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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 _{max} (ng/mL)	T _{max} (hr)	AUC (ng•hr/mL)	t _{1/2} (hr)	Cl (L/hr/kg)	V (L/kg)
Healthy Volunteers	8	IV (0.025 mg/kg/4hr)	---	---	598‡ ± 125	34.2 ± 7.7	0.040 ± 0.009	1.91 ± 0.31
	16	PO (5 mg)	29.7 ± 7.2	1.6 ± 0.7	243§ ± 73	34.8 ± 11.4	0.041† ± 0.008	1.94† ± 0.53
Kidney Transplant Pts	26	IV (0.02 mg/kg/12 hr)	---	---	294¶ ± 262	18.8 ± 16.7	0.083 ± 0.050	1.41 ± 0.66
		PO (0.2 mg/kg/day)	19.2 ± 10.3	3.0	203¶ ± 42	#	#	#
		PO (0.3 mg/kg/day)	24.2 ± 15.8	1.5	288¶ ± 93	#	#	#
Liver Transplant Pts	17	IV (0.05 mg/kg/12 hr)	---	---	3300¶ ± 2130	11.7 ± 3.9	0.053 ± 0.017	0.85 ± 0.30
		PO (0.3 mg/kg/day)	68.5 ± 30.0	2.3 ± 1.5	519¶ ± 179	#	#	#
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; ‡AUC₀₋₁₂₀; §AUC₀₋₇₂; ¶AUC_{0-inf}; ||AUC_{0-t}; *AUC₀₋₁₂; **: 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 $77.8 \pm 12.7\%$. Fecal elimination
161 accounted for $92.4 \pm 1.0\%$ 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 $94.9 \pm 30.7\%$. Fecal elimination accounted
166 for $92.6 \pm 30.7\%$, urinary elimination accounted for $2.3 \pm 1.1\%$ and the elimination
167 half-life based on radioactivity was 31.9 ± 10.5 hours whereas it was $48.4 \pm$
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 $0.172 \pm$
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_{max} were 337±167 ng·hr/mL and 48.4±27.9 ng/mL, respectively. The
 179 absolute bioavailability was 31±24%.

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 _{0-t} (ng·hr/ mL)	t _{1/2} (hr)	V (L/kg)	Cl (L/hr/kg)
Renal Impairment (n=12)	0.02 mg/kg/4hr IV	393±123 (t=60 hr)	26.3 ±9.2	1.07 ±0.20	0.038 ±0.014
Mild Hepatic Impairment (n=6)	0.02 mg/kg/4hr IV	367±107 (t=72 hr)	60.6±43.8 Range: 27.8 – 141	3.1±1.6	0.042 ±0.02
	7.7 mg PO	488±320 (t=72 hr)	66.1±44.8 Range: 29.5 – 138	3.7±4.7*	0.034 ±0.019*
Severe Hepatic Impairment (n=6, IV) (n=5, PO) [†]	0.02 mg/kg/4hr IV (n=2)	762±204 (t=120 hr)	198±158 Range:81-436	3.9±1.0	0.017 ±0.013
	0.01 mg/kg/8hr IV (n=4)	289±117 (t=144 hr)			
	8 mg PO (n=1)	658 (t=120 hr)	119±35 Range: 85-178	3.1±3.4*	0.016 ±0.011*
	5 mg PO (n=4) 4 mg PO (n=1)	533±156 (t=144 hr)			

191

192

*corrected for bioavailability

[†] 1 patient did not receive the PO dose

193

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 ± 1.6 and 12.0 ± 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 (≤ 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 ≤ 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

(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

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

345

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

346

* 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.

347

348

349

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

350

351

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

*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.

353

354

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**).

362
 363 **Incidence of Post Transplant Diabetes Mellitus and Insulin Use at 1 Year in**
 364 **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 ≥ 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**).

379
 380
 381 **Incidence of Post Transplant Diabetes Mellitus and Insulin Use at 1 Year in**
 382 **Heart Transplant Recipients**

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 STUDIES**). 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.**

458 459 **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**).

470 471 **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***

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	

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	lansoprazole***
563	omeprazole
564	protease inhibitors
565	nefazodone
566	magnesium-aluminum-hydroxide
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

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

575
576 *** Lansoprazole (CYP2C19, CYP3A4 substrate) may potentially inhibit
577 CYP3A4-mediated metabolism of tacrolimus and thereby substantially increase
578 tacrolimus whole blood concentrations, especially in transplant patients who are
579 intermediate or poor CYP2C19 metabolizers, as compared to those patients
580 who are efficient CYP2C19 metabolizers.

581
582

583 ****Drugs That May Decrease Tacrolimus Blood Concentrations***

584

<u>Anticonvulsants</u>	<u>Antimicrobials</u>
585 carbamazepine	586 rifabutin
587 phenobarbital	587 caspofungin
588 phenytoin	588 rifampin

589

590

<u>Herbal Preparations</u>	<u>Other Drugs</u>
591 St. John's Wort	592 sirolimus

593

594

595 *This table is not all inclusive.

596

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

601

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

606

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

612

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

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

626

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

634

635 **Other Drug Interactions**

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

640

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

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

650

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

656

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

663

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

677

678 **Pregnancy: Category C**

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

693

694 No reduction in male or female fertility was evident.

695

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

701

702 **Nursing Mothers**

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

704

705 **Pediatric Patients**

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

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

716
 717 **ADVERSE REACTIONS**

718 **Liver Transplantation**

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

724
 725 Hyperkalemia and hypomagnesemia have occurred in patients receiving
 726 Prograf therapy. Hyperglycemia has been noted in many patients; some may
 727 require insulin therapy (see **WARNINGS**).

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

741
 742

LIVER TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN $\geq 15\%$ OF PROGRAF-TREATED PATIENTS				
	U.S. STUDY		EUROPEAN STUDY	
	Prograf (N=250)	CBIR (N=250)	Prograf (N=264)	CBIR (N=265)
<u>Nervous System</u>				
Headache (see WARNINGS)	64%	60%	37%	26%
Tremor (see WARNINGS)	56%	46%	48%	32%
Insomnia	64%	68%	32%	23%
Paresthesia	40%	30%	17%	17%
<u>Gastrointestinal</u>				
Diarrhea	72%	47%	37%	27%
Nausea	46%	37%	32%	27%

Constipation	24%	27%	23%	21%
LFT Abnormal	36%	30%	6%	5%
Anorexia	34%	24%	7%	5%
Vomiting	27%	15%	14%	11%
<u>Cardiovascular</u>				
Hypertension (see PRECAUTIONS)	47%	56%	38%	43%
<u>Urogenital</u>				
Kidney Function Abnormal (see WARNINGS)	40%	27%	36%	23%
Creatinine Increased (see WARNINGS)	39%	25%	24%	19%
BUN Increased (see WARNINGS)	30%	22%	12%	9%
Urinary Tract Infection	16%	18%	21%	19%
Oliguria	18%	15%	19%	12%
<u>Metabolic and Nutritional</u>				
Hyperkalemia (see WARNINGS)	45%	26%	13%	9%
Hypokalemia	29%	34%	13%	16%
Hyperglycemia (see WARNINGS)	47%	38%	33%	22%
Hypomagnesemia	48%	45%	16%	9%
<u>Hemic and Lymphatic</u>				
Anemia	47%	38%	5%	1%
Leukocytosis	32%	26%	8%	8%
Thrombocytopenia	24%	20%	14%	19%
<u>Miscellaneous</u>				
Abdominal Pain	59%	54%	29%	22%
Pain	63%	57%	24%	22%
Fever	48%	56%	19%	22%
Asthenia	52%	48%	11%	7%
Back Pain	30%	29%	17%	17%
Ascites	27%	22%	7%	8%
Peripheral Edema	26%	26%	12%	14%
<u>Respiratory System</u>				
Pleural Effusion	30%	32%	36%	35%
Atelectasis	28%	30%	5%	4%
Dyspnea	29%	23%	5%	4%
<u>Skin and Appendages</u>				
Pruritus	36%	20%	15%	7%
Rash	24%	19%	10%	4%

743

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

747

748 **Kidney Transplantation**

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

752

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

755

KIDNEY TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN $\geq 15\%$ OF PROGRAF-TREATED PATIENTS		
	Prograf (N=205)	CBIR (N=207)
<u>Nervous System</u>		
Tremor (see WARNINGS)	54%	34%
Headache (see WARNINGS)	44%	38%
Insomnia	32%	30%
Paresthesia	23%	16%
Dizziness	19%	16%
<u>Gastrointestinal</u>		
Diarrhea	44%	41%
Nausea	38%	36%
Constipation	35%	43%
Vomiting	29%	23%
Dyspepsia	28%	20%
<u>Cardiovascular</u>		
Hypertension (see PRECAUTIONS)	50%	52%
Chest pain	19%	13%
<u>Urogenital</u>		
Creatinine Increased (see WARNINGS)	45%	42%
Urinary Tract Infection	34%	35%
<u>Metabolic and Nutritional</u>		
Hypophosphatemia	49%	53%
Hypomagnesemia	34%	17%
Hyperlipemia	31%	38%
Hyperkalemia (see WARNINGS)	31%	32%
Diabetes Mellitus (see WARNINGS)	24%	9%
Hypokalemia	22%	25%
Hyperglycemia (see WARNINGS)	22%	16%
Edema	18%	19%
<u>Hemic and Lymphatic</u>		
Anemia	30%	24%
Leukopenia	15%	17%
<u>Miscellaneous</u>		
Infection	45%	49%
Peripheral Edema	36%	48%

Asthenia	34%	30%
Abdominal Pain	33%	31%
Pain	32%	30%
Fever	29%	29%
Back Pain	24%	20%
<u>Respiratory System</u>		
Dyspnea	22%	18%
Cough Increased	18%	15%
<u>Musculoskeletal</u>		
Arthralgia	25%	24%
<u>Skin</u>		
Rash	17%	12%
Pruritus	15%	7%

756

757

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

761

762 ***Heart Transplantation***

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

766

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

769

HEART TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN ≥15% OF PROGRAF-TREATED PATIENTS		
COSTART Body System COSTART Term	Prograf+ Azathioprine (n=157)	CsA + Azathioprine (n=157)
Cardiovascular System		
Hypertension (See PRECAUTIONS)	62%	69%
Pericardial effusion	15%	14%
Body as a Whole		
CMV infection	32%	30%
Infection	24%	21%
Metabolic and Nutritional Disorders		
Hyperlipemia	18%	27%
Diabetes Mellitus (See WARNINGS)	26%	16%
Hyperglycemia (See WARNINGS)	23%	17%
Hemic and Lymphatic System		
Leukopenia	48%	39%
Anemia	50%	36%

Urogenital System		
Kidney function abnormal (See WARNINGS)	56%	57%
Urinary tract infection	16%	12%
Respiratory System		
Bronchitis	17%	18%
Nervous System		
Tremor (See WARNINGS)	15%	6%

770

771

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%).

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.

Less Frequently Reported Adverse Reactions

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

Nervous System (see **WARNINGS**)

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

Special Senses

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

810 ***Gastrointestinal***

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

817

818 ***Cardiovascular***

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

826

827 ***Urogenital*** (see **WARNINGS**)

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

832

833 ***Metabolic/Nutritional***

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

841

842 ***Endocrine*** (see **PRECAUTIONS**)

843 Cushing's syndrome, diabetes mellitus

844

845 ***Hemic/Lymphatic***

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

849

850 ***Miscellaneous***

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

855

856 ***Musculoskeletal***

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

859

860 ***Respiratory***

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

865

866 ***Skin***

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

870

871

872 **Post Marketing**

873 **Post Marketing Adverse Events**

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

882

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

886

887 Other events include:

888

889 ***Cardiovascular***

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

894

895 ***Gastrointestinal***

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

900

901 ***Hemic/Lymphatic***

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

904

905 ***Metabolic/Nutritional***

906 Glycosuria, increased amylase including pancreatitis, weight decreased

907

908 ***Miscellaneous***

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

911

912 ***Nervous System***

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

915

916 ***Respiratory***

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

919

920 ***Skin***

921 Stevens-Johnson syndrome, toxic epidermal necrolysis

922

923 ***Special Senses***

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

925

926 ***Urogenital***

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

929

930 **OVERDOSAGE**

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

943

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

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DOSAGE AND ADMINISTRATION
Prograf injection (tacrolimus injection)

For IV Infusion Only

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

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

Preparation for Administration/Stability

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

Prograf capsules (tacrolimus capsules)

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

Patient Population	Recommended Initial Oral Dose*	Typical Whole Blood Trough Concentrations
Adult kidney transplant patients	0.2 mg/kg/day	month 1-3 : 7-20 ng/mL month 4-12 : 5-15 ng/mL
Adult liver transplant patients	0.10-0.15 mg/kg/day	month 1-12 : 5-20 ng/mL
Pediatric liver transplant patients	0.15-0.20 mg/kg/day	month 1-12 : 5-20 ng/mL

Adult heart transplant patients	0.075 mg/kg/day	month 1-3: 10-20 ng/mL month ≥ 4: 5-15 ng/mL
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986 *Note: two divided doses, q12h

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989 ***Liver Transplantation***

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

1001

1002 Dosing should be titrated based on clinical assessments of rejection and
 1003 tolerability. Lower Prograf dosages may be sufficient as maintenance therapy.
 1004 Adjunct therapy with adrenal corticosteroids is recommended early post-
 1005 transplant.

1006

1007 Dosage and typical tacrolimus whole blood trough concentrations are shown in
 1008 the table above; blood concentration details are described in **Blood
 1009 Concentration Monitoring: Liver Transplantation** below.

1010

1011 ***Kidney Transplantation***

1012 The recommended starting oral dose of Prograf is 0.2 mg/kg/day administered
 1013 every 12 hours in two divided doses. The initial dose of Prograf may be
 1014 administered within 24 hours of transplantation, but should be delayed until
 1015 renal function has recovered (as indicated for example by a serum creatinine
 1016 ≤ 4 mg/dL). Black patients may require higher doses to achieve comparable
 1017 blood concentrations. Dosage and typical tacrolimus whole blood trough
 1018 concentrations are shown in the table above; blood concentration details are
 1019 described in **Blood Concentration Monitoring: Kidney Transplantation**
 1020 below.

1021

1022 The data in kidney transplant patients indicate that the Black patients required a
 1023 higher dose to attain comparable trough concentrations compared to Caucasian
 1024 patients.

1025

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

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Heart Transplantation

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

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

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

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Pediatric Patients

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

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Patients with Hepatic or Renal Dysfunction

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

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

1066 **Conversion from One Immunosuppressive Regimen to Another**
1067 Prograf should not be used simultaneously with cyclosporine. Prograf or
1068 cyclosporine should be discontinued at least 24 hours before initiating the other.
1069 In the presence of elevated Prograf or cyclosporine concentrations, dosing with
1070 the other drug usually should be further delayed.

1071

1072 **Blood Concentration Monitoring**

1073 Monitoring of tacrolimus blood concentrations in conjunction with other
1074 laboratory and clinical parameters is considered an essential aid to patient
1075 management for the evaluation of rejection, toxicity, dose adjustments and
1076 compliance. Factors influencing frequency of monitoring include but are not
1077 limited to hepatic or renal dysfunction, the addition or discontinuation of
1078 potentially interacting drugs and the posttransplant time. Blood concentration
1079 monitoring is not a replacement for renal and liver function monitoring and
1080 tissue biopsies.

1081

1082 Two methods have been used for the assay of tacrolimus, a microparticle
1083 enzyme immunoassay (MEIA) and ELISA. Both methods have the same
1084 monoclonal antibody for tacrolimus. Comparison of the concentrations in
1085 published literature to patient concentrations using the current assays must be
1086 made with detailed knowledge of the assay methods and biological matrices
1087 employed. Whole blood is the matrix of choice and specimens should be
1088 collected into tubes containing ethylene diamine tetraacetic acid (EDTA) anti-
1089 coagulant. Heparin anti-coagulation is not recommended because of the
1090 tendency to form clots on storage. Samples which are not analyzed
1091 immediately should be stored at room temperature or in a refrigerator and
1092 assayed within 7 days; if samples are to be kept longer they should be deep
1093 frozen at -20° C for up to 12 months.

1094

1095 **Liver Transplantation**

1096 Although there is a lack of direct correlation between tacrolimus concentrations
1097 and drug efficacy, data from Phase II and III studies of liver transplant patients
1098 have shown an increasing incidence of adverse events with increasing trough
1099 blood concentrations. Most patients are stable when trough whole blood
1100 concentrations are maintained between 5 to 20 ng/mL. Long-term post-
1101 transplant patients often are maintained at the low end of this target range.

1102

1103 Data from the U.S. clinical trial show that tacrolimus whole blood
1104 concentrations, as measured by ELISA, were most variable during the first
1105 week post-transplantation. After this early period, the median trough blood
1106 concentrations, measured at intervals from the second week to one year post-
1107 transplantation, ranged from 9.8 ng/mL to 19.4 ng/mL.

1108

1109 *Therapeutic Drug Monitoring*, 1995, Volume 17, Number 6 contains a
1110 consensus document and several position papers regarding the therapeutic
1111 monitoring of tacrolimus from the 1995 International Consensus Conference on

1112 Immunosuppressive Drugs. Refer to these manuscripts for further discussions
1113 of tacrolimus monitoring.

1114

1115 ***Kidney Transplantation***

1116 Data from the Phase 3 study indicate that trough concentrations of tacrolimus in
1117 whole blood, as measured by IMx[®] were most variable during the first week of
1118 dosing. During the first three months, 80% of the patients maintained trough
1119 concentrations between 7-20 ng/mL, and then between 5-15 ng/mL, through 1
1120 year.

1121

1122 The relative risk of toxicity is increased with higher trough concentrations.
1123 Therefore, monitoring of whole blood trough concentrations is recommended to
1124 assist in the clinical evaluation of toxicity.

1125

1126 ***Heart Transplantation***

1127 Data from a European Phase 3 study indicate that trough concentrations of
1128 tacrolimus in whole blood, as measured by IMx[®] were most variable during the
1129 first week of dosing. From 1 week to 3 months post transplant, approximately
1130 80% of patients maintained trough concentrations between 8-20 ng/mL and,
1131 from 3 months through 18 months post transplant, approximately 80% of
1132 patients maintained trough concentrations between 6-18 ng/mL.

1133

1134 The relative risk of toxicity; for example, nephrotoxicity and post-transplant
1135 diabetes mellitus, is increased with higher trough concentrations. Therefore,
1136 monitoring of whole blood trough concentrations is recommended to assist in
1137 the clinical evaluation of toxicity.

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1139

1140 **HOW SUPPLIED**

1141 **Prograf capsules (tacrolimus capsules)**

1142

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

1143

1144 Made in Japan

1145

1146 *Store and Dispense*
1147 Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).
1148
1149 **Prograf injection (tacrolimus injection)**
1150 **(for IV infusion only)**
1151
1152 NDC 0469-3016-01 Product Code 301601
1153 5 mg/mL (equivalent of 5 mg of anhydrous tacrolimus per mL) supplied as a
1154 sterile solution in a 1 mL ampule, in boxes of 10 ampules
1155
1156 Made in Ireland
1157
1158 *Store and Dispense*
1159 Store between 5°C and 25°C (41°F and 77°F).
1160
1161 **Rx only**
1162
1163 **Marketed by:**
1164 Astellas Pharma US, Inc.
1165 Deerfield, IL 60015-2548
1166
1167
1168 **REFERENCE**
1169 1. CDC: Recommendations of the Advisory Committee on Immunization
1170 Practices: Use of vaccines and immune globulins in persons with altered
1171 immunocompetence. MMWR 1993;42(RR-4):1-18.
1172
1173
1174 Revised: April 2006
1175
1176