

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

5 Revised: April 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.

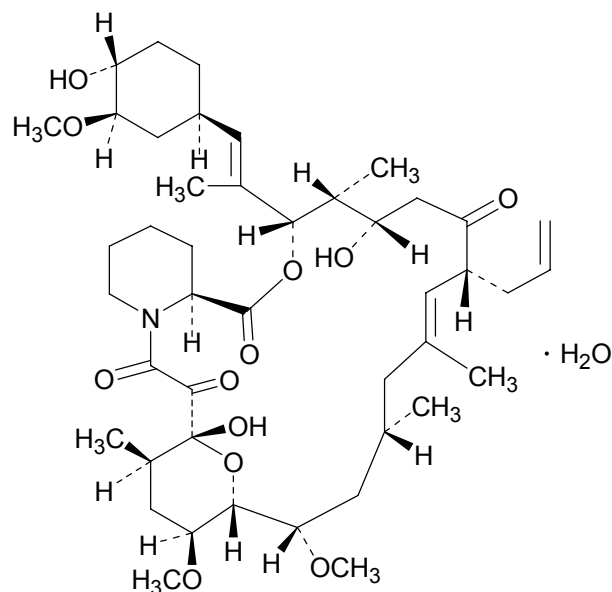
15 **DESCRIPTION**

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] oxazacyclotricosine-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).

75 **Pharmacokinetics**

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

81

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	---	#	#

82 †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>; \*\*:  
 83 Median [range]; \*\*\* Determined after the first dose; ---not applicable; #not available

84

85 Due to intersubject variability in tacrolimus pharmacokinetics, individualization  
 86 of dosing regimen is necessary for optimal therapy. (See **DOSAGE AND**

87 **ADMINISTRATION).** Pharmacokinetic data indicate that whole blood  
88 concentrations rather than plasma concentrations serve as the more  
89 appropriate sampling compartment to describe tacrolimus pharmacokinetics.

90  
91 ***Absorption***

92 Absorption of tacrolimus from the gastrointestinal tract after oral administration  
93 is incomplete and variable. The absolute bioavailability of tacrolimus was  
94  $17\pm 10\%$  in adult kidney transplant patients (N=26),  $22\pm 6\%$  in adult liver  
95 transplant patients (N=17),  $23\pm 9\%$  in adult heart transplant patients (N=11) and  
96  $18\pm 5\%$  in healthy volunteers (N=16).

97  
98 A single dose study conducted in 32 healthy volunteers established the  
99 bioequivalence of the 1 mg and 5 mg capsules. Another single dose study in  
100 32 healthy volunteers established the bioequivalence of the 0.5 mg and 1 mg  
101 capsules. Tacrolimus maximum blood concentrations ( $C_{max}$ ) and area under  
102 the curve (AUC) appeared to increase in a dose-proportional fashion in  
103 18 fasted healthy volunteers receiving a single oral dose of 3, 7, and 10 mg.

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

112  
113 ***Food Effects***

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

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

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

129  
130 In 11 liver transplant patients, Prograf administered 15 minutes after a high fat  
131 (400 kcal, 34% fat) breakfast, resulted in decreased AUC ( $27\pm 18\%$ ) and  $C_{max}$   
132 ( $50\pm 19\%$ ), as compared to a fasted state.

133

134 ***Distribution***

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

143

144 ***Metabolism***

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

152

153 ***Excretion***

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

159

160 In a mass balance study of IV administered radiolabeled tacrolimus to 6 healthy  
161 volunteers, the mean recovery of radiolabel was 77.8±12.7%. Fecal elimination  
162 accounted for 92.4±1.0% and the elimination half-life based on radioactivity was  
163 48.1±15.9 hours whereas it was 43.5±11.6 hours based on tacrolimus  
164 concentrations. The mean clearance of radiolabel was 0.029±0.015 L/hr/kg and  
165 clearance of tacrolimus was 0.029±0.009 L/hr/kg. When administered PO, the  
166 mean recovery of the radiolabel was 94.9±30.7%. Fecal elimination accounted  
167 for 92.6±30.7%, urinary elimination accounted for 2.3±1.1% and the elimination  
168 half-life based on radioactivity was 31.9±10.5 hours whereas it was 48.4±  
169 12.3 hours based on tacrolimus concentrations. The mean clearance of  
170 radiolabel was 0.226±0.116 L/hr/kg and clearance of tacrolimus 0.172±  
171 0.088 L/hr/kg.

172 **Special Populations**

173 *Pediatric*

174 Pharmacokinetics of tacrolimus have been studied in liver transplantation  
 175 patients, 0.7 to 13.2 years of age. Following IV administration of a  
 176 0.037 mg/kg/day dose to 12 pediatric patients, mean terminal half-life, volume  
 177 of distribution and clearance were 11.5±3.8 hours, 2.6±2.1 L/kg and 0.138±  
 178 0.071 L/hr/kg, respectively. Following oral administration to 9 patients, mean  
 179 AUC and C<sub>max</sub> were 337±167 ng·hr/mL and 48.4±27.9 ng/mL, respectively. The  
 180 absolute bioavailability was 31±24%.

181

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

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187 *Renal and Hepatic Insufficiency*

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

191

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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193

\*corrected for bioavailability

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

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

201

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

204

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

213

214 *Race*

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

220

221 *Gender*

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

227

## 228 **CLINICAL STUDIES**

### 229 **Liver Transplantation**

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

240

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

248

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

256

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

264

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

268

### 269 **Kidney Transplantation**

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

277

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

284



285 Because of the nature of the study design, comparisons of differences in  
286 secondary endpoints, such as incidence of acute rejection, refractory rejection  
287 or use of OKT3 for steroid-resistant rejection, could not be reliably made.  
288

### 289 ***Heart Transplantation***

290 Two open-label, randomized, comparative studies evaluated the safety and  
291 efficacy of Prograf-based and cyclosporine-based immunosuppression in  
292 primary orthotopic heart transplantation. In a Phase 3 study conducted in  
293 Europe, 314 patients received a regimen of antibody induction, corticosteroids  
294 and azathioprine in combination with Prograf or cyclosporine modified for  
295 18 months. In a 3-arm study conducted in the US, 331 patients received  
296 corticosteroids and Prograf plus sirolimus, Prograf plus mycophenolate mofetil  
297 (MMF) or cyclosporine modified plus MMF for 1 year.  
298

299 In the European Phase 3 study, patient/graft survival at 18 months  
300 posttransplant was similar between treatment arms, 91.7% in the tacrolimus  
301 group and 89.2% in the cyclosporine group. In the US study, patient and graft  
302 survival at 12 months was similar with 93.5% survival in the Prograf plus MMF  
303 group and 86.1% survival in the cyclosporine modified plus MMF group. In the  
304 European study, the cyclosporine trough concentrations were above the pre-  
305 defined target range (i.e., 100-200 ng/mL) at Day 122 and beyond in 32-68%  
306 of the patients in the cyclosporine treatment arm, whereas the tacrolimus  
307 trough concentrations were within the pre-defined target range (i.e., 5-15  
308 ng/mL) in 74-86% of the patients in the tacrolimus treatment arm.  
309

310 The US study contained a third arm of a combination regimen of  
311 sirolimus, 2 mg per day, and full-dose Prograf; however, this  
312 regimen was associated with increased risk of wound healing  
313 complications, renal function impairment, and insulin dependent post  
314 transplant diabetes mellitus, and is not recommended (see  
315 **WARNINGS**).  
316

### 317 **INDICATIONS AND USAGE**

318 Prograf is indicated for the prophylaxis of organ rejection in patients receiving  
319 allogeneic liver, kidney, or heart transplants. It is recommended that Prograf be  
320 used concomitantly with adrenal corticosteroids. Because of the risk of  
321 anaphylaxis, Prograf injection should be reserved for patients unable to take  
322 Prograf capsules orally. In heart transplant recipients, it is  
323 recommended that Prograf be used in conjunction with azathioprine  
324 or mycophenolate mofetil (MMF). The safety and efficacy of the use of  
325 Prograf with sirolimus has not been established (see **CLINICAL STUDIES**).  
326

### 327 **CONTRAINDICATIONS**

328

329 Prograf is contraindicated in patients with a hypersensitivity to tacrolimus.  
 330 Prograf injection is contraindicated in patients with a hypersensitivity to HCO-60  
 331 (polyoxyl 60 hydrogenated castor oil).  
 332  
 333

334 **WARNINGS**

335 (See boxed **WARNING**.)  
 336

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

344 **Incidence of Post Transplant Diabetes Mellitus and Insulin Use at 2 Years in Kidney**  
 345 **Transplant Recipients in the Phase III study**  
 346

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%)

347 \* use of insulin for 30 or more consecutive days, with < 5 day gap, without a prior history of  
 348 insulin dependent diabetes mellitus or non insulin dependent diabetes mellitus.  
 349

350 **Development of Post Transplant Diabetes Mellitus by Race and by Treatment Group**  
 351 **during First Year Post Kidney Transplantation in the Phase III study**  
 352

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%)

353 \*use of insulin for 30 or more consecutive days, with < 5 day gap, without a prior history of  
 354 insulin dependent diabetes mellitus or non insulin dependent diabetes mellitus.  
 355

356 **Insulin-dependent post-transplant diabetes mellitus was reported in 18%**  
 357 **and 11% of Prograf-treated liver transplant patients and was reversible in**  
 358 **45% and 31% of these patients at 1 year post transplant, in the U.S. and**  
 359 **European randomized studies, respectively (See Table below).**  
 360 Hyperglycemia was associated with the use of Prograf in 47% and 33% of liver  
 361 transplant recipients in the U.S. and European randomized studies,  
 362 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%)

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

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

370

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

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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%)

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

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

388 \*\*\*7-12 months for the US Study.

389

390

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

411

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

419

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

432

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

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

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

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

459

## 460 **PRECAUTIONS**

### 461 **General**

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

471

### 472 **Renally and Hepatically Impaired Patients**

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

476

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

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

483

#### 484 **Myocardial Hypertrophy**

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

496

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

501

#### 502 **Information for Patients**

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

508

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

512

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

517

#### 518 **Laboratory Tests**

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

522

#### 523 **Drug Interactions**

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

527 amphotericin B, and cisplatin. Initial clinical experience with the co-  
 528 administration of Prograf and cyclosporine resulted in additive/synergistic  
 529 nephrotoxicity. Patients switched from cyclosporine to Prograf should receive  
 530 the first Prograf dose no sooner than 24 hours after the last cyclosporine dose.  
 531 Dosing may be further delayed in the presence of elevated cyclosporine levels.  
 532

533 **Drugs that May Alter Tacrolimus Concentrations**

534 Since tacrolimus is metabolized mainly by the CYP3A enzyme systems,  
 535 substances known to inhibit these enzymes may decrease the metabolism or  
 536 increase bioavailability of tacrolimus as indicated by increased whole blood or  
 537 plasma concentrations. Drugs known to induce these enzyme systems may  
 538 result in an increased metabolism of tacrolimus or decreased bioavailability as  
 539 indicated by decreased whole blood or plasma concentrations. Monitoring of  
 540 blood concentrations and appropriate dosage adjustments are essential when  
 541 such drugs are used concomitantly.  
 542

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

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			
554	Gastrointestinal	Other	
555	<u>Prokinetic Agents</u>	<u>Drugs</u>	
556	cisapride	bromocriptine	
557	metoclopramide	chloramphenicol	
558		cimetidine	
559		cyclosporine	
560		danazol	
561		ethinyl estradiol	
562		methylprednisolone	
563		lansoprazole***	
564		omeprazole	
565		protease inhibitors	
566		nefazodone	
567		magnesium-aluminum-hydroxide	
568			

569 \*\*In a study of 6 normal volunteers, a significant increase in tacrolimus oral  
 570 bioavailability (14±5% vs. 30±8%) was observed with concomitant ketoconazole  
 571 administration (200 mg). The apparent oral clearance of tacrolimus during  
 572 ketoconazole administration was significantly decreased compared to

573 tacrolimus alone (0.430±0.129 L/hr/kg vs. 0.148±0.043 L/hr/kg). Overall, IV  
574 clearance of tacrolimus was not significantly changed by ketoconazole co-  
575 administration, although it was highly variable between patients.

576  
577 \*\*\* Lansoprazole (CYP2C19, CYP3A4 substrate) may potentially inhibit  
578 CYP3A4-mediated metabolism of tacrolimus and thereby substantially increase  
579 tacrolimus whole blood concentrations, especially in transplant patients who are  
580 intermediate or poor CYP2C19 metabolizers, as compared to those patients  
581 who are efficient CYP2C19 metabolizers.

582  
583

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

585

586 Anticonvulsants

587 carbamazepine

588 phenobarbital

589 phenytoin

590

591

592 Herbal Preparations

593 St. John's Wort

594

595

Antimicrobials

rifabutin

casprofungin

rifampin

Other Drugs

sirolimus

596 \*This table is not all inclusive.

597

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

602

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

607

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

613

614 Interaction studies with drugs used in HIV therapy have not been conducted.  
615 However, care should be exercised when drugs that are nephrotoxic (e.g.,  
616 ganciclovir) or that are metabolized by CYP3A (e.g., nelfinavir, ritonavir) are  
617 administered concomitantly with tacrolimus. Based on a clinical study of 5 liver  
618 transplant recipients, co-administration of tacrolimus with nelfinavir increased



619 blood concentrations of tacrolimus significantly and, as a result, a reduction in  
620 the tacrolimus dose by an average of 16-fold was needed to maintain mean  
621 trough tacrolimus blood concentrations of 9.7 ng/mL. Thus, frequent monitoring  
622 of tacrolimus blood concentrations and appropriate dosage adjustments are  
623 essential when nelfinavir is used concomitantly. Tacrolimus may affect the  
624 pharmacokinetics of other drugs (e.g., phenytoin) and increase their  
625 concentration. Grapefruit juice affects CYP3A-mediated metabolism and  
626 should be avoided (see **DOSAGE AND ADMINISTRATION**).

627

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

635

### 636 **Other Drug Interactions**

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

641

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

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

651

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

657

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

664

665 No impairment of fertility was demonstrated in studies of male and female rats.  
666 Tacrolimus, given orally at 1.0 mg/kg (0.7 – 1.4X the recommended clinical  
667 dose range of 0.1 – 0.2 mg/kg/day based on body surface area corrections) to  
668 male and female rats, prior to and during mating, as well as to dams during  
669 gestation and lactation, was associated with embryolethality and with adverse  
670 effects on female reproduction. Effects on female reproductive function  
671 (parturition) and embryolethal effects were indicated by a higher rate of pre-  
672 implantation loss and increased numbers of undelivered and nonviable pups.  
673 When given at 3.2 mg/kg (2.3 – 4.6X the recommended clinical dose range  
674 based on body surface area correction), tacrolimus was associated with  
675 maternal and paternal toxicity as well as reproductive toxicity including marked  
676 adverse effects on estrus cycles, parturition, pup viability, and pup  
677 malformations.

678

### 679 **Pregnancy: Category C**

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

694

695 No reduction in male or female fertility was evident.

696

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

702

### 703 **Nursing Mothers**

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

705

### 706 **Pediatric Patients**

707 Experience with Prograf in pediatric kidney and heart transplant patients is  
708 limited. Successful liver transplants have been performed in pediatric patients  
709 (ages up to 16 years) using Prograf. Two randomized active-controlled trials of  
710 Prograf in primary liver transplantation included 56 pediatric patients. Thirty-

711 one patients were randomized to Prograf-based and 25 to cyclosporine-based  
 712 therapies. Additionally, a minimum of 122 pediatric patients were studied in an  
 713 uncontrolled trial of tacrolimus in living related donor liver transplantation.  
 714 Pediatric patients generally required higher doses of Prograf to maintain blood  
 715 trough concentrations of tacrolimus similar to adult patients (see **DOSAGE AND**  
 716 **ADMINISTRATION**).

717  
 718 **ADVERSE REACTIONS**

719 **Liver Transplantation**

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

725  
 726 Hyperkalemia and hypomagnesemia have occurred in patients receiving  
 727 Prograf therapy. Hyperglycemia has been noted in many patients; some may  
 728 require insulin therapy (see **WARNINGS**).

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

742  
 743

<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%

744

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

748

749 **Kidney Transplantation**

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

753

754 Adverse events that occurred in  $\geq 15\%$  of Prograf-treated kidney transplant  
 755 patients are presented below:  
 756

<b>KIDNEY TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN <math>\geq 15\%</math> OF PROGRAF-TREATED PATIENTS</b>		
	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> )	50%	52%
Chest pain	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	49%	53%
Hypomagnesemia	34%	17%
Hyperlipemia	31%	38%
Hyperkalemia (see <b>WARNINGS</b> )	31%	32%
Diabetes Mellitus (see <b>WARNINGS</b> )	24%	9%
Hypokalemia	22%	25%
Hyperglycemia (see <b>WARNINGS</b> )	22%	16%
Edema	18%	19%
<b><u>Hemic and Lymphatic</u></b>		
Anemia	30%	24%
Leukopenia	15%	17%
<b><u>Miscellaneous</u></b>		
Infection	45%	49%
Peripheral Edema	36%	48%

Asthenia	34%	30%
Abdominal Pain	33%	31%
Pain	32%	30%
Fever	29%	29%
Back Pain	24%	20%
<b><u>Respiratory System</u></b>		
Dyspnea	22%	18%
Cough Increased	18%	15%
<b><u>Musculoskeletal</u></b>		
Arthralgia	25%	24%
<b><u>Skin</u></b>		
Rash	17%	12%
Pruritus	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%

771

772

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

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

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

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### 795 **Less Frequently Reported Adverse Reactions**

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

800

801

802

803

804

805

806

807

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

808

809

#### 808 ***Special Senses***

809

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

810

811 ***Gastrointestinal***

812 Anorexia, cholangitis, cholestatic jaundice, diarrhea, duodenitis, dyspepsia,  
813 dysphagia, esophagitis, flatulence, gastritis, gastroesophagitis, gastrointestinal  
814 hemorrhage, GGT increase, GI disorder, GI perforation, hepatitis, hepatitis  
815 granulomatous, ileus, increased appetite, jaundice, liver damage, liver function  
816 test abnormal, nausea, nausea and vomiting, oesophagitis ulcerative, oral  
817 moniliasis, pancreatic pseudocyst, rectal disorder, stomatitis, vomiting

818

819 ***Cardiovascular***

820 Abnormal ECG, angina pectoris, arrhythmia, atrial fibrillation, atrial flutter,  
821 bradycardia, cardiac fibrillation, cardiopulmonary failure, cardiovascular  
822 disorder, chest pain, congestive heart failure, deep thrombophlebitis,  
823 echocardiogram abnormal, electrocardiogram QRS complex abnormal,  
824 electrocardiogram ST segment abnormal, heart failure, heart rate decreased,  
825 hemorrhage, hypotension, peripheral vascular disorder, phlebitis, postural  
826 hypotension, syncope, tachycardia, thrombosis, vasodilatation

827

828 ***Urogenital*** (see **WARNINGS**)

829 Acute kidney failure, albuminuria, bladder spasm, cystitis, dysuria, hematuria,  
830 hydronephrosis, kidney failure, kidney tubular necrosis, nocturia, oliguria,  
831 pyuria, toxic nephropathy, urge incontinence, urinary frequency, urinary  
832 incontinence, urinary retention, vaginitis

833

834 ***Metabolic/Nutritional***

835 Acidosis, alkaline phosphatase increased, alkalosis, ALT (SGPT) increased,  
836 AST (SGOT) increased, bicarbonate decreased, bilirubinemia, BUN increased,  
837 dehydration, edema, GGT increased, gout, healing abnormal, hypercalcemia,  
838 hypercholesterolemia, hyperkalemia, hyperlipemia, hyperphosphatemia,  
839 hyperuricemia, hypervolemia, hypocalcemia, hypoglycemia, hypokalemia,  
840 hypomagnesemia, hyponatremia, hypophosphatemia, hypoproteinemia, lactic  
841 dehydrogenase increase, peripheral edema, weight gain

842

843 ***Endocrine*** (see **PRECAUTIONS**)

844 Cushing's syndrome, diabetes mellitus

845

846 ***Hemic/Lymphatic***

847 Coagulation disorder, ecchymosis, haematocrit increased, haemoglobin  
848 abnormal, hypochromic anemia, leukocytosis, leukopenia, polycythemia,  
849 prothrombin decreased, serum iron decreased, thrombocytopenia

850

851 ***Miscellaneous***

852 Abdomen enlarged, abdominal pain, abscess, accidental injury, allergic  
853 reaction, asthenia, back pain, cellulitis, chills, fall, feeling abnormal, fever, flu  
854 syndrome, generalized edema, hernia, mobility decreased, pain, peritonitis,  
855 photosensitivity reaction, sepsis, temperature intolerance, ulcer

856



857 ***Musculoskeletal***

858 Arthralgia, cramps, generalized spasm, joint disorder, leg cramps, myalgia,  
859 myasthenia, osteoporosis

860

861 ***Respiratory***

862 Asthma, bronchitis, cough increased, dyspnea, emphysema, hiccups, lung  
863 disorder, lung function decreased, pharyngitis, pleural effusion, pneumonia,  
864 pneumothorax, pulmonary edema, respiratory disorder, rhinitis, sinusitis, voice  
865 alteration

866

867 ***Skin***

868 Acne, alopecia, exfoliative dermatitis, fungal dermatitis, herpes simplex, herpes  
869 zoster, hirsutism, neoplasm skin benign, skin discoloration, skin disorder, skin  
870 ulcer, sweating.

871

872

873 **Post Marketing**

874 **Post Marketing Adverse Events**

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

883

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

887

888 Other events include:

889

890 ***Cardiovascular***

891 Atrial fibrillation, atrial flutter, cardiac arrhythmia, cardiac arrest,  
892 electrocardiogram T wave abnormal, flushing, myocardial infarction, myocardial  
893 ischaemia, pericardial effusion, QT prolongation, Torsade de Pointes, venous  
894 thrombosis deep limb, ventricular extrasystoles, ventricular fibrillation

895

896 ***Gastrointestinal***

897 Bile duct stenosis, colitis, enterocolitis, gastroenteritis, gastroesophageal reflux  
898 disease, hepatic cytolysis, hepatic necrosis, hepatotoxicity, impaired gastric  
899 emptying, liver fatty, mouth ulceration, pancreatitis haemorrhagic, pancreatitis  
900 necrotizing, stomach ulcer, venoocclusive liver disease

901

902 ***Hemic/Lymphatic***

903 Disseminated intravascular coagulation, neutropenia, pancytopenia,  
904 thrombocytopenic purpura, thrombotic thrombocytopenic purpura

905

906 ***Metabolic/Nutritional***

907 Glycosuria, increased amylase including pancreatitis, weight decreased

908

909 ***Miscellaneous***

910 Feeling hot and cold, feeling jittery, hot flushes, multi-organ failure, primary graft  
911 dysfunction

912

913 ***Nervous System***

914 Carpal tunnel syndrome, cerebral infarction, hemiparesis, leukoencephalopathy,  
915 mental disorder, mutism, quadriplegia, speech disorder, syncope

916

917 ***Respiratory***

918 Acute respiratory distress syndrome, lung infiltration, respiratory distress,  
919 respiratory failure

920

921 ***Skin***

922 Stevens-Johnson syndrome, toxic epidermal necrolysis

923

924 ***Special Senses***

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

926

927 ***Urogenital***

928 Acute renal failure, cystitis haemorrhagic, hemolytic-uremic syndrome,  
929 micturition disorder.

930

931 **OVERDOSAGE**

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

944

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

949

950 **DOSAGE AND ADMINISTRATION**

951 **Prograf injection (tacrolimus injection)**

952

953 **For IV Infusion Only**

954

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

957

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

967

968 ***Preparation for Administration/Stability***

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

982

983 **Prograf capsules (tacrolimus capsules)**

984

985 **Summary of Initial Oral Dosage Recommendations and Typical Whole Blood Trough**  
986 **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
---------------------------------	------------------------	---

987 \*Note: two divided doses, q12h

988

989

990 ***Liver Transplantation***

991 It is recommended that patients initiate oral therapy with Prograf capsules if  
 992 possible. If IV therapy is necessary, conversion from IV to oral Prograf is  
 993 recommended as soon as oral therapy can be tolerated. This usually occurs  
 994 within 2-3 days. The initial dose of Prograf should be administered no sooner  
 995 than 6 hours after transplantation. In a patient receiving an IV infusion, the first  
 996 dose of oral therapy should be given 8-12 hours after discontinuing the IV  
 997 infusion. The recommended starting oral dose of Prograf capsules is 0.10 to  
 998 0.15 mg/kg/day administered in two divided daily doses every 12 hours. Co-  
 999 administered grapefruit juice has been reported to increase tacrolimus blood  
 1000 trough concentrations in liver transplant patients. (See **Drugs that May Alter**  
 1001 **Tacrolimus Concentrations**).

1002

1003 Dosing should be titrated based on clinical assessments of rejection and  
 1004 tolerability. Lower Prograf dosages may be sufficient as maintenance therapy.  
 1005 Adjunct therapy with adrenal corticosteroids is recommended early post-  
 1006 transplant.

1007

1008 Dosage and typical tacrolimus whole blood trough concentrations are shown in  
 1009 the table above; blood concentration details are described in **Blood**  
 1010 **Concentration Monitoring: Liver Transplantation** below.

1011

1012 ***Kidney Transplantation***

1013 The recommended starting oral dose of Prograf is 0.2 mg/kg/day administered  
 1014 every 12 hours in two divided doses. The initial dose of Prograf may be  
 1015 administered within 24 hours of transplantation, but should be delayed until  
 1016 renal function has recovered (as indicated for example by a serum creatinine  
 1017 ≤ 4 mg/dL). Black patients may require higher doses to achieve comparable  
 1018 blood concentrations. Dosage and typical tacrolimus whole blood trough  
 1019 concentrations are shown in the table above; blood concentration details are  
 1020 described in **Blood Concentration Monitoring: Kidney Transplantation**  
 1021 below.

1022

1023 The data in kidney transplant patients indicate that the Black patients required a  
 1024 higher dose to attain comparable trough concentrations compared to Caucasian  
 1025 patients.

1026

<b>Time After Transplant</b>	<b>Caucasian n=114</b>	<b>Black n=56</b>
------------------------------	----------------------------	-----------------------

	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

1027

1028

1029 ***Heart Transplantation***

1030 The recommended starting oral dose of Prograf is 0.075 mg/kg/day  
 1031 administered every 12 hours in two divided doses. If possible, initiating oral  
 1032 therapy with Prograf capsules is recommended. If IV therapy is necessary,  
 1033 conversion from IV to oral Prograf is recommended as soon as oral therapy can  
 1034 be tolerated. This usually occurs within 2-3 days. The initial dose of Prograf  
 1035 should be administered no sooner than 6 hours after transplantation. In a  
 1036 patient receiving an IV infusion, the first dose of oral therapy should be given 8-  
 1037 12 hours after discontinuing the IV infusion.

1038

1039 Dosing should be titrated based on clinical assessments of rejection and  
 1040 tolerability. Lower Prograf dosages may be sufficient as maintenance therapy.  
 1041 Adjunct therapy with adrenal corticosteroids is recommended early post  
 1042 transplant.

1043

1044 Dosage and typical tacrolimus whole blood trough concentrations are shown in  
 1045 the table above; blood concentration details are described in **Blood**  
 1046 **Concentration Monitoring: *Heart Transplantation*** below.

1047

1048 ***Pediatric Patients***

1049 Pediatric liver transplantation patients without pre-existing renal or hepatic  
 1050 dysfunction have required and tolerated higher doses than adults to achieve  
 1051 similar blood concentrations. Therefore, it is recommended that therapy be  
 1052 initiated in pediatric patients at a starting IV dose of 0.03-0.05 mg/kg/day and a  
 1053 starting oral dose of 0.15-0.20 mg/kg/day. Dose adjustments may be required.  
 1054 Experience in pediatric kidney and heart transplantation patients is limited.

1055

1056 ***Patients with Hepatic or Renal Dysfunction***

1057 Due to the reduced clearance and prolonged half-life, patients with severe  
 1058 hepatic impairment (Pugh  $\geq$  10) may require lower doses of Prograf. Close  
 1059 monitoring of blood concentrations is warranted.

1060

1061 Due to the potential for nephrotoxicity, patients with renal or hepatic impairment  
 1062 should receive doses at the lowest value of the recommended IV and oral  
 1063 dosing ranges. Further reductions in dose below these ranges may be  
 1064 required. Prograf therapy usually should be delayed up to 48 hours or longer in  
 1065 patients with post-operative oliguria.

1066

1067 **Conversion from One Immunosuppressive Regimen to Another**  
1068 Prograf should not be used simultaneously with cyclosporine. Prograf or  
1069 cyclosporine should be discontinued at least 24 hours before initiating the other.  
1070 In the presence of elevated Prograf or cyclosporine concentrations, dosing with  
1071 the other drug usually should be further delayed.  
1072

### 1073 **Blood Concentration Monitoring**

1074 Monitoring of tacrolimus blood concentrations in conjunction with other  
1075 laboratory and clinical parameters is considered an essential aid to patient  
1076 management for the evaluation of rejection, toxicity, dose adjustments and  
1077 compliance. Factors influencing frequency of monitoring include but are not  
1078 limited to hepatic or renal dysfunction, the addition or discontinuation of  
1079 potentially interacting drugs and the posttransplant time. Blood concentration  
1080 monitoring is not a replacement for renal and liver function monitoring and  
1081 tissue biopsies.  
1082

1083 Two methods have been used for the assay of tacrolimus, a microparticle  
1084 enzyme immunoassay (MEIA) and ELISA. Both methods have the same  
1085 monoclonal antibody for tacrolimus. Comparison of the concentrations in  
1086 published literature to patient concentrations using the current assays must be  
1087 made with detailed knowledge of the assay methods and biological matrices  
1088 employed. Whole blood is the matrix of choice and specimens should be  
1089 collected into tubes containing ethylene diamine tetraacetic acid (EDTA) anti-  
1090 coagulant. Heparin anti-coagulation is not recommended because of the  
1091 tendency to form clots on storage. Samples which are not analyzed  
1092 immediately should be stored at room temperature or in a refrigerator and  
1093 assayed within 7 days; if samples are to be kept longer they should be deep  
1094 frozen at -20° C for up to 12 months.  
1095

### 1096 **Liver Transplantation**

1097 Although there is a lack of direct correlation between tacrolimus concentrations  
1098 and drug efficacy, data from Phase II and III studies of liver transplant patients  
1099 have shown an increasing incidence of adverse events with increasing trough  
1100 blood concentrations. Most patients are stable when trough whole blood  
1101 concentrations are maintained between 5 to 20 ng/mL. Long-term post-  
1102 transplant patients often are maintained at the low end of this target range.  
1103

1104 Data from the U.S. clinical trial show that tacrolimus whole blood  
1105 concentrations, as measured by ELISA, were most variable during the first  
1106 week post-transplantation. After this early period, the median trough blood  
1107 concentrations, measured at intervals from the second week to one year post-  
1108 transplantation, ranged from 9.8 ng/mL to 19.4 ng/mL.  
1109

1110 *Therapeutic Drug Monitoring*, 1995, Volume 17, Number 6 contains a  
1111 consensus document and several position papers regarding the therapeutic  
1112 monitoring of tacrolimus from the 1995 International Consensus Conference on

1113 Immunosuppressive Drugs. Refer to these manuscripts for further discussions  
1114 of tacrolimus monitoring.

1115

1116 ***Kidney Transplantation***

1117 Data from the Phase 3 study indicate that trough concentrations of tacrolimus in  
1118 whole blood, as measured by IMx<sup>®</sup> were most variable during the first week of  
1119 dosing. During the first three months, 80% of the patients maintained trough  
1120 concentrations between 7-20 ng/mL, and then between 5-15 ng/mL, through 1  
1121 year.

1122

1123 The relative risk of toxicity is increased with higher trough concentrations.  
1124 Therefore, monitoring of whole blood trough concentrations is recommended to  
1125 assist in the clinical evaluation of toxicity.

1126

1127 ***Heart Transplantation***

1128 Data from a European Phase 3 study indicate that trough concentrations of  
1129 tacrolimus in whole blood, as measured by IMx<sup>®</sup> were most variable during the  
1130 first week of dosing. From 1 week to 3 months post transplant, approximately  
1131 80% of patients maintained trough concentrations between 8-20 ng/mL and,  
1132 from 3 months through 18 months post transplant, approximately 80% of  
1133 patients maintained trough concentrations between 6-18 ng/mL.

1134

1135 The relative risk of toxicity; for example, nephrotoxicity and post-transplant  
1136 diabetes mellitus, is increased with higher trough concentrations. Therefore,  
1137 monitoring of whole blood trough concentrations is recommended to assist in  
1138 the clinical evaluation of toxicity.

1139

1140

1141 **HOW SUPPLIED**

1142 **Prograf capsules (tacrolimus capsules)**

1143

<b>strength</b>	<b>0.5 mg</b> (containing the equivalent of 0.5 mg anhydrous tacrolimus)	<b>1 mg</b> (containing the equivalent of 1 mg anhydrous tacrolimus)	<b>5 mg</b> (containing the equivalent of 5 mg anhydrous tacrolimus)
<b>shape/color</b>	oblong/light yellow	oblong/white	oblong/grayish red
<b>branding on capsule cap/body</b>	<b>f</b> 607	<b>f</b> 617	<b>f</b> 657
<b>100 count bottle</b>	<b>NDC 0469-0607-73</b>	<b>NDC 0469-0617-73</b>	<b>NDC 0469-0657-73</b>
<b>10 blister cards of 10 capsules</b>		<b>NDC 0469-0617-11</b>	<b>NDC 0469-0657-11</b>

1144

1145 Made in Japan

1146

1147 *Store and Dispense*  
1148 Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).  
1149  
1150 **Prograf injection (tacrolimus injection)**  
1151 **(for IV infusion only)**  
1152  
1153 NDC 0469-3016-01            Product Code 301601  
1154 5 mg/mL (equivalent of 5 mg of anhydrous tacrolimus per mL) supplied as a  
1155 sterile solution in a 1 mL ampule, in boxes of 10 ampules  
1156  
1157 Made in Ireland  
1158  
1159 *Store and Dispense*  
1160 Store between 5°C and 25°C (41°F and 77°F).  
1161  
1162 **Rx only**  
1163  
1164 **Marketed by:**  
1165 Astellas Pharma US, Inc.  
1166 Deerfield, IL 60015-2548  
1167  
1168  
1169 **REFERENCE**  
1170 1. CDC: Recommendations of the Advisory Committee on Immunization  
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1172 immunocompetence. MMWR 1993;42(RR-4):1-18.  
1173  
1174  
1175 Revised: April 2006  
1176  
1177