

1 Revised: May 2004

2 **Prograf[®]**

3 *tacrolimus capsules*

4 *tacrolimus injection (for intravenous infusion only)*

6 **WARNING**

7 Increased susceptibility to infection and the possible development of lymphoma may
8 result from immunosuppression. Only physicians experienced in immunosuppressive
9 therapy and management of organ transplant patients should prescribe Prograf. Patients
10 receiving the drug should be managed in facilities equipped and staffed with adequate
11 laboratory and supportive medical resources. The physician responsible for maintenance
12 therapy should have complete information requisite for the follow-up of the patient.

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14 **DESCRIPTION:**

15 Prograf is available for oral administration as capsules (tacrolimus capsules) containing
16 the equivalent of 0.5 mg, 1 mg or 5 mg of anhydrous tacrolimus. Inactive ingredients
17 include lactose, hydroxypropyl methylcellulose, croscarmellose sodium, and magnesium
18 stearate. The 0.5 mg capsule shell contains gelatin, titanium dioxide and ferric oxide, the
19 1 mg capsule shell contains gelatin and titanium dioxide, and the 5 mg capsule shell
20 contains gelatin, titanium dioxide and ferric oxide.

21 Prograf is also available as a sterile solution (tacrolimus injection) containing the
22 equivalent of 5 mg anhydrous tacrolimus in 1 mL for administration by intravenous
23 infusion only. Each mL contains polyoxyl 60 hydrogenated castor oil (HCO-60), 200
24 mg, and dehydrated alcohol, USP, 80.0% v/v. Prograf injection must be diluted with
25 0.9% Sodium Chloride Injection or 5% Dextrose Injection before use.

26 Tacrolimus, previously known as FK506, is the active ingredient in Prograf.
27 Tacrolimus is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*.
28 Chemically, tacrolimus is designated as [3*S*-[3*R**[*E*(1*S**,3*S**,4*S**),
29 4*S**,5*R**,8*S**,9*E*,12*R**,14*R**,15*S**,16*R**,18*S**,19*S**,26*aR**]]-
30 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26*a*-hexadecahydro-5,19-dihydroxy-3-[2-(4-
31 hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-
32 tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-*c*][1,4] oxazacyclotricosine-
33 1,7,20,21(4*H*,23*H*)-tetrone, monohydrate.

Population	N	Route (Dose)	Parameters					
			C _{max} (ng/mL)	T _{max} (hr)	AUC (ng•hr/mL)	t _{1/2} (hr)	CI (L/hr/kg)	V (L/kg)
Healthy Volunteers	8	IV (0.025 mg/kg/4hr)	---	---	598* ± 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** ± 73	34.8 ± 11.4	0.041† ± 0.008	1.94† ± 0.53
Kidney Transplant Pts	26	IV (0.02 mg/kg/12 hr)	---	---	294*** ± 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*** ± 42	#	#	#
		PO (0.3 mg/kg/day)	24.2 ± 15.8	1.5	288*** ± 93	#	#	#
Liver Transplant Pts	17	IV (0.05 mg/kg/12 hr)	---	---	3300*** ± 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*** ± 179	#	#	#

81 Corrected for individual bioavailability

82 *AUC₀₋₁₂₀

83 **AUC₀₋₇₂

84 ***AUC_{0-inf}

85 -- not applicable

86 # not available

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88 Due to intersubject variability in tacrolimus pharmacokinetics, individualization of
 89 dosing regimen is necessary for optimal therapy. (See **DOSAGE AND**
 90 **ADMINISTRATION**). Pharmacokinetic data indicate that whole blood concentrations
 91 rather than plasma concentrations serve as the more appropriate sampling compartment to
 92 describe tacrolimus pharmacokinetics.

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94 Absorption

95 Absorption of tacrolimus from the gastrointestinal tract after oral administration is
 96 incomplete and variable. The absolute bioavailability of tacrolimus was 17±10% in
 97 adult kidney transplant patients (N=26), 22±6% in adult liver transplant patients (N=17),
 98 and 18±5% in healthy volunteers (N=16).

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100 A single dose study conducted in 32 healthy volunteers established the
 101 bioequivalence of the 1 mg and 5 mg capsules. Another single dose study in 32 healthy
 102 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

103 increase in a dose-proportional fashion in 18 fasted healthy volunteers receiving a single
104 oral dose of 3, 7, and 10 mg.

105 In 18 kidney transplant patients, tacrolimus trough concentrations from 3 to 30
106 ng/mL measured at 10-12 hours post-dose (C_{min}) correlated well with the AUC
107 (correlation coefficient 0.93). In 24 liver transplant patients over a concentration range of
108 10 to 60 ng/mL, the correlation coefficient was 0.94.

109 *Food Effects:* The rate and extent of tacrolimus absorption were greatest under
110 fasted conditions. The presence and composition of food decreased both the rate and
111 extent of tacrolimus absorption when administered to 15 healthy volunteers.

112 The effect was most pronounced with a high-fat meal (848 kcal, 46% fat): mean
113 AUC and C_{max} were decreased 37% and 77%, respectively; T_{max} was lengthened 5-fold.
114 A high-carbohydrate meal (668 kcal, 85% carbohydrate) decreased mean AUC and mean
115 C_{max} by 28% and 65%, respectively.

116 In healthy volunteers (N=16), the time of the meal also affected tacrolimus
117 bioavailability. When given immediately following the meal, mean C_{max} was reduced
118 71%, and mean AUC was reduced 39%, relative to the fasted condition. When
119 administered 1.5 hours following the meal, mean C_{max} was reduced 63%, and mean AUC
120 was reduced 39%, relative to the fasted condition.

121 In 11 liver transplant patients, Prograf administered 15 minutes after a high fat
122 (400 kcal, 34% fat) breakfast, resulted in decreased AUC ($27\pm 18\%$) and C_{max} ($50\pm 19\%$),
123 as compared to a fasted state.

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125 Distribution

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

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134 Metabolism

135 Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily
136 the cytochrome P-450 system (CYP3A). A metabolic pathway leading to the formation
137 of 8 possible metabolites has been proposed. Demethylation and hydroxylation were
138 identified as the primary mechanisms of biotransformation in vitro. The major
139 metabolite identified in incubations with human liver microsomes is 13-demethyl
140 tacrolimus. In in vitro studies, a 31-demethyl metabolite has been reported to have the
141 same activity as tacrolimus.

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143 Excretion

144 The mean clearance following IV administration of tacrolimus is 0.040, 0.083 and 0.053
145 L/hr/kg in healthy volunteers, adult kidney transplant patients and adult liver transplant
146 patients, respectively. In man, less than 1% of the dose administered is excreted
147 unchanged in urine.

148 In a mass balance study of IV administered radiolabeled tacrolimus to 6 healthy
149 volunteers, the mean recovery of radiolabel was $77.8 \pm 12.7\%$. Fecal elimination
150 accounted for $92.4 \pm 1.0\%$ and the elimination half-life based on radioactivity was
151 48.1 ± 15.9 hours whereas it was 43.5 ± 11.6 hours based on tacrolimus concentrations.
152 The mean clearance of radiolabel was 0.029 ± 0.015 L/hr/kg and clearance of tacrolimus
153 was 0.029 ± 0.009 L/hr/kg. When administered PO, the mean recovery of the radiolabel
154 was $94.9 \pm 30.7\%$. Fecal elimination accounted for $92.6 \pm 30.7\%$, urinary elimination
155 accounted for $2.3 \pm 1.1\%$ and the elimination half-life based on radioactivity was
156 31.9 ± 10.5 hours whereas it was 48.4 ± 12.3 hours based on tacrolimus concentrations.
157 The mean clearance of radiolabel was 0.226 ± 0.116 L/hr/kg and clearance of tacrolimus
158 0.172 ± 0.088 L/hr/kg.

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160 Special Populations

161 Pediatric

162 Pharmacokinetics of tacrolimus have been studied in liver transplantation patients, 0.7 to
163 13.2 years of age. Following IV administration of a 0.037 mg/kg/day dose to 12 pediatric
164 patients, mean terminal half-life, volume of distribution and clearance were 11.5 ± 3.8
165 hours, 2.6 ± 2.1 L/kg and 0.138 ± 0.071 L/hr/kg, respectively. Following oral
166 administration to 9 patients, mean AUC and C_{\max} were 337 ± 167 ng·hr/mL and 43.4 ± 27.9
167 ng/mL, respectively. The absolute bioavailability was $31 \pm 21\%$.

168 Whole blood trough concentrations from 31 patients less than 12 years old
169 showed that pediatric patients needed higher doses than adults to achieve similar
170 tacrolimus trough concentrations. (See **DOSAGE AND ADMINISTRATION**).

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172 Renal and Hepatic Insufficiency

173 The mean pharmacokinetic parameters for tacrolimus following single administrations to
174 patients with renal and hepatic impairment are given in the following table.

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Population (No. of Patients)	Dose	AUC _{0-t} (ng·hr/mL)	t _{1/2} (hr)	V (L/kg)	CI (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/4hr IV	367±107 (t=72 hr)	60.6±43.8 Range: 27.8 – 141	3.1±1.6	0.042±0.02
	7.7 mg PO	488±320 (t=72 hr)	66.1±44.8 Range: 29.5 – 138	3.7±4.7*	0.034±0.019*
Severe Hepatic Impairment (n=6, IV) (n=5, PO)†	0.02 mg/kg/4hr IV (n=2)	762±204 (t=120 hr)	198±158 Range:81-436	3.9±1.0	0.017±0.013
	0.01 mg/kg/8hr IV (n=4)	289±117 (t=144 hr)			
	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) 4 mg PO (n=1)	533±156 (t=144 hr)			

*corrected for bioavailability

† 1 patient did not receive the PO dose

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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.**)

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Gender

A formal study to evaluate the effect of gender on tacrolimus pharmacokinetics has not been conducted, however, there was no difference 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.

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 randomized 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 encephopathy, 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 and 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.

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-based immunosuppression following kidney transplantation was assessed in a Phase III randomized, multicenter, non-blinded, prospective study. There were 412 kidney transplant patients enrolled at 19 clinical sites in the United States. Study

269 therapy was initiated when renal function was stable as indicated by a serum
 270 creatinine \leq 4 mg/dL (median of 4 days after transplantation, range 1 to 14 days).
 271 Patients less than 6 years of age were excluded.

272 There were 205 patients randomized to Prograf-based immunosuppression and
 273 207 patients were randomized to cyclosporine-based immunosuppression. All
 274 patients received prophylactic induction therapy consisting of an antilymphocyte
 275 antibody preparation, corticosteroids and azathioprine.

276 Overall one year patient and graft survival was 96.1% and 89.6%, respectively
 277 and was equivalent between treatment arms.

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

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282 **INDICATIONS AND USAGE:**

283 Prograf is indicated for the prophylaxis of organ rejection in patients receiving
 284 allogeneic liver or kidney transplants. It is recommended that Prograf be used
 285 concomitantly with adrenal corticosteroids. Because of the risk of anaphylaxis,
 286 Prograf injection should be reserved for patients unable to take Prograf capsules
 287 orally.

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289 **CONTRAINDICATIONS:**

290 Prograf is contraindicated in patients with a hypersensitivity to tacrolimus. Prograf
 291 injection is contraindicated in patients with a hypersensitivity to HCO-60 (polyoxyl
 292 60 hydrogenated castor oil).

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294 **WARNINGS:**

295 (See boxed **WARNING**.)

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

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303 **Incidence of Post Transplant Diabetes Mellitus and Insulin Use at 2 Years in**
 304 **Kidney Transplant Recipients in the Phase III Study**

Status of PTDM*	Prograf	CBIR
Patients without pretransplant history of diabetes mellitus.	151	151
New onset PTDM*, 1 st 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%)

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* 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.

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Development of Post Transplant Diabetes Mellitus by Race and by Treatment Group during First Year Post Kidney Transplantation in the Phase III Study

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.

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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 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 pretransplant history of diabetes mellitus.

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Prograf can cause neurotoxicity and 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**). More overt nephrotoxicity is seen early after transplantation, characterized by increasing serum creatinine and a decrease in urine output. Patients with impaired renal function should be monitored closely as the dosage of Prograf may need to be reduced. In patients with persistent elevations of serum creatinine who are unresponsive to dosage adjustments, consideration should be given to changing to another immunosuppressive therapy. Care should be taken in using tacrolimus with

338 other nephrotoxic drugs. **In particular, to avoid excess nephrotoxicity, Prograf**
339 **should not be used simultaneously with cyclosporine. Prograf or cyclosporine**
340 **should be discontinued at least 24 hours prior to initiating the other. In the**
341 **presence of elevated Prograf or cyclosporine concentrations, dosing with the**
342 **other drug usually should be further delayed.**

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

349 Neurotoxicity, including tremor, headache, and other changes in motor function,
350 mental status, and sensory function were reported in approximately 55% of liver
351 transplant recipients in the two randomized studies. Tremor occurred more often in
352 Prograf-treated kidney transplant patients (54%) compared to cyclosporine-treated
353 patients. The incidence of other neurological events in kidney transplant patients was
354 similar in the two treatment groups (see **ADVERSE REACTIONS**). Tremor and
355 headache have been associated with high whole-blood concentrations of tacrolimus
356 and may respond to dosage adjustment. Seizures have occurred in adult and pediatric
357 patients receiving Prograf (see **ADVERSE REACTIONS**). Coma and delirium also
358 have been associated with high plasma concentrations of tacrolimus. As in patients
359 receiving other immunosuppressants, patients receiving Prograf are at increased risk
360 of developing lymphomas and other malignancies, particularly of the skin. The risk
361 appears to be related to the intensity and duration of immunosuppression rather than
362 to the use of any specific agent. A lymphoproliferative disorder (LPD) related to
363 Epstein-Barr Virus (EBV) infection has been reported in immunosuppressed organ
364 transplant recipients. The risk of LPD appears greatest in young children who are at
365 risk for primary EBV infection while immunosuppressed or who are switched to
366 Prograf following long-term immunosuppression therapy. Because of the danger of
367 oversuppression of the immune system which can increase susceptibility to infection,
368 combination immunosuppressant therapy should be used with caution.

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

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

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382 **PRECAUTIONS:**
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General

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*).

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. The 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**).

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.

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.

429 Patients should be informed that Prograf can cause diabetes mellitus and should be
430 advised of the need to see their physician if they develop frequent urination, increased
431 thirst or hunger. As with other immunosuppressive agents, owing to the potential risk
432 of malignant skin changes, exposure to sunlight and ultraviolet (UV) light should be
433 limited by wearing protective clothing and using a sunscreen with a high protection
434 factor.

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436 ***Laboratory Tests***

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

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441 ***Drug Interactions***

442 Due to the potential for additive or synergistic impairment of renal function, care
443 should be taken when administering Prograf with drugs that may be associated with
444 renal dysfunction. These include, but are not limited to , aminoglycosides,
445 amphotericin B, and cisplatin. Initial clinical experience with the co-administration
446 of Prograf and cyclosporine resulted in additive/synergistic nephrotoxicity. Patients
447 switched from cyclosporine to Prograf should receive the first Prograf dose no sooner
448 than 24 hours after the last cyclosporine dose. Dosing may be further delayed in the
449 presence of elevated cyclosporine levels.

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451 ***Drugs that May Alter Tacrolimus Concentrations***

452 Since tacrolimus is metabolized mainly by the CYP3A enzyme systems, substances
453 know to inhibit these enzymes may decrease the metabolism or increase
454 bioavailability of tacrolimus as indicated by increased whole blood or plasma
455 concentrations. Drugs known to induce these enzyme systems may result in an
456 increased metabolism of tacrolimus or decreased bioavailability as indicated by
457 decreased whole blood or plasma concentrations. Monitoring of blood concentrations
458 and appropriate dosage adjustments are essential when such drugs are used
459 concomitantly.

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461 ***Drugs That May Increase Tacrolimus Blood Concentrations:***

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463 **Calcium**
464 **Channel Blockers**

465 diltiazem
466 nifedipine
467 nifedipine
468 verapamil

463 **Antifungal**
464 **Agents**

465 clotrimazole
466 fluconazole
467 itraconazole
468 ketoconazole
469 voriconazole

463 **Macrolide**
464 **Antibiotics**

465 clarithromycin
466 erythromycin
467 troleandomycin

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472 **Gastrointestinal**
473 **Prokinetic Agents**

474 cisapride
475 metoclopramide

472 **Other**
473 **Drugs**

474 bromocriptine
475 chloramphenicol
476 cimetidine
477 cyclosporine
478 danazol
479 ethinyl estradiol

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 481 omeprazole
 482 protease inhibitors
 483 nefazodone
 484 magnesium-aluminum-hydroxide
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486 In a study of 6 normal volunteers, a significant increase in tacrolimus oral
 487 bioavailability (14±5% vs. 30±8%) was observed with concomitant ketoconazole
 488 administration (200 mg). The apparent oral clearance of tacrolimus during
 489 ketoconazole administration was significantly decreased compared to tacrolimus
 490 alone (0.430±0.129 L/hr/kg vs. 0.148±0.043 L/hr/kg). Overall, IV clearance of
 491 tacrolimus was not significantly changed by ketoconazole co-administration, although
 492 it was highly variable between patients.

493
 494 ***Drugs That May Decrease Tacrolimus Blood Concentrations:**

495
 496 **Anticonvulsants**

497 carbamazepine
 498 phenobarbital
 499 phenytoin

495
 496 **Antimicrobials**

497 rifabutin
 498 caspofungin
 499 rifampin

500
 501
 502 **Herbal Preparations**

503 St. John's Wort

500
 501
 502 **Other Drugs**

503 sirolimus

504
 505
 506 *This table is not all inclusive.
 507

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

511 In a single-dose crossover study in healthy volunteers, co-administration of
 512 tacrolimus and magnesium-aluminum-hydroxide resulted in a 21% increase in the
 513 mean tacrolimus AUC and a 10% decrease in the mean tacrolimus C_{max} relative to
 514 tacrolimus administration alone.

515 In a study of 6 normal volunteers, a significant decrease in tacrolimus oral
 516 bioavailability (14±6% vs. 7±3%) was observed with concomitant rifampin
 517 administration (600 mg). In addition, there was a significant increase in tacrolimus
 518 clearance (0.036±0.008 L/hr/kg vs. 0.053±0.010 L/hr/kg) with concomitant rifampin
 519 administration.

520 Interaction studies with drugs used in HIV therapy have not been conducted.
 521 However, care should be exercised when drugs that are nephrotoxic (e.g., ganciclovir)
 522 or that are metabolized by CYP3A (e.g., nelfinavir, ritonavir) are administered
 523 concomitantly with tacrolimus. Based on a clinical study of 5 liver transplant
 524 recipients, co-administration of tacrolimus with nelfinavir increased blood
 525 concentrations of tacrolimus significantly and, as a result, a reduction in the
 526 tacrolimus dose by an average of 16-fold was needed to maintain mean trough
 527 tacrolimus blood concentrations of 9.7 mg/mL. Thus, frequent monitoring of
 528 tacrolimus blood concentrations and appropriate dosage adjustment are essential
 529 when nelfinavir is used concomitantly. Tacrolimus may affect the pharmacokinetics
 530 of other drugs (e.g., phenytoin) and increase their concentration. Grapefruit juice

531 affects CYP3A-mediated metabolism and should be avoided (see **DOSAGE AND**
532 **ADMINISTRATION**).

533 Following co-administration of tacrolimus and sirolimus (2 or 5 mg/day) in stable
534 renal transplant patients, mean tacrolimus AUC_{0-12} and C_{min} decreased approximately
535 by 30% relative to tacrolimus alone. Mean tacrolimus AUC_{0-12} and C_{min} following
536 co-administration of 1 mg/day of sirolimus decreased approximately 3% and 11%,
537 respectively. The safety and efficacy of tacrolimus used in combination with
538 sirolimus for the prevention of graft rejection has not been established and is not
539 recommended.

540

541 ***Other Drug Interactions***

542 Immunosuppressants may affect vaccination. Therefore, during treatment with
543 Prograf, vaccination may be less effective. The use of live vaccines should be
544 avoided; live vaccines may include, but are not limited to measles, mumps, rubella,
545 oral polio, BCG, yellow fever, and TY 21a typhoid.¹

546

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

548 An increased incidence of malignancy is a recognized complication of
549 immunosuppression in recipients of organ transplants. The most common forms of
550 neoplasms are non-Hodgkin's lymphomas and carcinomas of the skin. As with other
551 immunosuppressive therapies, the risk of malignancies in Prograf recipients may be
552 higher than in the normal, healthy population.

553 Lymphoproliferative disorders associated with Epstein-Barr Virus infection have
554 been seen. It has been reported that reduction or discontinuation of
555 immunosuppression may cause the lesions to regress.

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

561 Carcinogenicity studies were carried out in male and female rats and mice. In the
562 80-week mouse study and in the 104-week rat study no relationship of tumor
563 incidence to tacrolimus dosage was found. The highest doses used in the mouse and
564 rat studies were 0.8 – 2.5 times (mice) and 3.5 – 7.1 times (rats) the recommended
565 clinical dose range of 0.1 – 0.2 mg/kg/day when corrected for body surface area.

566 No impairment of fertility was demonstrated in studies of male and female rats.
567 Tacrolimus, given orally at 1.0 mg/kg (0.7 – 1.4X the recommended clinical dose
568 range of 0.1 – 0.2 mg/kg/day based on body surface area corrections) to male and
569 female rats, prior to and during mating, as well as to dams during gestation and
570 lactation, was associated with embryoletality and with adverse effects on female
571 reproduction. Effects on female reproductive function (parturition) and embryoletal
572 effects were indicated by a higher rate of pre-implantation loss and increased numbers
573 of undelivered and nonviable pups. When given at 3.2 mg/kg (2.3 – 4.6X the
574 recommended clinical dose range based on body surface area correction), tacrolimus
575 was associated with maternal and paternal toxicity as well as reproductive toxicity

576 including marked adverse effects on estrus cycles, parturition, pup viability, and pup
577 malformations.

578

579 ***Pregnancy: Category C***

580 In reproduction studies in rats and rabbits, adverse effects on the fetus were observed
581 mainly at dose levels that were toxic to dams. Tacrolimus at oral doses of 0.32 and
582 1.0 mg/kg during organogenesis in rabbits was associated with maternal toxicity as
583 well as an increase in incidence of abortions; these doses are equivalent to 0.5 – 1X
584 and 1.6 – 3.3X the recommended clinical dose range (0.1 – 0.2 mg/kg) based on body
585 surface area corrections. At the higher dose only, an increased incidence of
586 malformations and developmental variations was also seen. Tacrolimus, at oral doses
587 of 3.2 mg/kg during organogenesis in rats, was associated with maternal toxicity and
588 caused an increase in late resorptions, decreased numbers of live births, and decreased
589 pup weight and viability. Tacrolimus, given orally at 1.0 and 3.2 mg/kg (equivalent
590 to 0.7 – 1.4X and 2.3 – 4.6X the recommended clinical dose range based on body
591 surface area corrections) to pregnant rats after organogenesis and during lactation,
592 was associated with reduced pup weights.

593 No reduction in male or female fertility was evident.

594 There are no adequate and well-controlled studies in pregnant women.

595 Tacrolimus is transferred across the placenta. The use of tacrolimus during
596 pregnancy has been associated with neonatal hyperkalemia and renal dysfunction.

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

599

600 ***Nursing Mothers***

601 Since tacrolimus is excreted in human milk, nursing should be avoided.

602

603 ***Pediatric Patients***

604 Experience with Prograf in pediatric kidney transplant patients is limited. Successful
605 liver transplants have been performed in pediatric patients (ages up to 16 years) using
606 Prograf. Two randomized active-controlled trials of Prograf in primary liver
607 transplantation included 56 pediatric patients. Thirty-one patients were randomized
608 to Prograf-based and 25 to cyclosporine-based therapies. Additionally, a minimum of
609 122 pediatric patients were studied in an uncontrolled trial of tacrolimus in living
610 related donor liver transplantation. Pediatric patients generally required higher doses
611 of Prograf to maintain blood trough concentrations of tacrolimus similar to adult
612 patients (see **DOSAGE AND ADMINISTRATION**).

613

614 **ADVERSE REACTIONS:**

615 ***Liver Transplantation***

616 The principal adverse reactions of Prograf are tremor, headache, diarrhea,
617 hypertension, nausea, and renal dysfunction. These occur with oral and IV
618 administration of Prograf and may respond to a reduction in dosing. Diarrhea was
619 sometimes associated with other gastrointestinal complaints such as nausea and
620 vomiting.

621 Hyperkalemia and hypomagnesemia have occurred in patients receiving Prograf
 622 therapy. Hyperglycemia has been noted in many patients; some may require insulin
 623 therapy (see **WARNINGS**).

624 The incidence of adverse events was determined in two randomized comparative
 625 liver transplant trials among 514 patients receiving tacrolimus and steroids and 515
 626 patients receiving a cyclosporine-based regimen (CBIR). The proportion of patients
 627 reporting more than one adverse event was 99.8% in the tacrolimus group and 99.6%
 628 in the CBIR group. Precautions must be taken when comparing the incidence of
 629 adverse events in the U.S. study to that in the European study. The 12-month
 630 posttransplant information from the U.S. study and from the European study is
 631 presented below. The two studies also included different patient populations and
 632 patients were treated with immunosuppressive regimens of differing intensities.
 633 Adverse events reported in $\geq 15\%$ in tacrolimus patients (combined study results) are
 634 presented below for the two controlled trials in liver transplantation:
 635

LIVER TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN $\geq 15\%$ OF PROGRAF-TREATED PATIENTS				
	U.S. STUDY (%)		EUROPEAN STUDY (%)	
	Prograf (N=250)	CBIR (N=250)	Prograf (N=264)	CBIR (N=265)
<u>Nervous System</u>				
Headache (See WARNINGS)	64	60	37	26
Tremor (See WARNINGS)	56	46	48	32
Insomnia	64	68	32	23
Paresthesia	40	30	17	17
<u>Gastrointestinal</u>				
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
<u>Cardiovascular</u>				
Hypertension (See PRECAUTIONS)	47	56	38	43
<u>Urogenital</u>				
Kidney Function Abnormal (See WARNINGS)	40	27	36	23
Creatinine Increased (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
<u>Metabolic and Nutritional</u>				
Hyperkalemia (See WARNINGS)	45	26	13	9
Hypokalemia	29	34	13	16
Hyperglycemia (See WARNINGS)	47	38	33	22
Hypomagnesemia	48	45	16	9
<u>Hemic and Lymphatic</u>				
Anemia	47	38	5	1
Leukocytosis	32	26	8	8
Thrombocytopenia	24	20	14	19

<u>Miscellaneous</u>				
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
<u>Respiratory System</u>				
Pleural Effusion	30	32	36	35
Atelectasis	28	30	5	4
Dyspnea	29	23	5	4
<u>Skin and Appendages</u>				
Pruritus	36	20	15	7
Rash	24	19	10	4

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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 $\geq 15\%$ of Prograf-treated kidney transplant patients are presented below:

KIDNEY TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN $\geq 15\%$ OF PROGRAF-TREATED PATIENTS		
	Prograf (N=205)	CBIR (N=207)
<u>Nervous System</u>		
Tremor (see WARNINGS)	54	34
Headache (see WARNINGS)	44	38
Insomnia	32	30
Paresthesia	23	16
Dizziness	19	16
<u>Gastrointestinal</u>		
Diarrhea	44	41
Nausea	38	36
Constipation	35	43
Vomiting	29	23
Dyspepsia	28	20
<u>Cardiovascular</u>		

Hypertension (see PRECAUTIONS)	50	52
Chest pain	19	13
<u>Urogenital</u>		
Creatinine increased (see WARNINGS)	45	42
Urinary tract infection	34	35
<u>Metabolic and Nutritional</u>		
Hypophosphatemia	49	53
Hypomagnesemia	34	17
Hyperlipemia	31	38
Hyperkalemia (see WARNINGS)	31	32
Diabetes mellitus (see WARNINGS)	24	9
Hypokalemia	22	25
Hyperglycemia (see WARNINGS)	22	16
Edema	18	19
<u>Hemic and Lymphatic</u>		
Anemia	30	24
Leukopenia	15	17
<u>Miscellaneous</u>		
Infection	45	49
Peripheral edema	36	48
Asthenia	34	30
Abdominal pain	33	31
Pain	32	30
Fever	29	29
Back pain	24	20
<u>Respiratory System</u>		
Dyspnea	22	18
Cough increased	18	15
<u>Musculoskeletal</u>		
Arthralgia	25	24
<u>Skin</u>		
Rash	17	12
Pruritus	15	7

650

651

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

655

656 **Less Frequently Reported Adverse Reactions**

657 The following adverse events were reported in the range of 3% to less than 15%
 658 incidence in either liver or kidney transplant recipients who were treated with tacrolimus
 659 in the Phase 3 comparative trials.

660 **NERVOUS SYSTEM:** (see **WARNINGS**) abnormal dreams, agitation, amnesia,
 661 anxiety, confusion, convulsion, depression, dizziness, emotional lability, encephalopathy,
 662 hallucinations, hypertonia, incoordination, myoclonus, nervousness, neuropathy,
 663 psychosis, somnolence, thinking abnormal; **SPECIAL SENSES:** abnormal vision,
 664 amblyopia, ear pain, otitis media, tinnitus; **GASTROINTESTINAL:** anorexia,
 665 cholangitis, cholestatic jaundice, dyspepsia, dysphagia, esophagitis, flatulence, gastritis,
 666 gastrointestinal hemorrhage, GGT increase, GI perforation, hepatitis, ileus, increased

667 appetite, jaundice, liver damage, liver function test abnormal, oral moniliasis, rectal
668 disorder, stomatitis; **CARDIOVASCULAR**: angina pectoris, chest pain, deep
669 thrombophlebitis, abnormal ECG, hemorrhage, hypotension, postural hypotension,
670 peripheral vascular disorder, phlebitis, tachycardia, thrombosis, vasodilatation;
671 **UROGENITAL**: (see **WARNINGS**) albuminuria, cystitis, dysuria, hematuria,
672 hydronephrosis, kidney failure, kidney tubular necrosis, nocturia, pyuria, toxic
673 nephropathy, oliguria, urinary frequency, urinary incontinence, vaginitis;
674 **METABOLIC/NUTRITIONAL**: acidosis, alkaline phosphatase increased, alkalosis, ALT
675 (SGPT) increased, AST (SGOT) increased, bicarbonate decreased, bilirubinemia, BUN
676 increased, dehydration, GGT increased, healing abnormal, hypercalcemia,
677 hypercholesterolemia, hyperlipemia, hyperphosphatemia, hyperuricemia, hypervolemia,
678 hypocalcemia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, lactic
679 dehydrogenase increase, weight gain; **ENDOCRINE**: (see **PRECAUTIONS**) Cushing's
680 syndrome, diabetes mellitus; **HEMIC/LYMPHATIC**: coagulation disorder, ecchymosis,
681 hypochromic anemia, leukocytosis, leukopenia, polycythemia, prothrombin decreased,
682 serum iron decreased, thrombocytopenia; **MISCELLANEOUS**: abdomen enlarged,
683 abscess, accidental injury, allergic reaction, cellulitis, chills, flu syndrome, generalized
684 edema, hernia, peritonitis, photosensitivity reaction, sepsis, **MUSCULOSKELETAL**:
685 arthralgia, cramps, generalized spasm, joint disorder, leg cramps, myalgia, myasthenia,
686 osteoporosis; **RESPIRATORY**: asthma, bronchitis, cough increased, lung disorder,
687 pneumothorax, pulmonary edema, pharyngitis, pneumonia, respiratory disorder, rhinitis,
688 sinusitis, voice alteration; **SKIN**: acne, alopecia, exfoliative dermatitis, fungal dermatitis,
689 herpes simplex, hirsutism, skin discoloration, skin disorder, skin ulcer, sweating.

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

694 **Post Marketing**

695 The following have been reported: increased amylase including pancreatitis, hearing loss
696 including deafness, leukoencephalopathy, thrombocytopenic purpura, hemolytic-uremic
697 syndrome, acute renal failure, Stevens-Johnson syndrome, stomach ulcer, glycosuria,
698 cardiac arrhythmia, QT prolongation, Torsade de Pointes and gastroenteritis.

702 **OVERDOSAGE:**

703 Limited overdose experience is available. Acute overdoses of up to 30 times the
704 intended dose have been reported. Almost all cases have been asymptomatic and all
705 patients recovered with no sequelae. Occasionally, acute overdose has been followed
706 by adverse reactions consistent with those listed in the **ADVERSE REACTIONS**
707 section except in one case where transient urticaria and lethargy were observed. Based
708 on the poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is
709 anticipated that tacrolimus is not dialyzable to any significant extent; there is no
710 experience with charcoal hemoperfusion. The oral use of activated charcoal has been
711 reported in treating acute overdoses, but experience has not been sufficient to warrant

712 recommending its use. General supportive measures and treatment of specific symptoms
 713 should be followed in all cases of overdose.

714 In acute oral and IV toxicity studies, mortalities were seen at or above the
 715 following doses: in adult rats, 52X the recommended human oral dose; in immature rats,
 716 16X the recommended oral dose; and in adult rats, 16X the recommended human IV dose
 717 (all based on body surface area corrections).

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722 **DOSAGE AND ADMINISTRATION:**

723 ***Prograf injection (tacrolimus injection)***

724

725 ***For IV Infusion Only***

726

727 **NOTE: Anaphylactic reactions have occurred with injectables containing castor oil**
 728 **derivatives. See WARNINGS.**

729

730 In patients unable to take oral Prograf capsules, therapy may be initiated with Prograf
 731 injection. The initial dose of Prograf should be administered no sooner than 6 hours after
 732 transplantation. The recommended starting dose of Prograf injection is 0.03-0.05
 733 mg/kg/day as a continuous IV infusion. Adult patients should receive doses at the lower
 734 end of the dosing range. Concomitant adrenal corticosteroid therapy is recommended
 735 early post-transplantation. Continuous IV infusion of Prograf injection should be
 736 continued only until the patient can tolerate oral administration of Prograf capsules.

737

738 ***Preparation for Administration/Stability***

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

751

752 ***Prograf capsules (tacrolimus capsules) – Summary of Initial Oral Dosage***
 753 ***Recommendations and Typical Whole Blood Trough Concentrations***

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Patient Population	Recommended Initial Oral Dose*	Typical Whole Blood Trough Concentrations
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Adult kidney transplant patients	0.2 mg/kg/day	month 1-3 : 7-20 ng/mL month 4-12 : 5-15 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

*Note: two divided doses, q12h

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Liver Transplantation

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. 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 **Blood Concentration Monitoring: Liver Transplantation** below.

Kidney Transplantation

The recommended starting oral dose of Prograf is 0.2 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 \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 **Blood Concentration 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 Concentrations (ng/mL)	Dose (mg/kg)	Trough Concentrations (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

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790

Pediatric Patients

791 Pediatric liver transplantation patients without pre-existing renal or hepatic dysfunction
 792 have required and tolerated higher doses than adults to achieve similar blood
 793 concentrations. Therefore, it is recommended that therapy be initiated in pediatric
 794 patients at a starting IV dose of 0.03-0.05 mg/kg/day and a starting oral dose of 0.15-0.20
 795 mg/kg/day. Dose adjustments may be required. Experience in pediatric kidney
 796 transplantation patients is limited.

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Patients with Hepatic or Renal Dysfunction

799 Due to the reduced clearance and prolonged half-life, patients with severe hepatic
 800 impairment (Pugh \geq 10) may require lower doses of Prograf. Close monitoring of blood
 801 concentrations is warranted. Due to the potential for nephrotoxicity, patients with renal
 802 or hepatic impairment should receive doses at the lowest value of the recommended IV
 803 and oral dosing ranges. Further reductions in dose below these ranges may be required.
 804 Prograf therapy usually should be delayed up to 48 hours or longer in patients with post-
 805 operative oliguria.

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Conversion from One Immunosuppressive Regimen to Another

808 Prograf should not be used simultaneously with cyclosporine. Prograf or cyclosporine
 809 should be discontinued at least 24 hours before initiating the other. In the presence of
 810 elevated Prograf or cyclosporine concentrations, dosing with the other drug usually
 811 should be further delayed.

812

813

Blood Concentration Monitoring

814 Monitoring of tacrolimus blood concentrations in conjunction with other laboratory and
 815 clinical parameters is considered an essential aid to patient management for the
 816 evaluation of rejection, toxicity, dose adjustments and compliance. Factors influencing
 817 frequency of monitoring include but are not limited to hepatic or renal dysfunction, the
 818 addition or discontinuation of potentially interacting drugs and the posttransplant time.
 819 Blood concentration monitoring is not a replacement for renal and liver function
 820 monitoring and tissue biopsies.

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Two methods have been used for the assay of tacrolimus, a microparticle enzyme
 immunoassay (MEIA) and 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

826 and specimens should be collected into tubes containing ethylene diamine tetraacetic acid
827 (EDTA) anti-coagulant. Heparin anti-coagulation is not recommended because of the
828 tendency to form clots on storage. Samples which are not analyzed immediately should
829 be stored at room temperature or in a refrigerator and assayed within 7 days; if samples
830 are to be kept longer they should be deep frozen at -20° C for up to 12 months.

831

832 ***Liver Transplantation***

833 Although there is a lack of direct correlation between tacrolimus concentrations and drug
834 efficacy, data from Phase II and III studies of liver transplant patients have shown an
835 increasing incidence of adverse events with increasing trough blood concentrations.
836 Most patients are stable when trough whole blood concentrations are maintained between
837 5 to 20 ng/mL. Long-term post-transplant patients often are maintained at the low end of
838 this target range.

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

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

848

849 ***Kidney Transplantation***

850 Data from the Phase III study indicates that trough concentrations of tacrolimus in whole
851 blood, as measured by IMx[®] were most variable during the first week of dosing. During
852 the first three months, 80% of the patients maintained trough concentrations between 7-
853 20 ng/mL, and then between 5-15 ng/mL, through one-year.

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

857

858 **HOW SUPPLIED:**

859 **Prograf capsules (tacrolimus capsules)**

860 **0.5 mg**

861 Oblong, light yellow, branded with red "0.5 mg" on the capsule cap and f 607
862 on the capsule body, supplied in 100-count bottles
863 (NDC 0469-0607-73).

864

865 **Prograf capsules (tacrolimus capsules)**

866 **1 mg**

867 Oblong, white, branded with red "1 mg" on the capsule cap and f 617
868 on the capsule body, supplied in 100-count bottles
869 (NDC 0469-0617-73)

870 and 10 blister cards of 10 capsules (NDC 0469-0617-11), containing the equivalent of 1
871 mg anhydrous tacrolimus.

872

873 **Prograf capsules (tacrolimus capsules)**

874 **5 mg**

875 Oblong, grayish/red, branded with white “5 mg” on the capsule cap and

f

 657

876 on the capsule body, supplied in 100-count bottles

877 (NDC 0469-0657-73)

878 and 10 blister cards of 10 capsules (NDC 0469-0657-11), containing the equivalent of 5

879 mg anhydrous tacrolimus.

880

881 Made in Japan

882

883 *Store and Dispense*

884 Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).

885

886 **Prograf injection (tacrolimus injection)**

887 **5 mg (for IV infusion only)**

888 Supplied as a sterile solution in 1 mL ampules containing the equivalent of 5 mg of

889 anhydrous tacrolimus per mL, in boxes of 10 ampules (NDC 0469-3016-01).

890

891 Made in Ireland

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893 *Store and Dispense*

894 Store between 5°C and 25°C (41°F and 77°F).

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896 **Rx only**

897 Manufactured for:

898 Fujisawa Healthcare, Inc.

899 Deerfield, IL 60015-2548

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902 **REFERENCE:**

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

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907 Revised: March 2004

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