

1 **PROGRAF®**  
2 **tacrolimus capsules**  
3 **tacrolimus injection (for intravenous infusion only)**  
4

5 Revised: March 2006  
6

7 **WARNING**

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

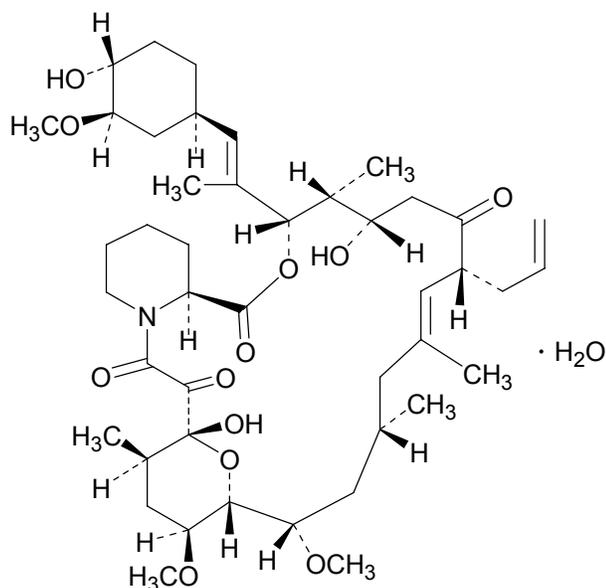
15 **DESCRIPTION**

16 Prograf is available for oral administration as capsules (tacrolimus capsules)  
17 containing the equivalent of 0.5 mg, 1 mg or 5 mg of anhydrous tacrolimus.  
18 Inactive ingredients include lactose, hydroxypropyl methylcellulose,  
19 croscarmellose sodium, and magnesium stearate. The 0.5 mg capsule shell  
20 contains gelatin, titanium dioxide and ferric oxide, the 1 mg capsule shell  
21 contains gelatin and titanium dioxide, and the 5 mg capsule shell contains  
22 gelatin, titanium dioxide and ferric oxide.  
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25 Prograf is also available as a sterile solution (tacrolimus injection) containing  
26 the equivalent of 5 mg anhydrous tacrolimus in 1 mL for administration by  
27 intravenous infusion only. Each mL contains polyoxyl 60 hydrogenated castor  
28 oil (HCO-60), 200 mg, and dehydrated alcohol, USP, 80.0% v/v. Prograf  
29 injection must be diluted with 0.9% Sodium Chloride Injection or 5% Dextrose  
30 Injection before use.

31  
32 Tacrolimus, previously known as FK506, is the active ingredient in Prograf.  
33 Tacrolimus is a macrolide immunosuppressant produced by *Streptomyces*  
34 *tsukubaensis*. Chemically, tacrolimus is designated as [3S-  
35 [3R\*[E(1S\*,3S\*,4S\*)], 4S\*,5R\*,8S\*,9E,12R\*,14R\*,15S\*,16R\*,18S\*,19S\*,26aR\*]]  
36 -5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-  
37 dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-  
38 dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-  
39 c][1,4] oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate.  
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41 The chemical structure of tacrolimus is:  
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Tacrolimus has an empirical formula of  $C_{44}H_{69}NO_{12} \cdot H_2O$  and a formula weight of 822.03. Tacrolimus appears as white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform.

**CLINICAL PHARMACOLOGY**

**Mechanism of Action**

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

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

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

**Pharmacokinetics**

75 Tacrolimus activity is primarily due to the parent drug. The pharmacokinetic  
 76 parameters (mean±S.D.) of tacrolimus have been determined following  
 77 intravenous (IV) and/or oral (PO) administration in healthy volunteers, and in  
 78 kidney transplant, liver transplant, and heart transplant patients. (See table  
 79 below.)  
 80

Population	N	Route (Dose)	Parameters					
			C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	AUC (ng•hr/mL)	t <sub>1/2</sub> (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	#	#	#
Heart Transplant Patients	11	IV (0.01 mg/kg/day as a continuous infusion)	---	---	954   ±334	23.6 ±9.22	0.051 ±0.015	#
	11	PO (0.075mg/kg/day)***	14.7 ±7.79	2.1 [0.5- 6.0]**	82.7* ±63.2	---	#	#
	14	PO (0.15mg/kg/day)***	24.5± 13.7	1.5 [0.4- 4.0]**	142*±116	---	#	#

81 †Corrected for individual bioavailability; ‡AUC<sub>0-120</sub>; §AUC<sub>0-72</sub>; ¶AUC<sub>0-inf</sub>; ||AUC<sub>0-t</sub>; \*AUC<sub>0-12</sub>; \*\*: Median [range]; \*\*\* Determined after the first dose; ---not applicable; #not available  
 82  
 83

84 Due to intersubject variability in tacrolimus pharmacokinetics, individualization  
 85 of dosing regimen is necessary for optimal therapy. (See **DOSAGE AND**  
 86 **ADMINISTRATION**). Pharmacokinetic data indicate that whole blood

87 concentrations rather than plasma concentrations serve as the more  
88 appropriate sampling compartment to describe tacrolimus pharmacokinetics.

89

### 90 **Absorption**

91 Absorption of tacrolimus from the gastrointestinal tract after oral administration  
92 is incomplete and variable. The absolute bioavailability of tacrolimus was  
93  $17\pm 10\%$  in adult kidney transplant patients (N=26),  $22\pm 6\%$  in adult liver  
94 transplant patients (N=17),  $23\pm 9\%$  in adult heart transplant patients (N=11) and  
95  $18\pm 5\%$  in healthy volunteers (N=16).

96

97 A single dose study conducted in 32 healthy volunteers established the  
98 bioequivalence of the 1 mg and 5 mg capsules. Another single dose study in  
99 32 healthy volunteers established the bioequivalence of the 0.5 mg and 1 mg  
100 capsules. Tacrolimus maximum blood concentrations ( $C_{max}$ ) and area under  
101 the curve (AUC) appeared to increase in a dose-proportional fashion in  
102 18 fasted healthy volunteers receiving a single oral dose of 3, 7, and 10 mg.

103

104 In 18 kidney transplant patients, tacrolimus trough concentrations from 3 to  
105 30 ng/mL measured at 10-12 hours post-dose ( $C_{min}$ ) correlated well with the  
106 AUC (correlation coefficient 0.93). In 24 liver transplant patients over a  
107 concentration range of 10 to 60 ng/mL, the correlation coefficient was 0.94. In  
108 25 heart transplant patients over a concentration range of 2 to 24 ng/mL, the  
109 correlation coefficient was 0.89 after an oral dose of 0.075 or 0.15 mg/kg/day at  
110 steady-state.

111

### 112 *Food Effects*

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

116

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

121

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

128

129 In 11 liver transplant patients, Prograf administered 15 minutes after a high fat  
130 (400 kcal, 34% fat) breakfast, resulted in decreased AUC ( $27\pm 18\%$ ) and  $C_{max}$   
131 ( $50\pm 19\%$ ), as compared to a fasted state.

132

133 ***Distribution***

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

142

143 ***Metabolism***

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

151

152 ***Excretion***

153 The mean clearance following IV administration of tacrolimus is 0.040,  
154 0.083, and 0.053, and 0.051 L/hr/kg in healthy volunteers, adult kidney  
155 transplant patients, adult liver transplant patients, and adult heart transplant  
156 patients, respectively. In man, less than 1% of the dose administered is  
157 excreted unchanged in urine.

158

159 In a mass balance study of IV administered radiolabeled tacrolimus to 6 healthy  
160 volunteers, the mean recovery of radiolabel was 77.8±12.7%. Fecal elimination  
161 accounted for 92.4±1.0% and the elimination half-life based on radioactivity was  
162 48.1±15.9 hours whereas it was 43.5±11.6 hours based on tacrolimus  
163 concentrations. The mean clearance of radiolabel was 0.029±0.015 L/hr/kg and  
164 clearance of tacrolimus was 0.029±0.009 L/hr/kg. When administered PO, the  
165 mean recovery of the radiolabel was 94.9±30.7%. Fecal elimination accounted  
166 for 92.6±30.7%, urinary elimination accounted for 2.3±1.1% and the elimination  
167 half-life based on radioactivity was 31.9±10.5 hours whereas it was 48.4±  
168 12.3 hours based on tacrolimus concentrations. The mean clearance of  
169 radiolabel was 0.226±0.116 L/hr/kg and clearance of tacrolimus 0.172±  
170 0.088 L/hr/kg.

171 **Special Populations**

172 *Pediatric*

173 Pharmacokinetics of tacrolimus have been studied in liver transplantation  
 174 patients, 0.7 to 13.2 years of age. Following IV administration of a  
 175 0.037 mg/kg/day dose to 12 pediatric patients, mean terminal half-life, volume  
 176 of distribution and clearance were 11.5±3.8 hours, 2.6±2.1 L/kg and 0.138±  
 177 0.071 L/hr/kg, respectively. Following oral administration to 9 patients, mean  
 178 AUC and C<sub>max</sub> were 337±167 ng·hr/mL and 43.4±27.9 ng/mL, respectively. The  
 179 absolute bioavailability was 31±21%.

180

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

185

186 *Renal and Hepatic Insufficiency*

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

190

Population (No. of Patients)	Dose	AUC <sub>0-t</sub> (ng·hr/ mL)	t <sub>1/2</sub> (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) <sup>†</sup>	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)			

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192

\*corrected for bioavailability

<sup>†</sup> 1 patient did not receive the PO dose

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194

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

200

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

203

204 Hepatic Insufficiency: Tacrolimus pharmacokinetics have been determined in  
205 six patients with mild hepatic dysfunction (mean Pugh score: 6.2) following  
206 single IV and oral administrations. The mean clearance of tacrolimus in  
207 patients with mild hepatic dysfunction was not substantially different from that in  
208 normal volunteers (see previous table). Tacrolimus pharmacokinetics were  
209 studied in 6 patients with severe hepatic dysfunction (mean Pugh score: >10).  
210 The mean clearance was substantially lower in patients with severe hepatic  
211 dysfunction, irrespective of the route of administration.

212

213 *Race*

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

219

220 *Gender*

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

226

## 227 **CLINICAL STUDIES**

### 228 **Liver Transplantation**

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

239

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

247

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

255

256 One-year patient survival and graft survival in the Prograf-based treatment  
257 groups were equivalent to those in the CBIR treatment groups in both studies.  
258 The overall 1-year patient survival (CBIR and Prograf-based treatment groups  
259 combined) was 88% in the U.S. study and 78% in the European study. The  
260 overall 1-year graft survival (CBIR and Prograf-based treatment groups  
261 combined) was 81% in the U.S. study and 73% in the European study. In both  
262 studies, the median time to convert from IV to oral Prograf dosing was 2 days.

263

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

267

### 268 **Kidney Transplantation**

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

276

277 There were 205 patients randomized to Prograf-based immunosuppression and  
278 207 patients were randomized to cyclosporine-based immunosuppression. All  
279 patients received prophylactic induction therapy consisting of an antilymphocyte  
280 antibody preparation, corticosteroids and azathioprine. Overall 1 year patient  
281 and graft survival was 96.1% and 89.6%, respectively and was equivalent  
282 between treatment arms.

283

284 Because of the nature of the study design, comparisons of differences in  
285 secondary endpoints, such as incidence of acute rejection, refractory rejection  
286 or use of OKT3 for steroid-resistant rejection, could not be reliably made.  
287

### 288 ***Heart Transplantation***

289 Two open-label, randomized, comparative studies evaluated the safety and  
290 efficacy of Prograf-based and cyclosporine-based immunosuppression in  
291 primary orthotopic heart transplantation. In a Phase 3 study conducted in  
292 Europe, 314 patients received a regimen of antibody induction, corticosteroids  
293 and azathioprine in combination with Prograf or cyclosporine modified for  
294 18 months. In a 3-arm study conducted in the US, 331 patients received  
295 corticosteroids and Prograf plus sirolimus, Prograf plus mycophenolate mofetil  
296 (MMF) or cyclosporine modified plus MMF for 1 year.  
297

298 In the European Phase 3 study, patient/graft survival at 18 months  
299 posttransplant was similar between treatment arms, 91.7% in the tacrolimus  
300 group and 89.2% in the cyclosporine group. In the US study, patient and graft  
301 survival at 12 months was similar with 93.5% survival in the Prograf plus MMF  
302 group and 86.1% survival in the cyclosporine modified plus MMF group. In the  
303 European study, the cyclosporine trough concentrations were above the pre-  
304 defined target range (i.e., 100-200 ng/mL) at Day 122 and beyond in 32-68%  
305 of the patients in the cyclosporine treatment arm, whereas the tacrolimus  
306 trough concentrations were within the pre-defined target range (i.e., 5-15  
307 ng/mL) in 74-86% of the patients in the tacrolimus treatment arm.  
308

309 The US study contained a third arm of a combination regimen of  
310 sirolimus, 2 mg per day, and full-dose Prograf; however, this  
311 regimen was associated with increased risk of wound healing  
312 complications, renal function impairment, and insulin dependent post  
313 transplant diabetes mellitus, and is not recommended (see  
314 **WARNINGS**).  
315

### 316 **INDICATIONS AND USAGE**

317 Prograf is indicated for the prophylaxis of organ rejection in patients receiving  
318 allogeneic liver, kidney, or heart transplants. It is recommended that Prograf be  
319 used concomitantly with adrenal corticosteroids. Because of the risk of  
320 anaphylaxis, Prograf injection should be reserved for patients unable to take  
321 Prograf capsules orally. In heart transplant recipients, it is  
322 recommended that Prograf be used in conjunction with azathioprine  
323 or mycophenolate mofetil (MMF). The safety and efficacy of the use of  
324 Prograf with sirolimus has not been established (see **CLINICAL STUDIES**).  
325

### 326 **CONTRAINDICATIONS**

327

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

331  
 332

**WARNINGS**

334 (See boxed **WARNING**.)

335

336 **Insulin-dependent post-transplant diabetes mellitus (PTDM) was reported**  
 337 **in 20% of Prograf-treated kidney transplant patients without pretransplant**  
 338 **history of diabetes mellitus in the Phase III study (See Tables Below). The**  
 339 **median time to onset of PTDM was 68 days. Insulin dependence was**  
 340 **reversible in 15% of these PTDM patients at one year and in 50% at**  
 341 **2 years post transplant. Black and Hispanic kidney transplant patients**  
 342 **were at an increased risk of development of PTDM.**

343

344 **Incidence of Post Transplant Diabetes Mellitus and Insulin Use at 2 Years in Kidney**  
 345 **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 <sup>st</sup> 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.

**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%)

352

353

354

\*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.

355 **Insulin-dependent post-transplant diabetes mellitus was reported in 18%**  
 356 **and 11% of Prograf-treated liver transplant patients and was reversible in**  
 357 **45% and 31% of these patients at 1 year post transplant, in the U.S. and**  
 358 **European randomized studies, respectively (See Table below).**  
 359 Hyperglycemia was associated with the use of Prograf in 47% and 33% of liver  
 360 transplant recipients in the U.S. and European randomized studies,  
 361 respectively, and may require treatment (see **ADVERSE REACTIONS**).

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**Incidence of Post Transplant Diabetes Mellitus and Insulin Use at 1 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%)

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

368 \*\*Patients without pretransplant history of diabetes mellitus.

369

370 **Insulin-dependent post-transplant diabetes mellitus was reported in 13%**  
 371 **and 22% of Prograf-treated heart transplant patients receiving**  
 372 **mycophenolate mofetil or azathioprine and was reversible in 30% and 17%**  
 373 **of these patients at one year post transplant, in the US and European**  
 374 **randomized studies, respectively (See Table below).** Hyperglycemia  
 375 defined as two fasting plasma glucose levels  $\geq 126$  mg/dL was reported with the  
 376 use of Prograf plus mycophenolate mofetil or azathioprine in 32% and 35% of  
 377 heart transplant recipients in the US and European randomized studies,  
 378 respectively, and may require treatment (see **ADVERSE REACTIONS**).

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381 **Incidence of Post Transplant Diabetes Mellitus and Insulin Use at 1 Year in**  
 382 **Heart Transplant Recipients**

383

Status of PTDM*	US Study			European Study	
	Prograf/Sirolimus	Prograf/MMF	Cyclosporine/MMF	Prograf/AZA	Cyclosporine/AZA
Patients at risk**	85	75	83	132	138
New Onset PTDM*	21 (25%)	10 (13%)	6 (7%)	29 (22%)	5 (4%)
Patients still on insulin at 1 year***	10 (12%)	7 (9%)	1 (1%)	24 (18%)	4 (3%)

384 \* use of insulin for 30 or more consecutive days without a prior history of insulin  
 385 dependent diabetes mellitus or non insulin dependent diabetes mellitus.

386 \*\*Patients without pretransplant history of diabetes mellitus.

387 \*\*\*7-12 months for the US Study.

388

389

390 Prograf can cause neurotoxicity and nephrotoxicity, particularly when used in  
391 high doses. Nephrotoxicity was reported in approximately 52% of kidney  
392 transplantation patients and in 40% and 36% of liver transplantation patients  
393 receiving Prograf in the U.S. and European randomized trials, respectively, and  
394 in 59% of heart transplantation patients in a European randomized trial (see  
395 **ADVERSE REACTIONS**). Use of Prograf with sirolimus in heart transplantation  
396 patients in a US study was associated with increased risk of renal function  
397 impairment, and is not recommended (See CLINICAL TRIALS). More overt  
398 nephrotoxicity is seen early after transplantation, characterized by increasing  
399 serum creatinine and a decrease in urine output. Patients with impaired renal  
400 function should be monitored closely as the dosage of Prograf may need to be  
401 reduced. In patients with persistent elevations of serum creatinine who are  
402 unresponsive to dosage adjustments, consideration should be given to  
403 changing to another immunosuppressive therapy. Care should be taken in  
404 using tacrolimus with other nephrotoxic drugs. **In particular, to avoid excess  
405 nephrotoxicity, Prograf should not be used simultaneously with  
406 cyclosporine. Prograf or cyclosporine should be discontinued at least 24  
407 hours prior to initiating the other. In the presence of elevated Prograf or  
408 cyclosporine concentrations, dosing with the other drug usually should  
409 be further delayed.**

410

411 Mild to severe hyperkalemia was reported in 31% of kidney transplant recipients  
412 and in 45% and 13% of liver transplant recipients treated with Prograf in the  
413 U.S. and European randomized trials, respectively, and in 8% of heart  
414 transplant recipients in a European randomized trial and may require treatment  
415 (see **ADVERSE REACTIONS**). **Serum potassium levels should be  
416 monitored and potassium-sparing diuretics should not be used during  
417 Prograf therapy (see PRECAUTIONS).**

418

419 Neurotoxicity, including tremor, headache, and other changes in motor function,  
420 mental status, and sensory function were reported in approximately 55% of liver  
421 transplant recipients in the two randomized studies. Tremor occurred more  
422 often in Prograf-treated kidney transplant patients (54%) and heart transplant  
423 patients (15%) compared to cyclosporine-treated patients. The incidence of  
424 other neurological events in kidney transplant and heart transplant patients was  
425 similar in the two treatment groups (see **ADVERSE REACTIONS**). Tremor and  
426 headache have been associated with high whole-blood concentrations of  
427 tacrolimus and may respond to dosage adjustment. Seizures have occurred in  
428 adult and pediatric patients receiving Prograf (see **ADVERSE REACTIONS**).  
429 Coma and delirium also have been associated with high plasma concentrations  
430 of tacrolimus.

431

432 As in patients receiving other immunosuppressants, patients receiving Prograf  
433 are at increased risk of developing lymphomas and other malignancies,  
434 particularly of the skin. The risk appears to be related to the intensity and

435 duration of immunosuppression rather than to the use of any specific agent. A  
436 lymphoproliferative disorder (LPD) related to Epstein-Barr Virus (EBV) infection  
437 has been reported in immunosuppressed organ transplant recipients. The risk  
438 of LPD appears greatest in young children who are at risk for primary EBV  
439 infection while immunosuppressed or who are switched to Prograf following  
440 long-term immunosuppression therapy. Because of the danger of  
441 oversuppression of the immune system which can increase susceptibility to  
442 infection, combination immunosuppressant therapy should be used with  
443 caution.

444  
445 A few patients receiving Prograf injection have experienced anaphylactic  
446 reactions. Although the exact cause of these reactions is not known, other  
447 drugs with castor oil derivatives in the formulation have been associated with  
448 anaphylaxis in a small percentage of patients. Because of this potential risk of  
449 anaphylaxis, Prograf injection should be reserved for patients who are unable to  
450 take Prograf capsules.

451  
452 **Patients receiving Prograf injection should be under continuous**  
453 **observation for at least the first 30 minutes following the start of the**  
454 **infusion and at frequent intervals thereafter. If signs or symptoms of**  
455 **anaphylaxis occur, the infusion should be stopped. An aqueous solution**  
456 **of epinephrine should be available at the bedside as well as a source of**  
457 **oxygen.**

## 458 **PRECAUTIONS**

### 460 **General**

461 Hypertension is a common adverse effect of Prograf therapy (see **ADVERSE**  
462 **REACTIONS**). Mild or moderate hypertension is more frequently reported than  
463 severe hypertension. Antihypertensive therapy may be required; the control of  
464 blood pressure can be accomplished with any of the common antihypertensive  
465 agents. Since tacrolimus may cause hyperkalemia, potassium-sparing diuretics  
466 should be avoided. While calcium-channel blocking agents can be effective in  
467 treating Prograf-associated hypertension, care should be taken since  
468 interference with tacrolimus metabolism may require a dosage reduction (see  
469 **Drug Interactions**).

### 471 **Renally and Hepatically Impaired Patients**

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

475  
476 The use of Prograf in liver transplant recipients experiencing post-transplant  
477 hepatic impairment may be associated with increased risk of developing renal  
478 insufficiency related to high whole-blood levels of tacrolimus. These patients  
479 should be monitored closely and dosage adjustments should be considered.

480 Some evidence suggests that lower doses should be used in these patients  
481 (see **DOSAGE AND ADMINISTRATION**).

482

### 483 **Myocardial Hypertrophy**

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

495

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

500

### 501 **Information for Patients**

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

507

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

511

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

516

### 517 **Laboratory Tests**

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

521

### 522 **Drug Interactions**

523 Due to the potential for additive or synergistic impairment of renal function, care  
524 should be taken when administering Prograf with drugs that may be associated  
525 with renal dysfunction. These include, but are not limited to, aminoglycosides,

526 amphotericin B, and cisplatin. Initial clinical experience with the co-  
 527 administration of Prograf and cyclosporine resulted in additive/synergistic  
 528 nephrotoxicity. Patients switched from cyclosporine to Prograf should receive  
 529 the first Prograf dose no sooner than 24 hours after the last cyclosporine dose.  
 530 Dosing may be further delayed in the presence of elevated cyclosporine levels.

531

532 **Drugs that May Alter Tacrolimus Concentrations**

533 Since tacrolimus is metabolized mainly by the CYP3A enzyme systems,  
 534 substances known to inhibit these enzymes may decrease the metabolism or  
 535 increase bioavailability of tacrolimus as indicated by increased whole blood or  
 536 plasma concentrations. Drugs known to induce these enzyme systems may  
 537 result in an increased metabolism of tacrolimus or decreased bioavailability as  
 538 indicated by decreased whole blood or plasma concentrations. Monitoring of  
 539 blood concentrations and appropriate dosage adjustments are essential when  
 540 such drugs are used concomitantly.

541

542 ***\*Drugs That May Increase Tacrolimus Blood Concentrations***

543

544 Calcium	Antifungal	Macrolide
545 <u>Channel Blockers</u>	<u>Agents</u>	<u>Antibiotics</u>
546 diltiazem	clotrimazole	clarithromycin
547 nicardipine	fluconazole	erythromycin
548 nifedipine	itraconazole	troleandomycin
549 verapamil	ketoconazole	
550	voriconazole	

551

552

553 Gastrointestinal	Other
554 <u>Prokinetic Agents</u>	<u>Drugs</u>
555 cisapride	bromocriptine
556 metoclopramide	chloramphenicol
557	cimetidine
558	cyclosporine
559	danazol
560	ethinyl estradiol
561	methylprednisolone
562	omeprazole
563	protease inhibitors
564	nefazodone
565	magnesium-aluminum-hydroxide
566	

567

568 In a study of 6 normal volunteers, a significant increase in tacrolimus oral  
 569 bioavailability (14±5% vs. 30±8%) was observed with concomitant ketoconazole  
 570 administration (200 mg). The apparent oral clearance of tacrolimus during  
 571 ketoconazole administration was significantly decreased compared to  
 tacrolimus alone (0.430±0.129 L/hr/kg vs. 0.148±0.043 L/hr/kg). Overall, IV

572 clearance of tacrolimus was not significantly changed by ketoconazole co-  
573 administration, although it was highly variable between patients.

574

575 **\*Drugs That May Decrease Tacrolimus Blood Concentrations**

576

577 Anticonvulsants

578 carbamazepine

579 phenobarbital

580 phenytoin

581

582

583 Herbal Preparations

584 St. John's Wort

585

586

Antimicrobials

rifabutin

caspofungin

rifampin

Other Drugs

sirolimus

587 \*This table is not all inclusive.

588

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

593

594 In a single-dose crossover study in healthy volunteers, co-administration of  
595 tacrolimus and magnesium-aluminum-hydroxide resulted in a 21% increase in  
596 the mean tacrolimus AUC and a 10% decrease in the mean tacrolimus C<sub>max</sub>  
597 relative to tacrolimus administration alone.

598

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

604

605 Interaction studies with drugs used in HIV therapy have not been conducted.  
606 However, care should be exercised when drugs that are nephrotoxic (e.g.,  
607 ganciclovir) or that are metabolized by CYP3A (e.g., nelfinavir, ritonavir) are  
608 administered concomitantly with tacrolimus. Based on a clinical study of 5 liver  
609 transplant recipients, co-administration of tacrolimus with nelfinavir increased  
610 blood concentrations of tacrolimus significantly and, as a result, a reduction in  
611 the tacrolimus dose by an average of 16-fold was needed to maintain mean  
612 trough tacrolimus blood concentrations of 9.7 ng/mL. Thus, frequent monitoring  
613 of tacrolimus blood concentrations and appropriate dosage adjustments are  
614 essential when nelfinavir is used concomitantly. Tacrolimus may affect the  
615 pharmacokinetics of other drugs (e.g., phenytoin) and increase their  
616 concentration. Grapefruit juice affects CYP3A-mediated metabolism and  
617 should be avoided (see **DOSE AND ADMINISTRATION**).

618  
619 Following co-administration of tacrolimus and sirolimus (2 or 5 mg/day) in stable  
620 renal transplant patients, mean tacrolimus AUC<sub>0-12</sub> and C<sub>min</sub> decreased  
621 approximately by 30% relative to tacrolimus alone. Mean tacrolimus AUC<sub>0-12</sub>  
622 and C<sub>min</sub> following co-administration of 1 mg/day of sirolimus decreased  
623 approximately 3% and 11%, respectively. The safety and efficacy of tacrolimus  
624 used in combination with sirolimus for the prevention of graft rejection has not  
625 been established and is not recommended.

626

### 627 **Other Drug Interactions**

628 Immunosuppressants may affect vaccination. Therefore, during treatment with  
629 Prograf, vaccination may be less effective. The use of live vaccines should be  
630 avoided; live vaccines may include, but are not limited to measles, mumps,  
631 rubella, oral polio, BCG, yellow fever, and TY 21a typhoid.<sup>1</sup>

632

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

634 An increased incidence of malignancy is a recognized complication of  
635 immunosuppression in recipients of organ transplants. The most common  
636 forms of neoplasms are non-Hodgkin's lymphomas and carcinomas of the skin.  
637 As with other immunosuppressive therapies, the risk of malignancies in Prograf  
638 recipients may be higher than in the normal, healthy population.  
639 Lymphoproliferative disorders associated with Epstein-Barr Virus infection have  
640 been seen. It has been reported that reduction or discontinuation of  
641 immunosuppression may cause the lesions to regress.

642

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

648

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

655

656 No impairment of fertility was demonstrated in studies of male and female rats.  
657 Tacrolimus, given orally at 1.0 mg/kg (0.7 – 1.4X the recommended clinical  
658 dose range of 0.1 – 0.2 mg/kg/day based on body surface area corrections) to  
659 male and female rats, prior to and during mating, as well as to dams during  
660 gestation and lactation, was associated with embryoletality and with adverse  
661 effects on female reproduction. Effects on female reproductive function  
662 (parturition) and embryoletal effects were indicated by a higher rate of pre-  
663 implantation loss and increased numbers of undelivered and nonviable pups.

664 When given at 3.2 mg/kg (2.3 – 4.6X the recommended clinical dose range  
665 based on body surface area correction), tacrolimus was associated with  
666 maternal and paternal toxicity as well as reproductive toxicity including marked  
667 adverse effects on estrus cycles, parturition, pup viability, and pup  
668 malformations.

669

### 670 **Pregnancy: Category C**

671 In reproduction studies in rats and rabbits, adverse effects on the fetus were  
672 observed mainly at dose levels that were toxic to dams. Tacrolimus at oral  
673 doses of 0.32 and 1.0 mg/kg during organogenesis in rabbits was associated  
674 with maternal toxicity as well as an increase in incidence of abortions; these  
675 doses are equivalent to 0.5 – 1X and 1.6 – 3.3X the recommended clinical dose  
676 range (0.1 – 0.2 mg/kg) based on body surface area corrections. At the higher  
677 dose only, an increased incidence of malformations and developmental  
678 variations was also seen. Tacrolimus, at oral doses of 3.2 mg/kg during  
679 organogenesis in rats, was associated with maternal toxicity and caused an  
680 increase in late resorptions, decreased numbers of live births, and decreased  
681 pup weight and viability. Tacrolimus, given orally at 1.0 and 3.2 mg/kg  
682 (equivalent to 0.7 – 1.4X and 2.3 – 4.6X the recommended clinical dose range  
683 based on body surface area corrections) to pregnant rats after organogenesis  
684 and during lactation, was associated with reduced pup weights.

685

686 No reduction in male or female fertility was evident.

687

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

693

### 694 **Nursing Mothers**

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

696

### 697 **Pediatric Patients**

698 Experience with Prograf in pediatric kidney and heart transplant patients is  
699 limited. Successful liver transplants have been performed in pediatric patients  
700 (ages up to 16 years) using Prograf. Two randomized active-controlled trials of  
701 Prograf in primary liver transplantation included 56 pediatric patients. Thirty-  
702 one patients were randomized to Prograf-based and 25 to cyclosporine-based  
703 therapies. Additionally, a minimum of 122 pediatric patients were studied in an  
704 uncontrolled trial of tacrolimus in living related donor liver transplantation.  
705 Pediatric patients generally required higher doses of Prograf to maintain blood  
706 trough concentrations of tacrolimus similar to adult patients (see **DOSAGE AND**  
707 **ADMINISTRATION**).

708

### 709 **ADVERSE REACTIONS**

710 **Liver Transplantation**

711 The principal adverse reactions of Prograf are tremor, headache, diarrhea,  
 712 hypertension, nausea, and abnormal renal function. These occur with oral and  
 713 IV administration of Prograf and may respond to a reduction in dosing.  
 714 Diarrhea was sometimes associated with other gastrointestinal complaints such  
 715 as nausea and vomiting.

716  
 717 Hyperkalemia and hypomagnesemia have occurred in patients receiving  
 718 Prograf therapy. Hyperglycemia has been noted in many patients; some may  
 719 require insulin therapy (see **WARNINGS**).

720  
 721 The incidence of adverse events was determined in two randomized  
 722 comparative liver transplant trials among 514 patients receiving tacrolimus and  
 723 steroids and 515 patients receiving a cyclosporine-based regimen (CBIR). The  
 724 proportion of patients reporting more than one adverse event was 99.8% in the  
 725 tacrolimus group and 99.6% in the CBIR group. Precautions must be taken  
 726 when comparing the incidence of adverse events in the U.S. study to that in the  
 727 European study. The 12-month posttransplant information from the U.S. study  
 728 and from the European study is presented below. The two studies also  
 729 included different patient populations and patients were treated with  
 730 immunosuppressive regimens of differing intensities. Adverse events reported  
 731 in  $\geq 15\%$  in tacrolimus patients (combined study results) are presented below  
 732 for the two controlled trials in liver transplantation:  
 733  
 734

<b>LIVER TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN <math>\geq 15\%</math> OF PROGRAF-TREATED PATIENTS</b>				
	U.S. STUDY		EUROPEAN STUDY	
	Prograf (N=250)	CBIR (N=250)	Prograf (N=264)	CBIR (N=265)
<b><u>Nervous System</u></b>				
Headache (see <b>WARNINGS</b> )	64%	60%	37%	26%
Tremor (see <b>WARNINGS</b> )	56%	46%	48%	32%
Insomnia	64%	68%	32%	23%
Paresthesia	40%	30%	17%	17%
<b><u>Gastrointestinal</u></b>				
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%
<b><u>Cardiovascular</u></b>				
Hypertension (see <b>PRECAUTIONS</b> )	47%	56%	38%	43%
<b><u>Urogenital</u></b>				

Kidney Function Abnormal (see <b>WARNINGS</b> )	40%	27%	36%	23%
Creatinine Increased (see <b>WARNINGS</b> )	39%	25%	24%	19%
BUN Increased (see <b>WARNINGS</b> )	30%	22%	12%	9%
Urinary Tract Infection	16%	18%	21%	19%
Oliguria	18%	15%	19%	12%
<b><u>Metabolic and Nutritional</u></b>				
Hyperkalemia (see <b>WARNINGS</b> )	45%	26%	13%	9%
Hypokalemia	29%	34%	13%	16%
Hyperglycemia (see <b>WARNINGS</b> )	47%	38%	33%	22%
Hypomagnesemia	48%	45%	16%	9%
<b><u>Hemic and Lymphatic</u></b>				
Anemia	47%	38%	5%	1%
Leukocytosis	32%	26%	8%	8%
Thrombocytopenia	24%	20%	14%	19%
<b><u>Miscellaneous</u></b>				
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%
<b><u>Respiratory System</u></b>				
Pleural Effusion	30%	32%	36%	35%
Atelectasis	28%	30%	5%	4%
Dyspnea	29%	23%	5%	4%
<b><u>Skin and Appendages</u></b>				
Pruritus	36%	20%	15%	7%
Rash	24%	19%	10%	4%

735

736

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

737

738

739

#### 740 **Kidney Transplantation**

741

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

742

743

744

745

Adverse events that occurred in  $\geq 15\%$  of Prograf-treated kidney transplant patients are presented below:

746

747

**KIDNEY TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN ≥ 15% OF PROGRAF-TREATED PATIENTS**

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

<b>Musculoskeletal</b> Arthralgia	18%	15%
<b>Skin</b> Rash Pruritus	25%	24%
	17%	12%
	15%	7%

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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** shown below.

### **Heart Transplantation**

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

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

<b>HEART TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN ≥15% OF PROGRAF-TREATED PATIENTS</b>		
<b>COSTART Body System COSTART Term</b>	<b>Prograf + Azathioprine (n=157)</b>	<b>CsA + Azathioprine (n=157)</b>
<b>Cardiovascular System</b>		
Hypertension (See <b>PRECAUTIONS</b> )	62%	69%
Pericardial effusion	15%	14%
<b>Body as a Whole</b>		
CMV infection	32%	30%
Infection	24%	21%
<b>Metabolic and Nutritional Disorders</b>		
Hyperlipemia	18%	27%
Diabetes Mellitus (See <b>WARNINGS</b> )	26%	16%
Hyperglycemia (See <b>WARNINGS</b> )	23%	17%
<b>Hemic and Lymphatic System</b>		
Leukopenia	48%	39%
Anemia	50%	36%
<b>Urogenital System</b>		
Kidney function abnormal (See <b>WARNINGS</b> )	56%	57%
Urinary tract infection	16%	12%
<b>Respiratory System</b>		
Bronchitis	17%	18%
<b>Nervous System</b>		
Tremor (See <b>WARNINGS</b> )	15%	6%

762

763 In the European study, the cyclosporine trough concentrations were above the  
764 pre-defined target range (i.e., 100-200 ng/mL) at Day 122 and beyond in 32-  
765 68% of the patients in the cyclosporine treatment arm, whereas the tacrolimus  
766 trough concentrations were within the pre-defined target range (i.e., 5-15  
767 ng/mL) in 74-86% of the patients in the tacrolimus treatment arm.

768

769 Only selected targeted treatment-emergent adverse events were collected in  
770 the US heart transplantation study. Those events that were reported at a rate  
771 of 15% or greater in patients treated with Prograf and mycophenolate mofetil  
772 include the following: any target adverse events (99.1%), hypertension (88.8%),  
773 hyperglycemia requiring antihyperglycemic therapy (70.1%) (see **WARNINGS**),  
774 hypertriglyceridemia (65.4%), anemia (hemoglobin <10.0 g/dL) (65.4%), fasting  
775 blood glucose >140 mg/dL (on two separate occasions) (60.7%) (see  
776 **WARNINGS**), hypercholesterolemia (57.0%), hyperlipidemia (33.6%), WBCs  
777 <3000 cells/mcL (33.6%), serious bacterial infections (29.9%), magnesium <1.2  
778 mEq/L (24.3%), platelet count <75,000 cells/mcL (18.7%), and other  
779 opportunistic infections (15.0%).

780

781 Other targeted treatment-emergent adverse events in Prograf-treated patients  
782 occurred at a rate of less than 15%, and include the following: Cushingoid  
783 features, impaired wound healing, hyperkalemia, *Candida* infection, and CMV  
784 infection/syndrome.

785

### 786 **Less Frequently Reported Adverse Reactions**

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

789

#### 790 ***Nervous System*** (see **WARNINGS**)

791 Abnormal dreams, agitation, amnesia, anxiety, confusion, convulsion, crying,  
792 depression, dizziness, elevated mood, emotional lability, encephalopathy,  
793 haemorrhagic stroke, hallucinations, headache, hypertonia, incoordination,  
794 insomnia, monoparesis, myoclonus, nerve compression, nervousness,  
795 neuralgia, neuropathy, paresthesia, paralysis flaccid, psychomotor skills  
796 impaired, psychosis, quadriparesis, somnolence, thinking abnormal, vertigo,  
797 writing impaired

798

#### 799 ***Special Senses***

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

801

#### 802 ***Gastrointestinal***

803 Anorexia, cholangitis, cholestatic jaundice, diarrhea, duodenitis, dyspepsia,  
804 dysphagia, esophagitis, flatulence, gastritis, gastroesophagitis, gastrointestinal  
805 hemorrhage, GGT increase, GI disorder, GI perforation, hepatitis, hepatitis  
806 granulomatous, ileus, increased appetite, jaundice, liver damage, liver function

807 test abnormal, nausea, nausea and vomiting, oesophagitis ulcerative, oral  
808 moniliasis, pancreatic pseudocyst, rectal disorder, stomatitis, vomiting

809

810 **Cardiovascular**

811 Abnormal ECG, angina pectoris, arrhythmia, atrial fibrillation, atrial flutter,  
812 bradycardia, cardiac fibrillation, cardiopulmonary failure, cardiovascular  
813 disorder, chest pain, congestive heart failure, deep thrombophlebitis,  
814 echocardiogram abnormal, electrocardiogram QRS complex abnormal,  
815 electrocardiogram ST segment abnormal, heart failure, heart rate decreased,  
816 hemorrhage, hypotension, peripheral vascular disorder, phlebitis, postural  
817 hypotension, syncope, tachycardia, thrombosis, vasodilatation

818

819 **Urogenital** (see **WARNINGS**)

820 Acute kidney failure, albuminuria, bladder spasm, cystitis, dysuria, hematuria,  
821 hydronephrosis, kidney failure, kidney tubular necrosis, nocturia, oliguria,  
822 pyuria, toxic nephropathy, urge incontinence, urinary frequency, urinary  
823 incontinence, urinary retention, vaginitis

824

825 **Metabolic/Nutritional**

826 Acidosis, alkaline phosphatase increased, alkalosis, ALT (SGPT) increased,  
827 AST (SGOT) increased, bicarbonate decreased, bilirubinemia, BUN increased,  
828 dehydration, edema, GGT increased, gout, healing abnormal, hypercalcemia,  
829 hypercholesterolemia, hyperkalemia, hyperlipemia, hyperphosphatemia,  
830 hyperuricemia, hypervolemia, hypocalcemia, hypoglycemia, hypokalemia,  
831 hypomagnesemia, hyponatremia, hypophosphatemia, hypoproteinemia, lactic  
832 dehydrogenase increase, peripheral edema, weight gain

833

834 **Endocrine** (see **PRECAUTIONS**)

835 Cushing's syndrome, diabetes mellitus

836

837 **Hemic/Lymphatic**

838 Coagulation disorder, ecchymosis, haematocrit increased, haemoglobin  
839 abnormal, hypochromic anemia, leukocytosis, leukopenia, polycythemia,  
840 prothrombin decreased, serum iron decreased, thrombocytopenia

841

842 **Miscellaneous**

843 Abdomen enlarged, abdominal pain, abscess, accidental injury, allergic  
844 reaction, asthenia, back pain, cellulitis, chills, fall, feeling abnormal, fever, flu  
845 syndrome, generalized edema, hernia, mobility decreased, pain, peritonitis,  
846 photosensitivity reaction, sepsis, temperature intolerance, ulcer

847

848 **Musculoskeletal**

849 Arthralgia, cramps, generalized spasm, joint disorder, leg cramps, myalgia,  
850 myasthenia, osteoporosis

851

852 **Respiratory**

853 Asthma, bronchitis, cough increased, dyspnea, emphysema, hiccups, lung  
854 disorder, lung function decreased, pharyngitis, pleural effusion, pneumonia,  
855 pneumothorax, pulmonary edema, respiratory disorder, rhinitis, sinusitis, voice  
856 alteration

857

### 858 **Skin**

859 Acne, alopecia, exfoliative dermatitis, fungal dermatitis, herpes simplex, herpes  
860 zoster, hirsutism, neoplasm skin benign, skin discoloration, skin disorder, skin  
861 ulcer, sweating.

862

863

### 864 **Post Marketing**

#### 865 **Post Marketing Adverse Events**

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

874

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

878

879 Other events include:

880

### 881 **Cardiovascular**

882 Atrial fibrillation, atrial flutter, cardiac arrhythmia, cardiac arrest,  
883 electrocardiogram T wave abnormal, flushing, myocardial infarction, myocardial  
884 ischaemia, pericardial effusion, QT prolongation, Torsade de Pointes, venous  
885 thrombosis deep limb, ventricular extrasystoles, ventricular fibrillation

886

### 887 **Gastrointestinal**

888 Bile duct stenosis, colitis, enterocolitis, gastroenteritis, gastroesophageal reflux  
889 disease, hepatic cytolysis, hepatic necrosis, hepatotoxicity, impaired gastric  
890 emptying, liver fatty, mouth ulceration, pancreatitis haemorrhagic, pancreatitis  
891 necrotizing, stomach ulcer, venoocclusive liver disease

892

### 893 **Hemic/Lymphatic**

894 Disseminated intravascular coagulation, neutropenia, pancytopenia,  
895 thrombocytopenic purpura, thrombotic thrombocytopenic purpura

896

### 897 **Metabolic/Nutritional**

898 Glycosuria, increased amylase including pancreatitis, weight decreased

899

900 **Miscellaneous**

901 Feeling hot and cold, feeling jittery, hot flushes, multi-organ failure, primary graft  
902 dysfunction

903

904 **Nervous System**

905 Carpal tunnel syndrome, cerebral infarction, hemiparesis, leukoencephalopathy,  
906 mental disorder, mutism, quadriplegia, speech disorder, syncope

907

908 **Respiratory**

909 Acute respiratory distress syndrome, lung infiltration, respiratory distress,  
910 respiratory failure

911

912 **Skin**

913 Stevens-Johnson syndrome, toxic epidermal necrolysis

914

915 **Special Senses**

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

917

918 **Urogenital**

919 Acute renal failure, cystitis haemorrhagic, hemolytic-uremic syndrome,  
920 micturition disorder.

921

922 **OVERDOSAGE**

923 Limited overdose experience is available. Acute overdoses of up to  
924 30 times the intended dose have been reported. Almost all cases have been  
925 asymptomatic and all patients recovered with no sequelae. Occasionally, acute  
926 overdose has been followed by adverse reactions consistent with those listed  
927 in the **ADVERSE REACTIONS** section except in one case where transient  
928 urticaria and lethargy were observed. Based on the poor aqueous solubility and  
929 extensive erythrocyte and plasma protein binding, it is anticipated that  
930 tacrolimus is not dialyzable to any significant extent; there is no experience with  
931 charcoal hemoperfusion. The oral use of activated charcoal has been reported  
932 in treating acute overdoses, but experience has not been sufficient to warrant  
933 recommending its use. General supportive measures and treatment of specific  
934 symptoms should be followed in all cases of overdose.

935

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

940

941 **DOSAGE AND ADMINISTRATION**

942 **Prograf injection (tacrolimus injection)**

943

944 **For IV Infusion Only**

945

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

948

949 In patients unable to take oral Prograf capsules, therapy may be initiated with  
950 Prograf injection. The initial dose of Prograf should be administered no sooner  
951 than 6 hours after transplantation. The recommended starting dose of Prograf  
952 injection is 0.01 mg/kg/day (heart) or 0.03-0.05 mg/kg/day (liver, kidney) as a  
953 continuous IV infusion. Adult patients should receive doses at the lower end of  
954 the dosing range. Concomitant adrenal corticosteroid therapy is recommended  
955 early post-transplantation. Continuous IV infusion of Prograf injection should be  
956 continued only until the patient can tolerate oral administration of Prograf  
957 capsules.

958

959 ***Preparation for Administration/Stability***

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

973

974 **Prograf capsules (tacrolimus capsules)**

975

976 **Summary of Initial Oral Dosage Recommendations and Typical Whole Blood Trough**  
977 **Concentrations**

<b>Patient Population</b>	<b>Recommended Initial Oral Dose*</b>	<b>Typical Whole Blood Trough Concentrations</b>
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
Adult heart transplant patients	<b>0.075 mg/kg/day</b>	month 1-3: 10-20 ng/mL month ≥ 4: 5-15 ng/mL

978

\*Note: two divided doses, q12h

979

980

981 **Liver Transplantation**

982 It is recommended that patients initiate oral therapy with Prograf capsules if  
983 possible. If IV therapy is necessary, conversion from IV to oral Prograf is  
984 recommended as soon as oral therapy can be tolerated. This usually occurs  
985 within 2-3 days. The initial dose of Prograf should be administered no sooner  
986 than 6 hours after transplantation. In a patient receiving an IV infusion, the first  
987 dose of oral therapy should be given 8-12 hours after discontinuing the IV  
988 infusion. The recommended starting oral dose of Prograf capsules is 0.10 to  
989 0.15 mg/kg/day administered in two divided daily doses every 12 hours. Co-  
990 administered grapefruit juice has been reported to increase tacrolimus blood  
991 trough concentrations in liver transplant patients. (See **Drugs that May Alter**  
992 **Tacrolimus Concentrations**).

993  
994 Dosing should be titrated based on clinical assessments of rejection and  
995 tolerability. Lower Prograf dosages may be sufficient as maintenance therapy.  
996 Adjunct therapy with adrenal corticosteroids is recommended early post-  
997 transplant.

998  
999 Dosage and typical tacrolimus whole blood trough concentrations are shown in  
1000 the table above; blood concentration details are described in **Blood**  
1001 **Concentration Monitoring: Liver Transplantation** below.

1002  
1003 **Kidney Transplantation**

1004 The recommended starting oral dose of Prograf is 0.2 mg/kg/day administered  
1005 every 12 hours in two divided doses. The initial dose of Prograf may be  
1006 administered within 24 hours of transplantation, but should be delayed until  
1007 renal function has recovered (as indicated for example by a serum creatinine  
1008  $\leq 4$  mg/dL). Black patients may require higher doses to achieve comparable  
1009 blood concentrations. Dosage and typical tacrolimus whole blood trough  
1010 concentrations are shown in the table above; blood concentration details are  
1011 described in **Blood Concentration Monitoring: Kidney Transplantation**  
1012 below.

1013  
1014 The data in kidney transplant patients indicate that the Black patients required a  
1015 higher dose to attain comparable trough concentrations compared to Caucasian  
1016 patients.

1017

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

1018

1019

1020 ***Heart Transplantation***

1021 The recommended starting oral dose of Prograf is 0.075 mg/kg/day  
1022 administered every 12 hours in two divided doses. If possible, initiating oral  
1023 therapy with Prograf capsules is recommended. If IV therapy is necessary,  
1024 conversion from IV to oral Prograf is recommended as soon as oral therapy can  
1025 be tolerated. This usually occurs within 2-3 days. The initial dose of Prograf  
1026 should be administered no sooner than 6 hours after transplantation. In a  
1027 patient receiving an IV infusion, the first dose of oral therapy should be given 8-  
1028 12 hours after discontinuing the IV infusion.

1029

1030 Dosing should be titrated based on clinical assessments of rejection and  
1031 tolerability. Lower Prograf dosages may be sufficient as maintenance therapy.  
1032 Adjunct therapy with adrenal corticosteroids is recommended early post  
1033 transplant.

1034

1035 Dosage and typical tacrolimus whole blood trough concentrations are shown in  
1036 the table above; blood concentration details are described in **Blood**  
1037 **Concentration Monitoring: *Heart Transplantation*** below.

1038

1039 ***Pediatric Patients***

1040 Pediatric liver transplantation patients without pre-existing renal or hepatic  
1041 dysfunction have required and tolerated higher doses than adults to achieve  
1042 similar blood concentrations. Therefore, it is recommended that therapy be  
1043 initiated in pediatric patients at a starting IV dose of 0.03-0.05 mg/kg/day and a  
1044 starting oral dose of 0.15-0.20 mg/kg/day. Dose adjustments may be required.  
1045 Experience in pediatric kidney and heart transplantation patients is limited.

1046

1047 ***Patients with Hepatic or Renal Dysfunction***

1048 Due to the reduced clearance and prolonged half-life, patients with severe  
1049 hepatic impairment (Pugh  $\geq$  10) may require lower doses of Prograf. Close  
1050 monitoring of blood concentrations is warranted.

1051

1052 Due to the potential for nephrotoxicity, patients with renal or hepatic impairment  
1053 should receive doses at the lowest value of the recommended IV and oral  
1054 dosing ranges. Further reductions in dose below these ranges may be  
1055 required. Prograf therapy usually should be delayed up to 48 hours or longer in  
1056 patients with post-operative oliguria.

1057

1058 ***Conversion from One Immunosuppressive Regimen to Another***

1059 Prograf should not be used simultaneously with cyclosporine. Prograf or  
1060 cyclosporine should be discontinued at least 24 hours before initiating the other.  
1061 In the presence of elevated Prograf or cyclosporine concentrations, dosing with  
1062 the other drug usually should be further delayed.

1063

1064 **Blood Concentration Monitoring**

1065 Monitoring of tacrolimus blood concentrations in conjunction with other  
1066 laboratory and clinical parameters is considered an essential aid to patient  
1067 management for the evaluation of rejection, toxicity, dose adjustments and  
1068 compliance. Factors influencing frequency of monitoring include but are not  
1069 limited to hepatic or renal dysfunction, the addition or discontinuation of  
1070 potentially interacting drugs and the posttransplant time. Blood concentration  
1071 monitoring is not a replacement for renal and liver function monitoring and  
1072 tissue biopsies.

1073

1074 Two methods have been used for the assay of tacrolimus, a microparticle  
1075 enzyme immunoassay (MEIA) and ELISA. Both methods have the same  
1076 monoclonal antibody for tacrolimus. Comparison of the concentrations in  
1077 published literature to patient concentrations using the current assays must be  
1078 made with detailed knowledge of the assay methods and biological matrices  
1079 employed. Whole blood is the matrix of choice and specimens should be  
1080 collected into tubes containing ethylene diamine tetraacetic acid (EDTA) anti-  
1081 coagulant. Heparin anti-coagulation is not recommended because of the  
1082 tendency to form clots on storage. Samples which are not analyzed  
1083 immediately should be stored at room temperature or in a refrigerator and  
1084 assayed within 7 days; if samples are to be kept longer they should be deep  
1085 frozen at -20° C for up to 12 months.

1086

#### 1087 ***Liver Transplantation***

1088 Although there is a lack of direct correlation between tacrolimus concentrations  
1089 and drug efficacy, data from Phase II and III studies of liver transplant patients  
1090 have shown an increasing incidence of adverse events with increasing trough  
1091 blood concentrations. Most patients are stable when trough whole blood  
1092 concentrations are maintained between 5 to 20 ng/mL. Long-term post-  
1093 transplant patients often are maintained at the low end of this target range.

1094

1095 Data from the U.S. clinical trial show that tacrolimus whole blood  
1096 concentrations, as measured by ELISA, were most variable during the first  
1097 week post-transplantation. After this early period, the median trough blood  
1098 concentrations, measured at intervals from the second week to one year post-  
1099 transplantation, ranged from 9.8 ng/mL to 19.4 ng/mL.

1100

1101 *Therapeutic Drug Monitoring*, 1995, Volume 17, Number 6 contains a  
1102 consensus document and several position papers regarding the therapeutic  
1103 monitoring of tacrolimus from the 1995 International Consensus Conference on  
1104 Immunosuppressive Drugs. Refer to these manuscripts for further discussions  
1105 of tacrolimus monitoring.

1106

#### 1107 ***Kidney Transplantation***

1108 Data from the Phase 3 study indicate that trough concentrations of tacrolimus in  
1109 whole blood, as measured by IMx<sup>®</sup> were most variable during the first week of  
1110 dosing. During the first three months, 80% of the patients maintained trough

1111 concentrations between 7-20 ng/mL, and then between 5-15 ng/mL, through 1  
1112 year.

1113  
1114 The relative risk of toxicity is increased with higher trough concentrations.  
1115 Therefore, monitoring of whole blood trough concentrations is recommended to  
1116 assist in the clinical evaluation of toxicity.

1117

### 1118 **Heart Transplantation**

1119 Data from a European Phase 3 study indicate that trough concentrations of  
1120 tacrolimus in whole blood, as measured by IMx<sup>®</sup> were most variable during the  
1121 first week of dosing. From 1 week to 3 months post transplant, approximately  
1122 80% of patients maintained trough concentrations between 8-20 ng/mL and,  
1123 from 3 months through 18 months post transplant, approximately 80% of  
1124 patients maintained trough concentrations between 6-18 ng/mL.

1125

1126 The relative risk of toxicity; for example, nephrotoxicity and post-transplant  
1127 diabetes mellitus, is increased with higher trough concentrations. Therefore,  
1128 monitoring of whole blood trough concentrations is recommended to assist in  
1129 the clinical evaluation of toxicity.

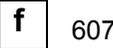
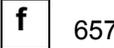
1130

1131

### 1132 **HOW SUPPLIED**

#### 1133 **Prograf capsules (tacrolimus capsules)**

1134

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

1135

1136 Made in Japan

1137

#### 1138 *Store and Dispense*

1139 Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).

1140

#### 1141 **Prograf injection (tacrolimus injection)** 1142 **(for IV infusion only)**

1143

1144 NDC 0469-3016-01                      Product Code 301601

1145 5 mg/mL (equivalent of 5 mg of anhydrous tacrolimus per mL) supplied as a  
1146 sterile solution in a 1 mL ampule, in boxes of 10 ampules

1147

1148 Made in Ireland

1149

1150 *Store and Dispense*

1151 Store between 5°C and 25°C (41°F and 77°F).

1152

1153 **Rx only**

1154

1155 **Marketed by:**

1156 Astellas Pharma US, Inc.

1157 Deerfield, IL 60015-2548

1158

1159

1160 **REFERENCE**

1161 1. CDC: Recommendations of the Advisory Committee on Immunization  
1162 Practices: Use of vaccines and immune globulins in persons with altered  
1163 immunocompetence. MMWR 1993;42(RR-4):1-18.

1164

1165

1166 Revised: March 2006

1167

1168

1169

1170 *Prograf HTx PI \_Mar17\_2006\_*