dyspepsia | 18 | 15 |
| **Injury, Poisoning, and Procedural Complications** | | |
| Post Procedural Pain | 29 | 27 |
| Incision Site Complication | 28 | 23 |
| Graft Dysfunction | 24 | 18 |
| **Metabolic and Nutritional Disorders** | | |
| Hypomagnesemia | 28 | 22 |
| Hypophosphatemia | 28 | 21 |
| Hyperkalemia (see WARNINGS) | 26 | 19 |
| Hyperglycemia (see WARNINGS) | 21 | 15 |
| Hyperlipidemia | 18 | 25 |
| Hypokalemia | 16 | 18 |
| **Nervous System Disorders** | | |
| Tremor | 34 | 20 |
| Headache | 24 | 25 |
| **Blood and Lymphatic System Disorders** | | |
| Anemia | 30 | 28 |
| Leukopenia | 16 | 12 |

| **Miscellaneous** | | |
|---|---|---|
| Edema peripheral | 35 | 46 |
| Hypertension (see PRECAUTIONS) | 32 | 35 |
| Insomnia | 30 | 21 |
| Urinary Tract Infection | 26 | 22 |
| Blood creatinine increased | 23 | 23 |

Less frequently observed adverse reactions in both liver transplantation and kidney transplantation patients are described under the subsection **Less Frequently Reported Adverse Reactions** shown below.

***Lupus Nephritis***

The major adverse reactions or abnormalities in clinical laboratory findings due to this product in 65 patients with lupus nephritis (capsules 65) were increased urinary β2-microglobulin (27.3%, 12/44), increased urinary NAG (22.2%, 14/63), nasopharyngitis (15.4%, 10/65), hyperuricemia (14.1%, 9/64), leukocytosis (14.1%, 9/64), increased creatinine (12.5%, 8/64), diarrhea (12.3%, 8/65), increased blood pressure (10.8%, 7/65), and hyperglycemia (10.9%, 7/64).
(At the time of latest approval of indication: January 2007)

**Less Frequently Reported Adverse Reactions**

The following adverse events were reported in the range of 3% to less than 15% incidence in either kidney, liver and/or heart transplant recipients who were treated with tacrolimus in clinical trials.
NERVOUS SYSTEM: (see WARNINGS) abnormal dreams, agitation, amnesia, anxiety, confusion, convulsion, crying, depression, dizziness, elevated mood, emotional lability, encephalopathy, haemorrhagic stroke, hallucinations, headache, hypertonia, incoordination, insomnia, monoparesis, myoclonus, nerve compression, nervousness, neuropathy, paresthesia, paralysis flaccid, psychomotor skills impaired, psychosis, quadriparesis, somnolence, thinking abnormal, writing impaired, brachial plexopathy, peripheral nerve lesion.

SPECIAL SENSES: abnormal vision, amblyopia, ear pain, otitis media, tinnitus.

GASTROINTESTINAL: anorexia, cholangitis, cholestatic jaundice, diarrhea, duodenitis, dyspepsia, dysphagia, esophagitis, flatulence, gastritis, gastroesophagitis, gastrointestinal hemorrhage, GGT increase, GI perforation, granulomatous liver disease, hepatitis, hepatocellular injury, ileus, increased appetite, jaundice, liver damage, liver function test abnormal, nausea, nausea and vomiting, oesophagitis ulcerative, oral moniliasis, pancreatic pseudocyst, rectal disorder, stomatitis, vomiting.

CARDIOVASCULAR: abnormal ECG, angina pectoris, cardiac fibrillation, cardiopulmonary failure, chest pain, deep thrombophlebitis, echocardiogram abnormal, electrocardiogram QRS complex abnormal, electrocardiogram ST segment abnormal, heart rate decreased, hemorrhage, hypotension, peripheral vascular disorder, phlebitis, postural hypotension, tachycardia, thrombosis, vasodilatation.

UROGENITAL: (see WARNINGS) albuminuria, BK nephropathy, bladder spasm, cystitis, dysuria, hematuria, hydronephrosis, kidney failure, kidney tubular necrosis, nocturia, oliguria, pyuria, toxic nephropathy, urge incontinence, urinary frequency, urinary incontinence, urinary retention, vaginitis.

METABOLIC/NUTRITIONAL: acidosis, alkaline phosphatase increased, alkalosis, ALT (SGPT) increased, AST (SGOT) increased, bicarbonate decreased,

bilirubinemia, BUN increased, dehydration, GGT increased, healing abnormal, hypercalcemia, hypercholesterolemia, hyperlipidemia, hyperphosphatemia, hyperuricemia, hypervolemia, hypocalcemia, hypoglycemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, hypoproteinemia, lactic dehydrogenase increase, weight gain.

ENDOCRINE: (see PRECAUTIONS) Cushing's syndrome, diabetes mellitus
HEMIC/LYMPHATIC: coagulation disorder, ecchymosis, haematocrit increased, haemoglobin abnormal, hypochromic anemia, leukocytosis, leukopenia, polycythemia, prothrombin decreased, serum iron decreased thrombocytopenia.

MISCELLANEOUS: abdomen enlarged, abdominal pain, abscess, accidental injury, allergic reaction, asthenia, back pain, cellulitis, chills, fall, feeling abnormal, fever, flu syndrome, generalized edema, hernia, pain*, peritonitis, photosensitivity reaction, sepsis, temperature intolerance, ulcer.

MUSCULOSKELETAL: arthralgia, joint disorder, mobility decreased, muscle spasms, myalgia, myasthenia, osteoporosis.

RESPIRATORY: asthma, bronchitis, cough increased, dyspnea, emphysema, hiccups, lung disorder, pharyngitis, pleural effusion, pneumonia, pneumothorax, pulmonary edema, respiratory disorder, rhinitis, sinusitis, voice alteration.

SKIN: acne, alopecia, exfoliative dermatitis, fungal dermatitis, herpes simplex, hirsutism, skin discoloration, skin disorder, skin ulcer, sweating.

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

**Post Marketing**
**Post Marketing Adverse Events**
The following adverse events have been reported from worldwide marketing experience with Prograf. 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.

There have been rare spontaneous reports of myocardial hypertrophy associated with clinically manifested ventricular dysfunction in patients receiving Prograf therapy (see PRECAUTIONS-Myocardial Hypertrophy).

Other events include:

***Cardiovascular***
Atrial fibrillation, atrial flutter, cardiac arrhythmia, cardiac arrest, electrocardiogram T wave abnormal, flushing, myocardial infarction, myocardial ischaemia, pericardial effusion, QT prolongation, *Torsades de pointes*, venous thrombosis deep limb, ventricular extrasystoles, ventricular fibrillation.

***Gastrointestinal***
Bile duct stenosis, colitis, enterocolitis, gastroenteritis, gastrooesophageal reflux disease, hepatic cytolysis, hepatic necrosis, hepatotoxicity, impaired gastric

emptying, liver fatty, mouth ulceration, pancreatitis haemorrhagic, pancreatitis necrotizing, stomach ulcer, venoocclusive liver disease, gastrointestinal perforation.

***Hemic/Lymphatic***
Agranulocytosis, disseminated intravascular coagulation, haemolytic anemia, neutropenia, febrile neutropenia, pancytopenia, thrombocytopenic purpura, thrombotic microangiopathy, thrombotic thrombocytopenic purpura, pure red cell aplasia (see Warnings).

***Metabolic/Nutritional***
Glycosuria, increased amylase including pancreatitis, weight decreased.

***Miscellaneous***
Feeling of body temperature change, feeling jittery, hot flushes, multi-organ failure, primary graft dysfunction.

***Nervous System***
Carpal tunnel syndrome, cerebral infarction, hemiparesis, leukoencephalopathy, mental disorder, mutism, posterior reversible encephalopathy syndrome (PRES), progressive multifocal leukoencephalopathy (PML), quadriplegia, speech disorder, syncope.

***Respiratory***
Acute respiratory distress syndrome, interstitial lung disease, lung infiltration, respiratory distress, respiratory failure.

***Skin***
Stevens-Johnson syndrome, toxic epidermal necrolysis.

***Special Senses***
Blindness, blindness cortical, optic neuropathy, hearing loss including deafness, photophobia.

***Urogenital***
Acute renal failure, cystitis haemorrhagic, haemolytic-uraemic syndrome, micturition disorder.

***Infections and infestations***
As it is well known for other potent immunosuppressive agents, patients receiving tacrolimus are at an increased risk for infections (viral, bacterial, fungal, and protozoal). The course of pre-existing infections may be aggravated. Overall, infections have been reported frequently in patients being treated with tacrolimus. Both generalised and localised infections can occur.

## 7 DRUG INTERACTIONS
Due to the potential for additive of synergistic impairment of renal function, care should be taken when administering Prograf with drugs that may be associated with renal dysfunction. These include, but are not limited to, aminoglycosides, amphotericin B, ibuprofen, and cisplatin. Initial clinical experience with the co-administration of Prograf and cyclosporine resulted in additive/synergistic nephrotoxicity. 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.

**Drugs that May Alter Tacrolimus Concentrations**

Since tacrolimus is metabolized mainly by the CYP3A enzyme systems, substances known to inhibit these enzymes may decrease the metabolism 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 and decreased whole blood or plasma levels. Monitoring of blood concentrations and appropriate dosage adjustments are essential when such drugs are used concomitantly.

***Drugs That May Increase Tacrolimus Blood Levels:***

| ***Calcium Channel Blocker*** | ***Antifungal Agents*** | ***Macrolide Antibiotics*** | ***Gastrointestinal Prokinetic Agents*** | ***Other Drugs*** | ***Herbal Remedy*** |
|---|---|---|---|---|---|
| diltiazem | clotrimazole | clarithromycin | cisapride | bromocriptine | *Schisandra sphenanthera* extracts |
| nicardipine | fluconazole | erythromycin | metoclopramide | chloramphenicol | |
| nifedipine | itraconazole | troleandomycin | | cimetidine | |
| verapamil | ketoconazole** | | | cyclosporine | |
| | voriconazole | | | danazol | |
| | | | | ethinyl estradiol | |
| | | | | amiodarone | |
| | | | | methylprednisolone | |
| | | | | lansoprazole*** | |
| | | | | omeprazole | |
| | | | | protease inhibitors**** | |
| | | | | nefazodone | |
| | | | | magnesium-aluminum-hydroxide | |
| | | | | letermovir | |
| | | | | cannabidiol | |

** In a study of 6 normal volunteers, a significant increase in tacrolimus oral bioavailability (14±5% vs. 30±8%) was observed with concomitant ketoconazole administration (200 mg). The apparent oral clearance of 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, IV clearance of tacrolimus was not significantly changed by ketoconazole co-administration, although it was highly variable between patients.

*** Lansoprazole (CYP2C19, CYP3A4 substrate) 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.

**** Most protease inhibitors inhibit CYP3A enzymes and may increase tacrolimus whole blood concentrations. It is recommended to avoid concomitant use of tacrolimus with nelfinavir unless the benefits outweigh the risks. Whole blood concentrations of tacrolimus are markedly increased when co-administered with telaprevir or with boceprevir. Monitoring of tacrolimus whole blood concentrations and tacrolimus-associated adverse reactions, and appropriate adjustments in the dosing regimen of tacrolimus are recommended when tacrolimus and protease inhibitors (e.g., ritonavir, telaprevir, boceprevir) are used concomitantly.

Significant tacrolimus dose reductions and prolongation of dosing interval may be required in order to maintain similar tacrolimus exposure when co-administered with strong CYP3A4 inhibitors, particularly telaprevir. Rapid increase in tacrolimus level may occur when co-administered with CYP3A4 inhibitors. 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 a strong CYP3A4 inhibitor, clarithromycin, despite immediate reduction of tacrolimus dose. Therefore 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.

***Drugs That May Decrease Tacrolimus Blood Levels:***

| *Anticonvulsants* | *Antimicrobials* | *Herbal Preparations* | *Other Drugs* |
|---|---|---|---|
| carbamazepine | rifabutin | St. John's wort | sirolimus |
| phenobarbital | caspofungin | | |
| phenytoin | rifampin | | |

* This table is not all inclusive.

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.

In a single-dose crossover study in healthy volunteers, co-administration of tacrolimus and magnesium-aluminum-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.

In a study of 6 normal volunteers, a significant decrease in tacrolimus oral bioavailability (14±6% vs. 7±3%) was observed with concomitant rifampin administration (600 mg). 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 rifampin administration.

Interaction studies with drugs used in HIV therapy have not been conducted. However, care should be exercised when drugs that are nephrotoxic (e.g., ganciclovir) or that are metabolized by CYP3A (e.g., nelfinavir, ritonavir) are administered concomitantly with tacrolimus.

Based on a clinical study of 5 liver transplant recipients, co-administration of tacrolimus 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 mean trough tacrolimus blood concentrations of 9.7 ng/mL. Thus, frequent monitoring of tacrolimus blood concentrations and appropriate dosage adjustments are essential when nelfinavir is used concomitantly.

In a single dose study in 9 healthy volunteers, co-administration of tacrolimus (0.5 mg single dose) with telaprevir (750 mg three times daily for 13 days) increased the tacrolimus dose normalized $C_{max}$ by 9.3-fold and AUC by 70-fold compared to tacrolimus alone.
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.
Tacrolimus may affect the pharmacokinetics of other drugs (e.g., phenytoin) and increase their concentration. Grapefruit juice affects CYP3A-mediated metabolism and should be avoided (see DOSAGE AND ADMINISTRATION).

Following co-administration of tacrolimus and sirolimus (2 or 5 mg/day) in stable renal transplant patients, mean tacrolimus $AUC_{0-12}$ and $C_{min}$ decreased approximately by 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 tacrolimus used in combination with sirolimus for the prevention of graft rejection has not been established and is not recommended.

***Other Drug Interactions***
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.[1]

At a given MMF dose, mycophenolic acid (MPA) exposure is higher with Prograf co-administration than with cyclosporine co-administration due to the differences in the interruption of the enterohepatic recirculation of MPA. Clinicians should be aware that there is also a potential for increased MPA exposure after crossover from cyclosporine to tacrolimus in patients concomitantly receiving MMF or MPA.

Impact of direct-acting antiviral (DAA) therapy. The pharmacokinetics of tacrolimus may be impacted by changes in liver function during DAA therapy, related to clearance of HCV virus. A close monitoring and potential dose adjustment of tacrolimus is warranted to ensure continued efficacy and safety.

## 8 USE IN SPECIFIC POPULATIONS

### *Pregnancy: Category C*

Tacrolimus is transferred across the placenta and infants exposed to tacrolimus *in utero* may be at a risk of prematurity, birth defects/congenital anomalies, low birth weight, and fetal distress. The use of tacrolimus during pregnancy has been associated with preterm delivery, neonatal 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.
Prograf should be used during pregnancy only if the potential benefit to the mother justifies potential risk to the fetus.
In rats and rabbits, tacrolimus caused embryofoetal toxicity at doses which demonstrated maternal toxicity.

### *Nursing Mothers*

Tacrolimus is excreted in human milk. The effects of tacrolimus on the breast-fed infant, or on milk production have not been assessed. As detrimental effects on the newborn cannot be excluded, women should not breast-feed whilst receiving tacrolimus.

### *Pediatric Patients*

Experience with Prograf in pediatric kidney transplant patients is limited. Successful liver transplants have been performed in pediatric patients (ages up to 16 years) using Prograf. The two randomized active-controlled trial of Prograf in primary liver transplantation included 56 pediatric patients. Thirty-one patients were randomized to Prograf-based and 25 to cyclosporine-based therapies. Additionally, a minimum of 122 pediatric patients were studied in an uncontrolled 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 DOSAGE AND ADMINISTRATION).

The safety of this product in pediatric patient has not been established in lupus nephritis (no clinical experiences in lupus nephritis).

### *Renally and Hepatically Impaired Patients*

For patients with renal insufficiency some evidence suggests that lower doses should be used (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

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 dosage adjustments should be considered. Some evidence suggests that lower doses should be used in these patients (see DOSAGE AND ADMINISTRATION).

## 9 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

## 10 OVERDOSAGE

Limited overdosage experience is available. Acute overdosages of up to 30 times the intended dose have been reported. Almost all cases have been asymptomatic and all patients recovered with no sequelae. Occasionally, acute overdosage has been followed by adverse reactions consistent with those listed in the ADVERSE REACTIONS section except in one case where transient urticaria and lethargy were observed. Based on the 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.

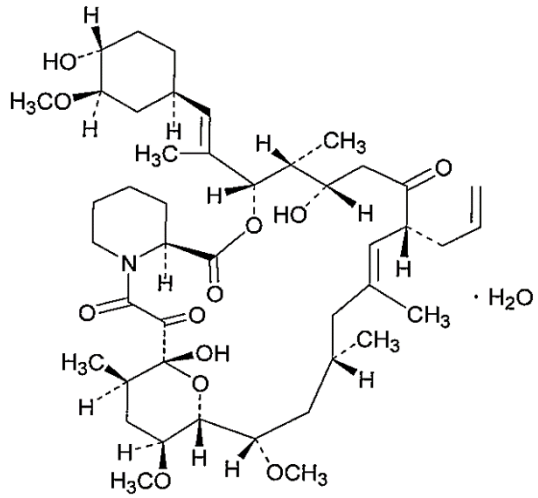
In acute oral and IV toxicity studies, mortalities were seen at or above the following doses: in adult rats 52X the recommended human oral dose; in immature rats, 16X the recommended oral dose; and in adult rats, 16X the recommended human IV dose (all based on body surface area corrections).

## 11 DESCRIPTION

Prograf is available for oral administration as capsules (tacrolimus capsules) containing the equivalent of 0.5 mg, 1 mg of anhydrous tacrolimus. Inactive ingredients include lactose, hydroxypropyl methylcellulose, croscarmellose sodium, and magnesium stearate. The 0.5 mg capsule shell contains gelatin, titanium dioxide and ferric oxide yellow and the 1 mg capsules shell contains gelatin and titanium dioxide.

Prograf is also available as a sterile solution (tacrolimus 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 80.0% v/v. Prograf injection must be diluted with 0.9 % Sodium Chloride Injection or 5% Dextrose Injection before use. Tacrolimus, previously known as FK506, is the active ingredient in Prograf. Tacrolimus is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. Chemically, tacrolimus is designated as [3*S*-[3*R**[E(1*S**,3*S**,4*S**)],4S*, 5*R**8*S**,9*E*,12*R**,14*R**15*S**16*R**,18*S**,19*S**,26a*R**]]-5,6,8,11,12,13,14,15,16,17, 18,19,24,25,26a-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.

The chemical structure of tacrolimus is:



Tacrolimus has an empirical formula of $C_{44}H_{69}NO_{12}H_2O$ and a formula weight of 822.03. Tacrolimus appears as white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform.

## 12 CLINICAL PHARMACOLOGY

### Mechanism of Action

Tacrolimus inhibits T-lymphocyte activation although the exact mechanism of action is not known. 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 dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component through to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). The net result is the inhibition of T-lymphocyte activation (i.e., immunosuppression).

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.

In animals, tacrolimus has been demonstrated to suppress some humoral immunity and, to a greater extent, cell-mediated reactions such as allograft rejection, delayed type hypersensitivity, collagen-induced arthritis, experimental allergic encephalomyelitis, and graft versus host disease.

### Pharmacokinetics

Tacrolimus activity is primarily due to the parent drug. The pharmacokinetics parameters (mean±S.D.) of tacrolimus have been determined following intravenous (IV) and/or oral (PO) administration in healthy volunteers, liver transplant and kidney transplant patients (see table below).

| Population | N | Route (Dose) | Parameters | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | $C_{max}$ (ng/mL) | $T_{max}$ (hr) | AUC (ng·hr/mL) | $t_{1/2}$ (hr) | Cl (L/hr/kg) | V (L/kg) |
| Healthy Volunteers | 8 | IV (0.025 mg/kg/4hr) | - | - | 598[a] ±125 | 34.2 ±7.7 | 0.040 ±0.009 | 1.91 ±0.31 |
| | 16 | PO (5 mg) | 29.7 ±7.2 | 1.6 ±0.7 | 243[b] ±73 | 34.8 ±11.4 | 0.0041* ±0.008 | 1.94* ±0.53 |
| Kidney Transplant Pts | 26 | IV (0.02 mg/kg/12hr) | - | - | 294[c] ±262 | 18.8 ±16.7 | 0.083 ±0.050 | 1.41 ±0.66 |
| | | PO (0.2 mg/kg/day) | 19.2 ±10.3 | 3.0 | 203[c] ±42 | NA | NA | NA |
| | | PO (0.3 mg/kg/day) | 24.2 ±15.8 | 1.5 | 288[c] ±93 | NA | NA | NA |
| Liver Transplant Pts | 17 | IV (0.05 mg/kg/12hr) | - | - | 3300[c] ±2130 | 11.7 ±3.9 | 0.053 ±0.017 | 0.85 ±0.30 |
| | | PO (0.3 mg/kg/day) | 68.5 ±30.0 | 2.3 ±1.5 | 519[c] ±179 | NA | NA | NA |

* Corrected for individual bioavailability [a]$AUC_{0-120}$ [b]$AUC_{0-72}$ [c]$AUC_{0-inf}$ NA = not available - = not applicable

Due to intersubject variability in tacrolimus pharmacokinetics, individualization of dosing regimen is necessary for optimal therapy (see DOSAGE AND ADMINISTRATION). Pharmacokinetics 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 variable. The absolute bioavailability of tacrolimus was 17±10% in adult kidney transplant patients (N = 26), 22 ± 6% in adult liver transplant patients (N = 17) and 18±5% in healthy volunteers (N = 16).

A single dose study conducted in 32 healthy volunteers established the bioequivalence of the 1 mg and 5 mg capsules. Another single dose study in 32 healthy volunteers established the bioequivalence of the 0.5 mg and 1 mg capsules. Tacrolimus maximum blood concentration ($C_{max}$) and area under the curve (AUC) appeared to increase in a dose-proportional fashion in 18 fasted healthy volunteers receiving a single oral dose of 3, 7 and 10 mg.

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 (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.

*Food Effects*: The rate and extent of tacrolimus absorption were greatest under fasted conditions. The presence and composition of food decreased both the rate and extent of tacrolimus absorption when administered to 15 healthy volunteers. The effect was most pronounced with a high-fat meal (848 kcal, 46% fat): mean AUC and $C_{max}$ were decreased 37% and 77%, respectively; $T_{max}$ was lengthened 5-fold. A high-carbohydrate meal (668 kcal, 85% carbohydrate) decreased mean AUC and mean $C_{max}$ by 28% and 65%, respectively.

In healthy volunteers (N = 16), the time of the meal also affected tacrolimus bioavailability. When given immediately following the meal, mean $C_{max}$ was reduced 71%, and mean AUC was reduced 39% relative to the fasted condition. When administered 1.5 hours following the meal, mean $C_{max}$ reduced 63%, and mean AUC was reduced 39%, relative to the fasted condition.

In 11 liver transplant patients, Prograf administered 15 minutes after a high fat (400 kcal, 34% fat) breakfast, resulted in decreased AUC (27±18%) and $C_{max}$ (50±19%), as compared to a fasted state.

***Distribution***
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 mainly to 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 averaged 35 (range 12 to 67).

***Metabolism***
Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P450-3A4 (CYP3A4) and the cytochrome P450-3A5 (CYP3A5). 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.

***Excretion***
The mean clearance following IV administration of tacrolimus is 0.040, 0.083 and 0.053 L/hr/kg in healthy volunteers, adult kidney transplant patients and adult liver transplant patients, respectively. In man, less than 1% of the dose administered is excreted unchanged in urine.
In a mass balance study of IV administered radiolabeled tacrolimus to 6 healthy volunteers, the mean recovery of radiolabel was 77.8%±12.7%. Fecal elimination accounted for 92.4±1.0% and the elimination half-life based on radioactivity was 48.1±15.9 hours whereas it was 43.5±11.6 hours based on tacrolimus concentrations. The mean clearance of radiolabel was 0.029±0.015 L/hr/kg and clearance of tacrolimus was 0.029±0.009 L/hr/kg. When administered PO, the mean recovery of the radiolabel was 94.9±30.7%. Fecal elimination accounted for 92.6±30.7%, urinary elimination accounted for 2.3±1.1% and the elimination half-life based on radioactivity was 31.9±10.5 hours whereas it was 48.4±12.3 hours based on tacrolimus concentrations. The mean clearance of radiolabel was 0.226±0.116 L/hr/kg and clearance of tacrolimus 0.172±0.088 L/hr/kg.

***Special Populations***
*Pediatric*
Pharmacokinetics of tacrolimus have been studied in liver transplantation patients, 0.7 to 13.2 years of age. Following IV administration of a 0.037 mg/kg/day dose to 12 pediatric patients, mean terminal half-life, volume of distribution and clearance were 11.5±3.8 hours, 2.6±2.1 L/kg and 0.138±0.071 L/hr/kg, respectively.

Following oral administration to 9 patients, mean AUC and $C_{max}$ were 337±167 ng·hr/mL and 48.4±27.9 ng/mL, respectively. The absolute bioavailability was 31±24%.

Whole blood trough concentrations from 31 patients less than 12 years old showed that pediatric patients need higher doses than adults to achieve similar tacrolimus trough concentrations (see DOSAGE AND ADMINISTRATION).

*Renal and Hepatic Insufficiency*
The mean pharmacokinetic parameters for tacrolimus following single administrations to patients with renal and hepatic impairment are given in the following table.

| Population (No. of Patients) | Dose | $AUC_{0-6}$ (ng·hr/mL) | $t_{1/2}$ (hr) | V (L/kg) | Cl (L/hr/kg) |
|---|---|---|---|---|---|
| Renal Impairment (n = 12) | 0.02 mg/kg/4hr IV | 393±123 (t = 60 hr) | 26.3±9.2 | 1.07±0.20 | 0.038±0.014 |
| Mild Hepatic Impairment (n = 6) | 0.02 mg/kg/4 hr IV | 367±107 (t = 72 hr) | 60.6±43.8 (27.8-141) | 3.1±1.6 | 0.042±0.02 |
| | 7.7 mg PO | 488±320 (t = 72 hr) | 66.1±44.8 (29.5-138) | 3.7±4.7* | 0.034±0.019* |
| Severe Hepatic Impairment (n = 6, IV) | 0.02 mg/kg/4 hr IV (n = 2) | 762±204 (t = 120 hr) | 198±158 (81-436) | 3.9±1.0 | 0.017±0.013 |
| | 0.01 mg/kg/8 hr IV (n = 4) | 289±117 (t = 144 hr) | | | |
| (n = 5, PO)** | 8 mg PO (n = 1) | 658 (t = 120 hr) | 119±35 (85-178) | 3.1±3.4* | 0.016±0.011* |
| | 5 mg PO (n = 4) 4 mg PO (n = 1) | 533±156 (t = 144 hr) | | | |

* corrected for bioavailability
** 1 patient did not receive the PO dose

*Renal Insufficiency*
Tacrolimus pharmacokinetics following a single IV administration were determined in 12 patients (7 not on dialysis and 5 on dialysis, serum creatinine of 3.9±1.6 and 12.0±2.4 mg/dL, respectively) prior to their kidney transplant. The pharmacokinetic parameters obtained were similar for both groups.

The mean clearance of tacrolimus in patients with renal dysfunction was similar to that in normal volunteers (see previous table).

*Hepatic Insufficiency*
Tacrolimus pharmacokinetics have been determined in six patients with mild hepatic dysfunction (mean Pugh score: 6.2) following single IV and oral administrations. The mean clearance of tacrolimus in patients with mild hepatic dysfunction was not substantially different from that in normal volunteers (see previous table). 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.

*Race*
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 DOSAGE AND ADMINISTRATION).

*Gender*
The effect of gender on tacrolimus pharmacokinetics has not been evaluated, however there was no difference in dosing by gender in the kidney transplant trial.

## 13 NONCLINICAL TOXICOLOGY

***Carcinogenesis, Mutagenesis and Impairment of Fertility***

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. As with other immunosuppressive therapies, the risk of malignancies in Prograf recipients may be higher than in the normal, healthy population. 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.

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

Carcinogenicity studies were carried out in male and female rats and mice. In the 80-week mouse study and in the 104-week rat study no relationship of tumor incidence to tacrolimus dosage was found. The highest doses used in the mouse and rat studies were 0.8-2.5 times (mice) and 3.5-7.1 times (rats) the recommended clinical dose range of 0.1 - 0.2 mg/kg/day when corrected for body surface area.

Embryotoxicity was observed in animal studies. Tacrolimus subcutaneously administered to male rats at a doses of 2 or 3 mg/kg/day (1.6 to 6.4 times the clinical dose range based on body surface area) resulted in a dose-related decrease in sperm count. Tacrolimus given orally at 1.0 mg/kg (0.8 to 2.2 times the clinical dose range based on body surface area) to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryolethality and adverse effects on female reproduction which were indicated by a higher rate of post-implantation loss and increased numbers of undelivered and nonviable pups. When given at 3.2 mg/kg (2.6 to 6.9 times the clinical dose range based on body surface area correction), tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on estrus cycles, parturition, pup viability, and pup malformations.

## 14 CLINICAL STUDIES

***Liver Transplantation***

The safety and efficacy of Prograf-based immunosuppression following orthotopic liver transplantation were assessed in two prospective, randomized, non-blinded multicenter studies. The active control groups were treated with a cyclosporine-based immunosuppressive regimen. Both studies used concomitant adrenal corticosteroids as part of the immunosuppressive regimens. These studies were designed to evaluate whether the two regimens were therapeutically equivalent, with patient and graft survival at 12 months following transplantation as the primary endpoints. The Prograf-based immunosuppressive regimen was found to be equivalent to the cyclosporine-based immunosuppressive regimens.

In one trial, 529 patients were enrolled at 12 clinical sites in the United States; prior to surgery, 263 were randomized to the Prograf-based immunosuppressive regimen and 266 to a cyclosporine-based immunosuppressive regimen (CBIR). In 10 of the 12 sites, the same CBIR protocol was used, while 2 sites used different control protocols. This trial excluded patients with renal dysfunction, fulminant hepatic failure with Stage IV encephalopathy, and cancers; pediatric patients (< 12 years old) were allowed.

In the second trial, 545 patients were enrolled at 8 clinical sites in Europe; prior to surgery, 270 were randomize to the Prograf-based immunosuppressive regimen and 275 to CBIR. In this study, each center used its local standard CBIR protocol in the active-control arm. This trial excluded pediatric patients, but did allow enrollment of subjects with renal dysfunction, fulminant hepatic failure in Stage IV encephalopathy, and cancers other than primary hepatic with metastases.

One year patient survival and graft survival in the Prograf-based treatment groups were equivalent to those in the CBIR treatment groups in both studies. The overall one-year patient survival (CBIR and Prograf-based treatment groups combined) was 88% in the U.S. study an 78% in the European study. The overall one-year graft survival (CBIR and Prograf-based treatment groups combined) was 81% in the U.S. study and 73% in the European study. In both studies, the median time to convert from IV to oral Prograf dosing was 2 days.

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

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.

Because of the nature of the study design, comparisons of differences in secondary endpoints, such as incidence of acute rejection, refractory rejection or use of OKT3 for steroid-resistant rejection, could not be reliably made.

***Kidney Transplantation***

*Prograf/azathioprine*

Prograf-based immunosuppression in conjunction with azathioprine and corticosteroids following kidney transplantation was assessed in a Phase 3 randomized, multicenter, non-blinded, prospective study. There were 412 kidney transplant patients enrolled at 19 clinical sites in the United States. Study therapy was initiated when renal function was stable as indicated by a serum creatinine $\leq$ 4 mg/dL (median of 4 days after transplantation, range 1 to 14 days). Patients less than 6 years of age were excluded.

There were 205 patients 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. Overall one year patient and graft survival was 96.1% and 89.6%, respectively and was equivalent between treatment arms.

Data from a Phase 3 US study of Prograf in conjunction with azathioprine indicates 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 of that trial, 80% of the patients maintained trough concentrations between 7-20 ng/mL, and then between 5-15 ng/mL, through 1 year.

Because of the nature of the study design, comparisons of differences in secondary endpoints, such as incidence of acute rejection, refractory rejection or use of OKT3 for steroid-resistant rejection, could not be reliably made.

*Prograf/mycophenolate mofetil (MMF)*

Prograf-based immunosuppression in conjunction with MMF, corticosteroids, and induction has been studied. In a randomized, open-label, multi-center trial (Study 1), 1589 kidney transplant patients received Prograf (Group C, n = 401), sirolimus (Group D, n = 399), or one of two cyclosporine regimens (Group A, n = 390 and Group B, n = 399) in combination with MMF and corticosteroids; all patients, except those in one of the two cyclosporine groups, also received induction with daclizumab. The study was conducted outside the United States; the study population was 93% Caucasian. In this study, mortality at 12 months in patients receiving Prograf/MMF was similar (2.7%) compared to patients receiving cyclosporine/MMF (3.3% and 1.8%) or sirolimus/MMF (3.0%). Patients in the Prograf group exhibited higher estimated creatinine clearance rates (eCLcr) using the Cockcroft-Gault formula (Table 1) and experienced fewer efficacy failures, defined as biopsy proven acute rejection (BPAR), graft loss, death, and/or lost to follow-up (Table 2) in comparison to each of the other three groups. Patients randomized to Prograf/MMF were more likely to develop diarrhea and diabetes after the transplantation and experienced similar rates of infections compared to patients randomized to either cyclosporine/MMF regimen (see ADVERSE REACTIONS).

**Table 1: Estimated Creatinine Clearance at 12 Months in Study 1**

| Group | eCLcr [mL/min] at Month 12[a] | | | | |
|---|---|---|---|---|---|
| | N | MEAN | SD | MEDIAN | Treatment Difference with Group C (99.2% CI[b]) |
| (A) CsA/MMF/CS | 390 | 56.5 | 25.8 | 56.9 | -8.6 (-13.7, -3.7) |
| (B) CsA/MMF/CS/Daclizumab | 399 | 58.9 | 25.6 | 60.9 | -6.2 (-11.2, -1.2) |
| (C) Tac/MMF/CS/Daclizumab | 401 | 65.1 | 27.4 | 66.2 | - |
| (D) Siro/MMF/CS/Daclizumab | 399 | 56.2 | 27.4 | 57.3 | -8.9 (-14.1, -3.9) |
| Total | 1589 | 59.2 | 26.8 | 60.5 | |

Key: CsA = Cyclosporine, CS = Corticosteroids, Tac = Tacrolimus, Siro = Sirolimus

a)All death/graft loss (n = 41, 27, 23 and 42 in Groups A, B, C and D) and patients whose last recorded creatinine values were prior to month 3 visit (n = 10, 9, 7 and 9 in Groups A, B, C and D)were inputted with GFR of 10 mL/min; a subject's last observed creatinine value from month 3 on was used for the remainder of subjects with missing creatinine at month 12 (n = 11, 12, 15 and 19 for Groups A, B, C and D). Weight was also imputed in the calculation of estimated GFR, if missing.

b) Adjusted for multiple (6) pairwise comparisons using Bonferroni corrections.

**Table 2: Incidence of BPAR, Graft Loss, Death or Loss to Follow-up at 12 Months in Study 1**

| | A N = 390 | B N = 399 | C N = 401 | D N = 399 |
|---|---|---|---|---|
| Overall Failure | 141 (36.2%) | 126 (31.6%) | 82 (20.4%) | 185 (46.4%) |
| Components of efficacy failure | | | | |
| BPAR | 113 (29.0%) | 106 (26.6%) | 60 (15.0%) | 152 (38.1%) |
| Graft loss excluding death | 28 (7.2%) | 20 (5.0%) | 12 (3.0%) | 30 (7.5%) |
| Mortality | 13 (3.3%) | 7 (1.8%) | 11 (2.7%) | 12 (3.0%) |
| Lost to follow-up | 5 (1.3%) | 7 (1.8%) | 5 (1.3%) | 6 (1.5%) |
| Treatment Difference of efficacy failure compared to Group C (99.2% CI[a]) | 15.8% (7.1%, 24.3%) | 11.2% (2.7%, 19.5%) | - | 26.0% (17.2%, 34.7%) |

Group A = CsA/MMF/CS, B = CsA/MMF/CS/Daclizumab, C = Tac/MMF/CS/Daclizumab, and D = Siro/MMF/CS/Daclizumab

a) Adjusted for multiple (6) pairwise comparisons using Bonferroni corrections.

The protocol-specified target tacrolimus trough concentrations ($C_{troughs}$, Tac) were 3-7 ng/mL; however, the observed median $C_{troughs}$, Tac approximated 7 ng/mL throughout the 12 month study (Table 3). Approximately 80% of patients maintained tacrolimus whole blood concentrations between 4-11 ng/mL through 1 year post-transplant.

**Table 3: Tacrolimus Whole Blood Trough Concentrations (Study 1)**

| Time | Median (P10-P90[a]) tacrolimus whole blood trough concentrations (ng/mL) |
|---|---|
| Day 30 (N = 366) | 6.9 (4.4 – 11.3) |
| Day 90 (N = 351) | 6.8 (4.1 – 10.7) |
| Day 180 (N = 355) | 6.5 (4.0 – 9.6) |
| Day 365 (N = 346) | 6.5 (3.8 – 10.0) |

a) Range of $C_{troughs}$, Tac that excludes lowest 10% and highest 10% of $C_{troughs}$, Tac

The protocol-specified target cyclosporine trough concentrations ($C_{trough}$, CsA) for Group B were 50-100 ng/mL; however, the observed median $C_{trough}$, CsA approximated 100 ng/mL throughout the 12 month study. The protocol-specified target $C_{trough}$, CsA for Group A were 150-300 ng/mL for the first 3 months and 100-200 ng/mL from month 4 to month 12; the observed median $C_{trough}$, CsA approximated 225 ng/mL for the first 3 months and 140 ng/mL from month 4 to month 12.

While patients in all groups started MMF at 1g BID, the MMF dose was reduced to < 2 g/day in 63% of patients in the tacrolimus treatment arm by month 12 (table 4); approximately 50% of these MMF dose reductions were due to adverse events. By comparison, the MMF dose was reduced to < 2 g/day in 49% and 45% of patients in the two cyclosporine arms (Group A and Group B, respectively), by month 12 and approximately 40% of MMF dose reductions were due to adverse events.

**Table 4: MMF Dose Over Time in Prograf/MMF (Group C) (Study 1)**

| Time period (Days) | Time-averaged MMF dose (g/day)[a] | | |
|---|---|---|---|
| | < 2.0 | 2.0 | > 2.0 |
| 0-30 (N = 364) | 37% | 60% | 2% |
| 0-90 (N = 373) | 47% | 51% | 2% |
| 0-180 (N = 377) | 56% | 42% | 2% |
| 0-365 (N = 380) | 63% | 36% | 1% |

Time-averaged MMF dose = (total MMF dose)/(duration of treatment)

a) Percentage of patients for each time-averaged MMF dose range during various treatment periods. Two g/day of time-averaged MMF dose means that MMF dose was not reduced in those patients during the treatment periods.

In a second randomized, open-label, multi-center trial (Study 2), 424 kidney transplant patients received Prograf (n = 212) or cyclosporine (n = 212) in combination with MMF 1 gram BID, basiliximab induction, and corticosteroids. In this study, the rate for the combined endpoint of biopsy proven acute rejection, graft failure, death, and/or lost to follow-up at 12 months in the Prograf/MMF group was similar to the rate in the cyclosporine/MMF group. There was, however, an imbalance in mortality at 12 months in those patients receiving Prograf/MMF (4.2%) compared to those receiving cyclosporine/MMF (2.4%), including cases attributed to over-immunosuppression (Table 5).

**Table 5: Incidence of BPAR, Graft Loss, Death or Loss to Follow-up at 12 Months in Study 2**

| | Prograf/MMF (n = 212) | Cyclosporine/MMF (n = 212) |
|---|---|---|
| Overall Failure | 32 (15.1%) | 36 (17.0%) |
| Components of efficacy failure<br>BPAR<br>Graft loss excluding death<br>Mortality<br>Lost to follow-up | <br>16 (17.5%)<br>6 (2.8%)<br>9 (4.2%)<br>4 (1.9%) | <br>29 (13.7%)<br>4 (1.9%)<br>5 (2.4%)<br>1 (0.5%) |
| Treatment Difference of efficacy failure compared to Prograf/MMF group (95% CI[a]) | - | 1.9% (-5.2%, 9.0%) |

a) 95% confidence interval calculated using Fisher's Exact Test

The protocol-specified target tacrolimus whole blood trough concentrations ($C_{trough}$, Tac) in Study 2 were 7-16 ng/mL for the first three months and 5-15 ng/mL thereafter. The observed median $C_{trough}$, Tac approximated 10 ng/mL during the first three months and 8 ng/mL from month 4 to month 12 (Table 6).

**Table 6: Tacrolimus Whole Blood Trough Concentrations (Study 2)**

| Time | Median (P10-P90[a]) tacrolimus whole blood trough concentrations (ng/mL) |
|---|---|
| Day 30 (N = 174) | 10.5 (6.3 – 16.8) |
| Day 60 (N = 179) | 9.2 (5.9 – 15.3) |
| Day 120 (N = 176) | 8.3 (4.6 – 13.3) |
| Day 180 (N = 171) | 7.8 (5.5 – 13.2) |
| Day 365 (N = 178) | 7.1 (4.2 – 12.4) |

a) Range of $C_{trough}$, Tac that excludes lowest 10% and highest 10% of $C_{trough}$, Tac

The protocol-specified target cyclosporine whole blood concentrations ($C_{trough}$, CsA) were 125 to 400 ng/mL for the first three months, and 100 to 300 ng/mL thereafter. The observed median $C_{trough}$, CsA approximated 280 ng/mL during the first three months and 190 ng/mL from month 4 to month 12.

Patients in both groups started MMF at 1g BID. The MMF dose was reduced to < 2 g/day by month 12 in 62% of patients in the Prograf/MMF group (Table 7) and in 47% of patients in the cyclosporine/MMF group. Approximately 63% and 55% of these MMF dose reductions were because of adverse events in the Prograf/MMF group and the cyclosporine/MMF group, respectively.

**Table 7: MMF Dose Over Time in the Prograf/MMF group (Study 2)**

| Time period (Days) | Time-averaged MMF dose (g/day)[a] | | |
|---|---|---|---|
| | < 2.0 | 2.0 | > 2.0 |
| 0-30 (N = 212) | 25% | 69% | 6% |
| 0-90 (N = 212) | 41% | 53% | 6% |
| 0-180 (N = 212) | 52% | 41% | 7% |
| 0-365 (N = 212) | 62% | 34% | 4% |

Time-averaged MMF dose = (total MMF dose)/(duration of treatment)

a) Percentage of patients for each time-averaged MMF dose range during various treatment periods. Two g/day of time-averaged MMF dose means that MMF dose was not reduced in those patients during the treatment periods.

***Lupus nephritis***

Patients with lupus nephritis who were refractory to steroid monotherapy and exhibited clinical signs of chronic nephritis with immunological activity were treated with this product for 28 weeks in the Phase III trial. The rate of change in the total

score* of disease activity at the final measurement was −32.9%. The rate of change in the actual values of daily urinary protein excretion and complement (C3), which are indexes of chronic nephritis and immunological activity, respectively, were −60.8% and 16.4%, and the change in creatinine clearance (CCr) was −22.0%.

| | Tacrolimus group [n = 27] | Placebo group [n = 34] | 95% confidence intervals for the differences between groups |
|---|---|---|---|
| The rate of change in the total score of disease activity* (%), mean ± SD | –32.9 ± 31.0 | 2.3 ± 38.2 | − |
| The rate of change in the actual value of daily urinary protein excretion (%), median (1st quartile, 3rd quartile) | –60.8 (–73.7, –37.2) | 8.7 (–14.0, 90.0) | [–115.0 to –48.7] |
| The rate of change in the actual value of complement (C3) (%), median (1st quartile, 3rd quartile) | 16.4 (10.3, 27.5) | –2.8 (–11.1, 18.2) | [8.5 to 26.7] |
| The rate of change in the actual value of CCr (%), median (1st quartile, 3rd quartile) | –22.0** (–33.5, –4.2) | –1.4 (–19.3, 16.9) | [–30.5 to –3.4] |

* Total score of disease activity consists of the sum of the scores (a 4-point scale, ranging from 0 to 3 per item) of 5 items: daily urinary protein excretion, urinary red blood cells, serum creatinine, anti-ds DNA antibody, and complement (C3).

** As for the evaluation of CCr only, the number of cases for the tacrolimus group was 26.

## 15 HOW SUPPLIED/STORAGE AND HANDLING

**Prograf capsules (tacrolimus capsules) 0.5 mg**
Supplied in 5 blister cards of 10 capsules.

**Prograf capsules (tacrolimus capsules) 1 mg**
Supplied in 5 blister cards of 10 capsules.

***Store***
Store below 30°C.

**Prograf injection (tacrolimus injection) 5 mg (for intravenous infusion only)**
Supplied as a sterile solution in 1-mL ampoules, in boxes of 10 ampoules.

***Store***
Store below 25°C, protect from light.

**Instructions for use and handling**

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.

**Reference:**

1. CDC: Recommendations of the Advisory Committee on Immunization Practices: Use of vaccines and immune globulins in persons with altered immunocompetence. MMWR 1993;42 (RR-4):1-18.

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