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PROGRAF[®]
tacrolimus capsules
tacrolimus injection

FOR INTRAVENOUS INFUSION ONLY

Revised: July 2005

WARNING

Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Prograf. 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.

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18

DESCRIPTION

19 Prograf is available for oral administration as capsules (tacrolimus capsules)
20 containing the equivalent of 0.5 mg, 1 mg or 5 mg of anhydrous tacrolimus.
21 Inactive ingredients include lactose, hydroxypropyl methylcellulose,
22 croscarmellose sodium, and magnesium stearate. The 0.5 mg capsule shell
23 contains gelatin, titanium dioxide and ferric oxide, the 1 mg capsule shell
24 contains gelatin and titanium dioxide, and the 5 mg capsule shell contains
25 gelatin, titanium dioxide and ferric oxide.
26

27 Prograf is also available as a sterile solution (tacrolimus injection) containing
28 the equivalent of 5 mg anhydrous tacrolimus in 1 mL for administration by
29 intravenous infusion only. Each mL contains polyoxyl 60 hydrogenated castor
30 oil (HCO-60), 200 mg, and dehydrated alcohol, USP, 80.0% v/v. Prograf
31 injection must be diluted with 0.9% Sodium Chloride Injection or 5% Dextrose
32 Injection before use.
33

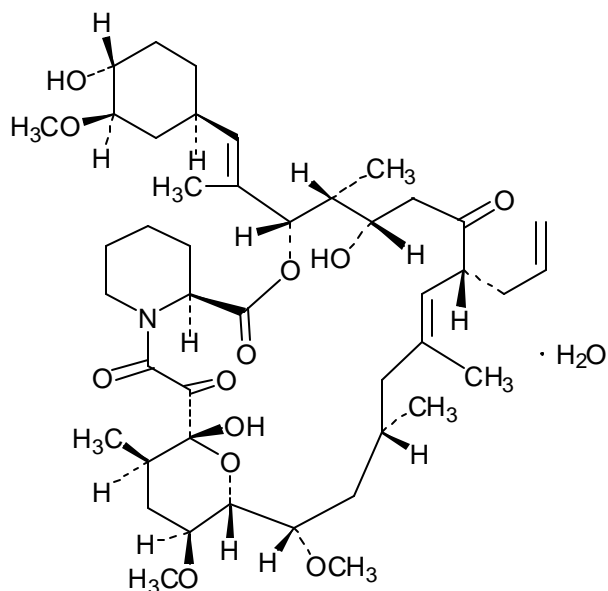
34 Tacrolimus, previously known as FK506, is the active ingredient in Prograf.
35 Tacrolimus is a macrolide immunosuppressant produced by *Streptomyces*
36 *tsukubaensis*. Chemically, tacrolimus is designated as [3S-
37 [3R*[E(1S*,3S*,4S*)], 4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]
38 -5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-
39 dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-
40 dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-
41 c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate.
42

43 The chemical structure of tacrolimus is:

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45

46



75 an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium,
 76 calmodulin, and calcineurin is then formed and the phosphatase activity of
 77 calcineurin inhibited. This effect may prevent the dephosphorylation and
 78 translocation of nuclear factor of activated T-cells (NF-AT), a nuclear
 79 component thought to initiate gene transcription for the formation of
 80 lymphokines (such as interleukin-2, gamma interferon). The net result is the
 81 inhibition of T-lymphocyte activation (i.e., immunosuppression).

82

83 Pharmacokinetics

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

88

89

90

91

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* ± 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	#	#	#

92 †Corrected for individual bioavailability

93 *AUC₀₋₁₂₀

94 **AUC₀₋₇₂

95 ***AUC_{0-inf}

96 --- not applicable

97 # not available

98

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

104

105 **Absorption**

106 Absorption of tacrolimus from the gastrointestinal tract after oral administration
107 is incomplete and variable. The absolute bioavailability of tacrolimus was
108 17±10% in adult kidney transplant patients (N=26), 22±6% in adult liver
109 transplant patients (N=17), and 18±5% in healthy volunteers (N=16).

110

111 A single dose study conducted in 32 healthy volunteers established the
112 bioequivalence of the 1 mg and 5 mg capsules. Another single dose study in
113 32 healthy volunteers established the bioequivalence of the 0.5 mg and 1 mg
114 capsules. Tacrolimus maximum blood concentrations (C_{max}) and area under
115 the curve (AUC) appeared to increase in a dose-proportional fashion in 18
116 fasted healthy volunteers receiving a single oral dose of 3, 7, and 10 mg.

117

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

122

123 *Food Effects*

124 The rate and extent of tacrolimus absorption were greatest under fasted
125 conditions. The presence and composition of food decreased both the rate and
126 extent of tacrolimus absorption when administered to 15 healthy volunteers.

127

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

132

133 In healthy volunteers (N=16), the time of the meal also affected tacrolimus
134 bioavailability. When given immediately following the meal, mean C_{max} was

135 reduced 71%, and mean AUC was reduced 39%, relative to the fasted
136 condition. When administered 1.5 hours following the meal, mean C_{max} was
137 reduced 63%, and mean AUC was reduced 39%, relative to the fasted
138 condition.

139

140 In 11 liver transplant patients, Prograf administered 15 minutes after a high fat
141 (400 kcal, 34% fat) breakfast, resulted in decreased AUC ($27\pm 18\%$) and C_{max}
142 ($50\pm 19\%$), as compared to a fasted state.

143

144 ***Distribution***

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

153

154 ***Metabolism***

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

162

163 ***Excretion***

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

168

169 In a mass balance study of IV administered radiolabeled tacrolimus to 6 healthy
170 volunteers, the mean recovery of radiolabel was $77.8\pm 12.7\%$. Fecal elimination
171 accounted for $92.4\pm 1.0\%$ and the elimination half-life based on radioactivity was
172 48.1 ± 15.9 hours whereas it was 43.5 ± 11.6 hours based on tacrolimus
173 concentrations. The mean clearance of radiolabel was 0.029 ± 0.015 L/hr/kg and
174 clearance of tacrolimus was 0.029 ± 0.009 L/hr/kg. When administered PO, the
175 mean recovery of the radiolabel was $94.9\pm 30.7\%$. Fecal elimination accounted
176 for $92.6\pm 30.7\%$, urinary elimination accounted for $2.3\pm 1.1\%$ and the elimination
177 half-life based on radioactivity was 31.9 ± 10.5 hours whereas it was 48.4 ± 12.3
178 hours based on tacrolimus concentrations. The mean clearance of radiolabel
179 was 0.226 ± 0.116 L/hr/kg and clearance of tacrolimus 0.172 ± 0.088 L/hr/kg.

180

181 **Special Populations**

182 *Pediatric*

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

190

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

195

196 *Renal and Hepatic Insufficiency*

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

200

Population (No. of Patients)	Dose	AUC _{0-t} (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/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)			

201

202

*corrected for bioavailability

[†] 1 patient did not receive the PO dose

203

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

209

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

212

213 *Hepatic Insufficiency:* Tacrolimus pharmacokinetics have been determined in
214 six patients with mild hepatic dysfunction (mean Pugh score: 6.2) following
215 single IV and oral administrations. The mean clearance of tacrolimus in
216 patients with mild hepatic dysfunction was not substantially different from that in
217 normal volunteers (see previous table). Tacrolimus pharmacokinetics were
218 studied in 6 patients with severe hepatic dysfunction (mean Pugh score: >10).
219 The mean clearance was substantially lower in patients with severe hepatic
220 dysfunction, irrespective of the route of administration.

221

222 *Race*

223 A formal study to evaluate the pharmacokinetic disposition of tacrolimus in
224 Black transplant patients has not been conducted. However, a retrospective
225 comparison of Black and Caucasian kidney transplant patients indicated that
226 Black patients required higher tacrolimus doses to attain similar trough
227 concentrations. (See **DOSAGE AND ADMINISTRATION.**)

228

229 *Gender*

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

235

236 **CLINICAL STUDIES**

237 **Liver Transplantation**

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

248

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

256
257 In the second trial, 545 patients were enrolled at 8 clinical sites in Europe; prior
258 to surgery, 270 were randomized to the Prograf-based immunosuppressive
259 regimen and 275 to CBIR. In this study, each center used its local standard
260 CBIR protocol in the active-control arm. This trial excluded pediatric patients,
261 but did allow enrollment of subjects with renal dysfunction, fulminant hepatic
262 failure in Stage IV encephalopathy, and cancers other than primary hepatic with
263 metastases.

264
265 One-year patient survival and graft survival in the Prograf-based treatment
266 groups were equivalent to those in the CBIR treatment groups in both studies.
267 The overall one-year patient survival (CBIR and Prograf-based treatment
268 groups combined) was 88% in the U.S. study and 78% in the European study.
269 The overall one-year graft survival (CBIR and Prograf-based treatment groups
270 combined) was 81% in the U.S. study and 73% in the European study. In both
271 studies, the median time to convert from IV to oral Prograf dosing was 2 days.

272
273 Because of the nature of the study design, comparisons of differences in
274 secondary endpoints, such as incidence of acute rejection, refractory rejection
275 or use of OKT3 for steroid-resistant rejection, could not be reliably made.

276 277 **Kidney Transplantation**

278 Prograf-based immunosuppression following kidney transplantation was
279 assessed in a Phase III randomized, multicenter, non-blinded, prospective
280 study. There were 412 kidney transplant patients enrolled at 19 clinical sites in
281 the United States. Study therapy was initiated when renal function was stable
282 as indicated by a serum creatinine = 4 mg/dL (median of 4 days after
283 transplantation, range 1 to 14 days). Patients less than 6 years of age were
284 excluded.

285
286 There were 205 patients randomized to Prograf-based immunosuppression and
287 207 patients were randomized to cyclosporine-based immunosuppression. All
288 patients received prophylactic induction therapy consisting of an antilymphocyte
289 antibody preparation, corticosteroids and azathioprine. Overall one year
290 patient and graft survival was 96.1% and 89.6%, respectively and was
291 equivalent between treatment arms.

292

293 Because of the nature of the study design, comparisons of differences in
 294 secondary endpoints, such as incidence of acute rejection, refractory rejection
 295 or use of OKT3 for steroid-resistant rejection, could not be reliably made.
 296

297 **INDICATIONS AND USAGE**

298 Prograf is indicated for the prophylaxis of organ rejection in patients receiving
 299 allogeneic liver or kidney transplants. It is recommended that Prograf be used
 300 concomitantly with adrenal corticosteroids. Because of the risk of anaphylaxis,
 301 Prograf injection should be reserved for patients unable to take Prograf
 302 capsules orally.
 303

304 **CONTRAINDICATIONS**

305 Prograf is contraindicated in patients with a hypersensitivity to tacrolimus.
 306 Prograf injection is contraindicated in patients with a hypersensitivity to HCO-60
 307 (polyoxyl 60 hydrogenated castor oil).
 308
 309

310 **WARNINGS**

311 (See boxed **WARNING**.)

312 **Insulin-dependent post-transplant diabetes mellitus (PTDM) was reported**
 313 **in 20% of Prograf-treated kidney transplant patients without pretransplant**
 314 **history of diabetes mellitus in the Phase III study (See Tables Below). The**
 315 **median time to onset of PTDM was 68 days. Insulin dependence was**
 316 **reversible in 15% of these PTDM patients at one year and in 50% at two**
 317 **years post transplant. Black and Hispanic kidney transplant patients were**
 318 **at an increased risk of development of PTDM.**
 319

320 **Incidence of Post Transplant Diabetes Mellitus and Insulin Use at 2 Years in Kidney**
 321 **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%)

322 * use of insulin for 30 or more consecutive days, with < 5 day gap, without a prior history of
 323 insulin dependent diabetes mellitus or non insulin dependent diabetes mellitus.
 324

325 **Development of Post Transplant Diabetes Mellitus by Race and by Treatment Group**
 326 **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%)

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

329

330 **Insulin-dependent post-transplant diabetes mellitus was reported in 18%**
331 **and 11% of Prograf-treated liver transplant patients and was reversible in**
332 **45% and 31% of these patients at one year post transplant, in the U.S. and**
333 **European randomized studies, respectively (See Table below).**
334 Hyperglycemia was associated with the use of Prograf in 47% and 33% of liver
335 transplant recipients in the U.S. and European randomized studies,
336 respectively, and may require treatment (see **ADVERSE REACTIONS**).

337

338 **Incidence of Post Transplant Diabetes Mellitus and Insulin Use at One Year in Liver**
339 **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%)

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

342

**Patients without pretransplant history of diabetes mellitus.

343

344 Prograf can cause neurotoxicity and nephrotoxicity, particularly when used in
345 high doses. Nephrotoxicity was reported in approximately 52% of kidney
346 transplantation patients and in 40% and 36% of liver transplantation patients
347 receiving Prograf in the U.S. and European randomized trials, respectively (see
348 **ADVERSE REACTIONS**). More overt nephrotoxicity is seen early after
349 transplantation, characterized by increasing serum creatinine and a decrease in
350 urine output. Patients with impaired renal function should be monitored closely
351 as the dosage of Prograf may need to be reduced. In patients with persistent
352 elevations of serum creatinine who are unresponsive to dosage adjustments,
353 consideration should be given to changing to another immunosuppressive
354 therapy. Care should be taken in using tacrolimus with other nephrotoxic drugs.
355 **In particular, to avoid excess nephrotoxicity, Prograf should not be used**
356 **simultaneously with cyclosporine. Prograf or cyclosporine should be**
357 **discontinued at least 24 hours prior to initiating the other. In the presence**
358 **of elevated Prograf or cyclosporine concentrations, dosing with the other**
359 **drug usually should be further delayed.**

360
361 Mild to severe hyperkalemia was reported in 31% of kidney transplant recipients
362 and in 45% and 13% of liver transplant recipients treated with Prograf in the
363 U.S. and European randomized trials, respectively, and may require treatment
364 (see **ADVERSE REACTIONS**). **Serum potassium levels should be**
365 **monitored and potassium-sparing diuretics should not be used during**
366 **Prograf therapy (see PRECAUTIONS).**

367
368 Neurotoxicity, including tremor, headache, and other changes in motor function,
369 mental status, and sensory function were reported in approximately 55% of liver
370 transplant recipients in the two randomized studies. Tremor occurred more
371 often in Prograf-treated kidney transplant patients (54%) compared to
372 cyclosporine-treated patients. The incidence of other neurological events in
373 kidney transplant patients was similar in the two treatment groups (see
374 **ADVERSE REACTIONS**). Tremor and headache have been associated with
375 high whole-blood concentrations of tacrolimus and may respond to dosage
376 adjustment. Seizures have occurred in adult and pediatric patients receiving
377 Prograf (see **ADVERSE REACTIONS**). Coma and delirium also have been
378 associated with high plasma concentrations of tacrolimus.

379
380 As in patients receiving other immunosuppressants, patients receiving Prograf
381 are at increased risk of developing lymphomas and other malignancies,
382 particularly of the skin. The risk appears to be related to the intensity and
383 duration of immunosuppression rather than to the use of any specific agent. A
384 lymphoproliferative disorder (LPD) related to Epstein-Barr Virus (EBV) infection
385 has been reported in immunosuppressed organ transplant recipients. The risk
386 of LPD appears greatest in young children who are at risk for primary EBV
387 infection while immunosuppressed or who are switched to Prograf following
388 long-term immunosuppression therapy. Because of the danger of
389 oversuppression of the immune system which can increase susceptibility to
390 infection, combination immunosuppressant therapy should be used with
391 caution.

392
393 A few patients receiving Prograf injection have experienced anaphylactic
394 reactions. Although the exact cause of these reactions is not known, other
395 drugs with castor oil derivatives in the formulation have been associated with
396 anaphylaxis in a small percentage of patients. Because of this potential risk of
397 anaphylaxis, Prograf injection should be reserved for patients who are unable to
398 take Prograf capsules.

399
400 **Patients receiving Prograf injection should be under continuous**
401 **observation for at least the first 30 minutes following the start of the**
402 **infusion and at frequent intervals thereafter. If signs or symptoms of**
403 **anaphylaxis occur, the infusion should be stopped. An aqueous solution**
404 **of epinephrine should be available at the bedside as well as a source of**
405 **oxygen.**

406

407 **PRECAUTIONS**

408 **General**

409 Hypertension is a common adverse effect of Prograf therapy (see **ADVERSE**
410 **REACTIONS**). Mild or moderate hypertension is more frequently reported than
411 severe hypertension. Antihypertensive therapy may be required; the control of
412 blood pressure can be accomplished with any of the common antihypertensive
413 agents. Since tacrolimus may cause hyperkalemia, potassium-sparing diuretics
414 should be avoided. While calcium-channel blocking agents can be effective in
415 treating Prograf-associated hypertension, care should be taken since
416 interference with tacrolimus metabolism may require a dosage reduction (see
417 **Drug Interactions**).

418

419 **Renally and Hepatically Impaired Patients**

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

423

424 The use of Prograf in liver transplant recipients experiencing post-transplant
425 hepatic impairment may be associated with increased risk of developing renal
426 insufficiency related to high whole-blood levels of tacrolimus. These patients
427 should be monitored closely and dosage adjustments should be considered.
428 Some evidence suggests that lower doses should be used in these patients
429 (see **DOSAGE AND ADMINISTRATION**).

430

431 **Myocardial Hypertrophy**

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

443

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

448

449 **Information for Patients**

450 Patients should be informed of the need for repeated appropriate laboratory
451 tests while they are receiving Prograf. They should be given complete dosage

452 instructions, advised of the potential risks during pregnancy, and informed of
453 the increased risk of neoplasia. Patients should be informed that changes in
454 dosage should not be undertaken without first consulting their physician.

455
456 Patients should be informed that Prograf can cause diabetes mellitus and
457 should be advised of the need to see their physician if they develop frequent
458 urination, increased thirst or hunger.

459
460 As with other immunosuppressive agents, owing to the potential risk of
461 malignant skin changes, exposure to sunlight and ultraviolet (UV) light should
462 be limited by wearing protective clothing and using a sunscreen with a high
463 protection factor.

464
465 **Laboratory Tests**

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

469
470 **Drug Interactions**

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

479
480 **Drugs that May Alter Tacrolimus Concentrations**

481 Since tacrolimus is metabolized mainly by the CYP3A enzyme systems,
482 substances known to inhibit these enzymes may decrease the metabolism or
483 increase bioavailability of tacrolimus as indicated by increased whole blood or
484 plasma concentrations. Drugs known to induce these enzyme systems may
485 result in an increased metabolism of tacrolimus or decreased bioavailability as
486 indicated by decreased whole blood or plasma concentrations. Monitoring of
487 blood concentrations and appropriate dosage adjustments are essential when
488 such drugs are used concomitantly.

489
490 ****Drugs That May Increase Tacrolimus Blood Concentrations***

491
492

493 Calcium	Antifungal	Macrolide
494 <u>Channel Blockers</u>	<u>Agents</u>	<u>Antibiotics</u>
495 diltiazem	clotrimazole	clarithromycin
496 nifedipine	fluconazole	erythromycin
497 nifedipine	itraconazole	troleandomycin

498	verapamil	ketoconazole
499		voriconazole
500		
501		
502	Gastrointestinal	Other
503	<u>Prokinetic Agents</u>	<u>Drugs</u>
504	cisapride	bromocriptine
505	metoclopramide	chloramphenicol
506		cimetidine
507		cyclosporine
508		danazol
509		ethinyl estradiol
510		methylprednisolone
511		omeprazole
512		protease inhibitors
513		nefazodone
514		magnesium-aluminum-hydroxide

515
516 In a study of 6 normal volunteers, a significant increase in tacrolimus oral
517 bioavailability ($14\pm 5\%$ vs. $30\pm 8\%$) was observed with concomitant ketoconazole
518 administration (200 mg). The apparent oral clearance of tacrolimus during
519 ketoconazole administration was significantly decreased compared to
520 tacrolimus alone (0.430 ± 0.129 L/hr/kg vs. 0.148 ± 0.043 L/hr/kg). Overall, IV
521 clearance of tacrolimus was not significantly changed by ketoconazole co-
522 administration, although it was highly variable between patients.

523
524 ****Drugs That May Decrease Tacrolimus Blood Concentrations***

525		
526	<u>Anticonvulsants</u>	<u>Antimicrobials</u>
527	carbamazepine	rifabutin
528	phenobarbital	caspofungin
529	phenytoin	rifampin
530		
531		
532	<u>Herbal Preparations</u>	<u>Other Drugs</u>
533	St. John's Wort	sirolimus

534
535
536 *This table is not all inclusive.

537
538 St. John's Wort (*Hypericum perforatum*) induces CYP3A4 and P-glycoprotein.
539 Since tacrolimus is a substrate for CYP3A4, there is the potential that the use of
540 St. John's Wort in patients receiving Prograf could result in reduced tacrolimus
541 levels.

542

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

547
548 In a study of 6 normal volunteers, a significant decrease in tacrolimus oral
549 bioavailability ($14\pm 6\%$ vs. $7\pm 3\%$) was observed with concomitant rifampin
550 administration (600 mg). In addition, there was a significant increase in
551 tacrolimus clearance (0.036 ± 0.008 L/hr/kg vs. 0.053 ± 0.010 L/hr/kg) with
552 concomitant rifampin administration.

553
554 Interaction studies with drugs used in HIV therapy have not been conducted.
555 However, care should be exercised when drugs that are nephrotoxic (e.g.,
556 ganciclovir) or that are metabolized by CYP3A (e.g., nelfinavir, ritonavir) are
557 administered concomitantly with tacrolimus. Based on a clinical study of 5 liver
558 transplant recipients, co-administration of tacrolimus with nelfinavir increased
559 blood concentrations of tacrolimus significantly and, as a result, a reduction in
560 the tacrolimus dose by an average of 16-fold was needed to maintain mean
561 trough tacrolimus blood concentrations of 9.7 ng/mL. Thus, frequent monitoring
562 of tacrolimus blood concentrations and appropriate dosage adjustments are
563 essential when nelfinavir is used concomitantly. Tacrolimus may affect the
564 pharmacokinetics of other drugs (e.g., phenytoin) and increase their
565 concentration. Grapefruit juice affects CYP3A-mediated metabolism and
566 should be avoided (see **DOSAGE AND ADMINISTRATION**).

567
568 Following co-administration of tacrolimus and sirolimus (2 or 5 mg/day) in stable
569 renal transplant patients, mean tacrolimus AUC_{0-12} and C_{min} decreased
570 approximately by 30% relative to tacrolimus alone. Mean tacrolimus AUC_{0-12}
571 and C_{min} following co-administration of 1 mg/day of sirolimus decreased
572 approximately 3% and 11%, respectively. The safety and efficacy of tacrolimus
573 used in combination with sirolimus for the prevention of graft rejection has not
574 been established and is not recommended.

575

576 **Other Drug Interactions**

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

581

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

583 An increased incidence of malignancy is a recognized complication of
584 immunosuppression in recipients of organ transplants. The most common
585 forms of neoplasms are non-Hodgkin's lymphomas and carcinomas of the skin.
586 As with other immunosuppressive therapies, the risk of malignancies in Prograf
587 recipients may be higher than in the normal, healthy population.
588 Lymphoproliferative disorders associated with Epstein-Barr Virus infection have

589 been seen. It has been reported that reduction or discontinuation of
590 immunosuppression may cause the lesions to regress.

591
592 No evidence of genotoxicity was seen in bacterial (*Salmonella* and *E. coli*) or
593 mammalian (Chinese hamster lung-derived cells) in vitro assays of
594 mutagenicity, the in vitro CHO/HGPRT assay of mutagenicity, or in vivo
595 clastogenicity assays performed in mice; tacrolimus did not cause unscheduled
596 DNA synthesis in rodent hepatocytes.

597
598 Carcinogenicity studies were carried out in male and female rats and mice. In
599 the 80-week mouse study and in the 104-week rat study no relationship of
600 tumor incidence to tacrolimus dosage was found. The highest doses used in
601 the mouse and rat studies were 0.8 – 2.5 times (mice) and 3.5 – 7.1 times (rats)
602 the recommended clinical dose range of 0.1 – 0.2 mg/kg/day when corrected for
603 body surface area.

604
605 No impairment of fertility was demonstrated in studies of male and female rats.
606 Tacrolimus, given orally at 1.0 mg/kg (0.7 – 1.4X the recommended clinical
607 dose range of 0.1 – 0.2 mg/kg/day based on body surface area corrections) to
608 male and female rats, prior to and during mating, as well as to dams during
609 gestation and lactation, was associated with embryoletality and with adverse
610 effects on female reproduction. Effects on female reproductive function
611 (parturition) and embryoletal effects were indicated by a higher rate of pre-
612 implantation loss and increased numbers of undelivered and nonviable pups.
613 When given at 3.2 mg/kg (2.3 – 4.6X the recommended clinical dose range
614 based on body surface area correction), tacrolimus was associated with
615 maternal and paternal toxicity as well as reproductive toxicity including marked
616 adverse effects on estrus cycles, parturition, pup viability, and pup
617 malformations.

618
619 **Pregnancy: Category C**

620 In reproduction studies in rats and rabbits, adverse effects on the fetus were
621 observed mainly at dose levels that were toxic to dams. Tacrolimus at oral
622 doses of 0.32 and 1.0 mg/kg during organogenesis in rabbits was associated
623 with maternal toxicity as well as an increase in incidence of abortions; these
624 doses are equivalent to 0.5 – 1X and 1.6 – 3.3X the recommended clinical dose
625 range (0.1 – 0.2 mg/kg) based on body surface area corrections. At the higher
626 dose only, an increased incidence of malformations and developmental
627 variations was also seen. Tacrolimus, at oral doses of 3.2 mg/kg during
628 organogenesis in rats, was associated with maternal toxicity and caused an
629 increase in late resorptions, decreased numbers of live births, and decreased
630 pup weight and viability. Tacrolimus, given orally at 1.0 and 3.2 mg/kg
631 (equivalent to 0.7 – 1.4X and 2.3 – 4.6X the recommended clinical dose range
632 based on body surface area corrections) to pregnant rats after organogenesis
633 and during lactation, was associated with reduced pup weights.

634

635 No reduction in male or female fertility was evident.

636

637 There are no adequate and well-controlled studies in pregnant women.
638 Tacrolimus is transferred across the placenta. The use of tacrolimus during
639 pregnancy has been associated with neonatal hyperkalemia and renal
640 dysfunction. Prograf should be used during pregnancy only if the potential
641 benefit to the mother justifies potential risk to the fetus.

642

643 **Nursing Mothers**

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

645

646 **Pediatric Patients**

647 Experience with Prograf in pediatric kidney transplant patients is limited.
648 Successful liver transplants have been performed in pediatric patients (ages up
649 to 16 years) using Prograf. Two randomized active-controlled trials of Prograf
650 in primary liver transplantation included 56 pediatric patients. Thirty-one
651 patients were randomized to Prograf-based and 25 to cyclosporine-based
652 therapies. Additionally, a minimum of 122 pediatric patients were studied in an
653 uncontrolled trial of tacrolimus in living related donor liver transplantation.
654 Pediatric patients generally required higher doses of Prograf to maintain blood
655 trough concentrations of tacrolimus similar to adult patients (see **DOSAGE AND**
656 **ADMINISTRATION**).

657

658 **ADVERSE REACTIONS**

659 **Liver Transplantation**

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

665

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

669

670 The incidence of adverse events was determined in two randomized
671 comparative liver transplant trials among 514 patients receiving tacrolimus and
672 steroids and 515 patients receiving a cyclosporine-based regimen (CBIR). The
673 proportion of patients reporting more than one adverse event was 99.8% in the
674 tacrolimus group and 99.6% in the CBIR group. Precautions must be taken
675 when comparing the incidence of adverse events in the U.S. study to that in the
676 European study. The 12-month posttransplant information from the U.S. study
677 and from the European study is presented below. The two studies also
678 included different patient populations and patients were treated with
679 immunosuppressive regimens of differing intensities. Adverse events reported

680 in = 15% in tacrolimus patients (combined study results) are presented below
 681 for the two controlled trials in liver transplantation:
 682

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)
<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

683

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

687

688 **Kidney Transplantation**

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

692

693 Adverse events that occurred in =15% of Prograf-treated kidney transplant
694 patients are presented below:

695

KIDNEY TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN = 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

696

697

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

701

702 **Less Frequently Reported Adverse Reactions**

703 The following adverse events were reported in either liver or kidney transplant
704 recipients who were treated with tacrolimus in clinical trials.

705

706 ***Nervous System*** (see **WARNINGS**)

707 Abnormal dreams, agitation, amnesia, anxiety, confusion, convulsion, crying,
708 depression, dizziness, elevated mood, emotional lability, encephalopathy,
709 haemorrhagic stroke, hallucinations, hypertonia, incoordination, monoparesis,
710 myoclonus, nerve compression, nervousness, neuropathy, paralysis flaccid,

711 psychomotor skills impaired, psychosis, quadriplegia, somnolence, thinking
712 abnormal, writing impaired

713

714 **Special Senses**

715 Abnormal vision, amblyopia, ear pain, otitis media, tinnitus

716

717 **Gastrointestinal**

718 Anorexia, cholangitis, cholestatic jaundice, duodenitis, dyspepsia, dysphagia,
719 esophagitis, flatulence, gastritis, gastroesophagitis, gastrointestinal
720 hemorrhage, GGT increase, GI perforation, hepatitis, hepatitis granulomatous,
721 ileus, increased appetite, jaundice, liver damage, liver function test abnormal,
722 oesophagitis ulcerative, oral moniliasis, pancreatic pseudocyst, rectal disorder,
723 stomatitis

724

725 **Cardiovascular**

726 Angina pectoris, cardiac fibrillation, cardiopulmonary failure, chest pain, deep
727 thrombophlebitis, abnormal ECG, echocardiogram abnormal, electrocardiogram
728 QRS complex abnormal, electrocardiogram ST segment abnormal, heart rate
729 decreased, hemorrhage, hypotension, postural hypotension, peripheral vascular
730 disorder, phlebitis, tachycardia, thrombosis, vasodilatation

731

732 **Urogenital (see WARNINGS)**

733 Albuminuria, bladder spasm, cystitis, dysuria, hematuria, hydronephrosis,
734 kidney failure, kidney tubular necrosis, nocturia, oliguria, pyuria, toxic
735 nephropathy, urge incontinence, urinary frequency, urinary incontinence,
736 urinary retention, vaginitis

737

738 **Metabolic/Nutritional**

739 Acidosis, alkaline phosphatase increased, alkalosis, ALT (SGPT) increased,
740 AST (SGOT) increased, bicarbonate decreased, bilirubinemia, BUN increased,
741 dehydration, GGT increased, healing abnormal, hypercalcemia,
742 hypercholesterolemia, hyperlipemia, hyperphosphatemia, hyperuricemia,
743 hypervolemia, hypocalcemia, hypoglycemia, hyponatremia, hypophosphatemia,
744 hypoproteinemia, lactic dehydrogenase increase, weight gain

745

746 **Endocrine (see PRECAUTIONS)**

747 Cushing's syndrome, diabetes mellitus

748

749 **Hemic/Lymphatic**

750 Coagulation disorder, ecchymosis, haematocrit increased, haemoglobin
751 abnormal, hypochromic anemia, leukocytosis, leukopenia, polycythemia,
752 prothrombin decreased, serum iron decreased, thrombocytopenia

753

754 **Miscellaneous**

755 Abdomen enlarged, abscess, accidental injury, allergic reaction, cellulitis, chills,
756 fall, feeling abnormal, flu syndrome, generalized edema, hernia, mobility

757 decreased, peritonitis, photosensitivity reaction, sepsis, temperature
758 intolerance, ulcer

759

760 ***Musculoskeletal***

761 Arthralgia, cramps, generalized spasm, joint disorder, leg cramps, myalgia,
762 myasthenia, osteoporosis

763

764 ***Respiratory***

765 Asthma, bronchitis, cough increased, emphysema, hiccups, lung disorder,
766 pneumothorax, pulmonary edema, pharyngitis, pneumonia, respiratory disorder,
767 rhinitis, sinusitis, voice alteration

768

769 ***Skin***

770 Acne, alopecia, exfoliative dermatitis, fungal dermatitis, herpes simplex,
771 hirsutism, skin discoloration, skin disorder, skin ulcer, sweating.

772

773 **Post Marketing**

774 **Post Marketing Adverse Events**

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

783

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

787

788 Other events include:

789

790 ***Cardiovascular***

791 Atrial fibrillation, atrial flutter, cardiac arrhythmia, cardiac arrest,
792 electrocardiogram T wave abnormal, flushing, myocardial infarction, myocardial
793 ischaemia, pericardial effusion, QT prolongation, Torsade de Pointes, venous
794 thrombosis deep limb, ventricular extrasystoles, ventricular fibrillation

795

796 ***Gastrointestinal***

797 Bile duct stenosis, colitis, enterocolitis, gastroenteritis, gastroesophageal reflux
798 disease, hepatic cytolysis, hepatic necrosis, hepatotoxicity, impaired gastric
799 emptying, liver fatty, mouth ulceration, pancreatitis haemorrhagic, pancreatitis
800 necrotizing, stomach ulcer, venoocclusive liver disease

801

802 ***Hemic/Lymphatic***

803 Disseminated intravascular coagulation, neutropenia, pancytopenia,
804 thrombocytopenic purpura, thrombotic thrombocytopenic purpura

805

806 ***Metabolic/Nutritional***

807 Glycosuria, increased amylase including pancreatitis, weight decreased;

808

809 ***Miscellaneous***

810 Feeling hot and cold, feeling jittery, hot flushes, multi-organ failure, primary graft
811 dysfunction

812

813 ***Nervous System***

814 Carpal tunnel syndrome, cerebral infarction, hemiparesis, leukoencephalopathy,
815 mental disorder, mutism, quadriplegia, speech disorder, syncope

816

817 ***Respiratory***

818 Acute respiratory distress syndrome, lung infiltration, respiratory distress,
819 respiratory failure

820

821 ***Skin***

822 Stevens-Johnson syndrome, toxic epidermal necrolysis

823

824

825 ***Special Senses***

826 Blindness, blindness cortical, hearing loss including deafness, photophobia

827

828 ***Urogenital***

829 Acute renal failure, cystitis haemorrhagic, hemolytic-uremic syndrome,
830 micturition disorder.

831

832 **OVERDOSAGE**

833 Limited overdose experience is available. Acute overdoses of up to 30
834 times the intended dose have been reported. Almost all cases have been
835 asymptomatic and all patients recovered with no sequelae. Occasionally, acute
836 overdose has been followed by adverse reactions consistent with those listed
837 in the **ADVERSE REACTIONS** section except in one case where transient
838 urticaria and lethargy were observed. Based on the poor aqueous solubility and
839 extensive erythrocyte and plasma protein binding, it is anticipated that
840 tacrolimus is not dialyzable to any significant extent; there is no experience with
841 charcoal hemoperfusion. The oral use of activated charcoal has been reported
842 in treating acute overdoses, but experience has not been sufficient to warrant
843 recommending its use. General supportive measures and treatment of specific
844 symptoms should be followed in all cases of overdose.

845

846 In acute oral and IV toxicity studies, mortalities were seen at or above the
847 following doses: in adult rats, 52X the recommended human oral dose; in

848 immature rats, 16X the recommended oral dose; and in adult rats, 16X the
849 recommended human IV dose (all based on body surface area corrections).

850

851 **DOSAGE AND ADMINISTRATION**

852 **Prograf injection (tacrolimus injection)**

853

854 **For IV Infusion Only**

855

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

858

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

867

868 ***Preparation for Administration/Stability***

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

882

883 **Prograf capsules (tacrolimus capsules)**

884

885 **Summary of Initial Oral Dosage Recommendations and Typical Whole Blood Trough** 886 **Concentrations**

Patient Population	Recommended Initial Oral Dose*	Typical Whole Blood Trough Concentrations
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
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*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 = 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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927

Pediatric Patients

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

935

Patients with Hepatic or Renal Dysfunction

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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.

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945

Due to the potential for nephrotoxicity, patients with renal or hepatic impairment should receive doses at the lowest value of the recommended IV 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.

946

Conversion from One Immunosuppressive Regimen to Another

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950

951

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.

952

Blood Concentration Monitoring

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Monitoring of tacrolimus blood concentrations in conjunction with other laboratory and clinical parameters is considered an essential aid to patient management for the evaluation of rejection, toxicity, dose adjustments and compliance. Factors influencing frequency of monitoring include but are not limited to hepatic or renal dysfunction, the addition or discontinuation of potentially interacting drugs and the posttransplant time. Blood concentration monitoring is not a replacement for renal and liver function 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 and specimens should be collected into tubes containing ethylene diamine tetraacetic acid (EDTA) anti-coagulant. Heparin anti-coagulation is not recommended because of the

970 tendency to form clots on storage. Samples which are not analyzed
971 immediately should be stored at room temperature or in a refrigerator and
972 assayed within 7 days; if samples are to be kept longer they should be deep
973 frozen at -20° C for up to 12 months.

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975 ***Liver Transplantation***

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

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

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

994

995 ***Kidney Transplantation***

996 Data from the Phase III study indicates that trough concentrations of tacrolimus
997 in whole blood, as measured by IMx[®] were most variable during the first week
998 of dosing. During the first three months, 80% of the patients maintained trough
999 concentrations between 7-20 ng/mL, and then between 5-15 ng/mL, through
1000 one-year.

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1002 The relative risk of toxicity is increased with higher trough concentrations.
1003 Therefore, monitoring of whole blood trough concentrations is recommended to
1004 assist in the clinical evaluation of toxicity.

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1006 **HOW SUPPLIED**

1007 **Prograf capsules (tacrolimus capsules)**

1008

strength	0.5 mg (containing the equivalent of 0.5 mg anhydrous tacrolimus)	1 mg (containing the equivalent of 1 mg anhydrous tacrolimus)	5 mg (containing the equivalent of 5 mg anhydrous tacrolimus)
shape/color	oblong/light yellow	oblong/white	oblong/grayish red

branding on capsule cap/body	f 607	f 617	f 657
100 count bottle	NDC 0469-0607-73	NDC 0469-0617-73	NDC 0469-0657-73
10 blister cards of 10 capsules		NDC 0469-0617-11	NDC 0469-0657-11

1009

1010 Made in Japan

1011

1012 *Store and Dispense*

1013 Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).

1014

1015 **Prograf injection (tacrolimus injection)**

1016 **(for IV infusion only)**

1017

1018 NDC 0469-3016-01 Product Code 301601

1019 5 mg/mL (equivalent of 5 mg of anhydrous tacrolimus per mL) supplied as a
1020 sterile solution in a 1 mL ampule, in boxes of 10 ampules

1021

1022 Made in Ireland

1023

1024 *Store and Dispense*

1025 Store between 5°C and 25°C (41°F and 77°F).

1026

1027 **Rx only**

1028

1029 **Marketed by:**

1030 Astellas Pharma US, Inc.

1031 Deerfield, IL 60015-2548

1032

1033

1034 **REFERENCE**

1035 1. CDC: Recommendations of the Advisory Committee on Immunization
1036 Practices: Use of vaccines and immune globulins in persons with
1037 altered immunocompetence. MMWR 1993;42(RR-4):1-18.

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