

PROPOSED PACKAGE INSERT

1 Revised: May 2000

2 **Prograf[®]**

3 *tacrolimus capsules*

4 *tacrolimus injection (for intravenous*

5 *infusion only)*

6

WARNING

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

7

8 **DESCRIPTION:**

9 Prograf is available for oral administration as
10 capsules (tacrolimus capsules) containing the
11 equivalent of 0.5 mg, 1 mg or 5 mg of
12 anhydrous tacrolimus. Inactive ingredients
13 include lactose, hydroxypropyl
14 methylcellulose, croscarmellose sodium, and
15 magnesium stearate. The 0.5 mg capsule shell

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16 contains gelatin, titanium dioxide and ferric
17 oxide, the 1 mg capsule shell contains gelatin
18 and titanium dioxide, and the 5 mg capsule
19 shell contains gelatin, titanium dioxide and
20 ferric oxide.

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

31 Tacrolimus, previously known as
32 FK506, is the active ingredient in Prograf.
33 Tacrolimus is a macrolide immunosuppressant
34 produced by *Streptomyces tsukubaensis*.
35 Chemically, tacrolimus is designated as [3S-
36 [3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R
37 *,15S*,16R*,18S*,19S*,26aR*]]-
38 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a
39 -hexadecahydro-5,19-dihydroxy-3-[2-(4-
40 hydroxy-3-methoxycyclohexyl)-1-
41 methylethenyl]-14,16-dimethoxy-4,10,12,18-
42 tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-
43 pyrido[2,1-c][1,4] oxaazacyclotricosine-
44 1,7,20,21(4H,23H)-tetrone, monohydrate.
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46 The chemical structure of tacrolimus is:

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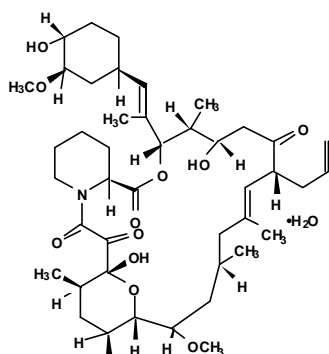
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CLINICAL PHARMACOLOGY:

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Mechanism of Action

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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.

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

97

98 *Pharmacokinetics*

99 Tacrolimus activity is primarily due to the
100 parent drug. The pharmacokinetic parameters
101 (mean±S.D.) of tacrolimus have been
102 determined following intravenous (IV) and oral
103 (PO) administration in healthy volunteers, and
104 in kidney transplant and liver transplant
105 patients. (See table below.)

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Population	N	Route (Dose)	Parameters					
			C _{max} (ng/mL)	T _{max} (hr)	AUC (ng•hr/mL)	t 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	0.041H "0.008	1.94H "0.53
Kidney Transplant Pts	26	IV (0.02 mg/kg/12hr)	--	--	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	#	#	#

108 H Corrected for individual bioavailability
 109 * AUC₀₋₁₂₀
 110 ** AUC₀₋₇₂
 111 *** AUC_{0-inf}
 112 -- not applicable
 113 # not available
 114

115 Due to intersubject variability in tacrolimus
 116 pharmacokinetics, individualization of dosing
 117 regimen is necessary for optimal therapy. (See
 118 **DOSAGE AND ADMINISTRATION**).
 119 Pharmacokinetic data indicate that whole

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120 blood concentrations rather than plasma
121 concentrations serve as the more appropriate
122 sampling compartment to describe tacrolimus
123 pharmacokinetics.

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125 Absorption

126 Absorption of tacrolimus from the
127 gastrointestinal tract after oral administration
128 is incomplete and variable. The absolute
129 bioavailability of tacrolimus was 17% in
130 adult kidney transplant patients (N=26),
131 22% in adult liver transplant patients
132 (N=17), and 18% in healthy volunteers
133 (N=16).

134 A single dose study conducted in 32
135 healthy volunteers established the
136 bioequivalence of the 1 mg and 5 mg capsules.
137 Another single dose study in 32 healthy
138 volunteers established the bioequivalence of
139 the 0.5 mg and 1 mg capsules. Tacrolimus
140 maximum blood concentration (C_{max}) and area
141 under the curve (AUC) appeared to increase in
142 a dose-proportional fashion in 18 fasted
143 healthy volunteers receiving a single oral dose
144 of 3, 7 and 10 mg.

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

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155 *Food Effects:* The rate and extent of
156 tacrolimus absorption were greatest under
157 fasted conditions. The presence and
158 composition of food decreased both the rate
159 and extent of tacrolimus absorption when
administered to 15 healthy volunteers.

160

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

167

168 In healthy volunteers (N=16), the time
169 of the meal also affected tacrolimus
170 bioavailability. When given immediately
171 following the meal, mean C_{max} was reduced
172 71%, and mean AUC was reduced 39%,
173 relative to the fasted condition. When
174 administered 1.5 hours following the meal,
175 mean C_{max} was reduced 63%, and mean AUC
176 was reduced 39%, relative to the fasted
condition.

177

178 In 11 liver transplant patients, Prograf
179 administered 15 minutes after a high fat (400
180 kcal, 34% fat) breakfast, resulted in decreased
181 AUC (27" 18%) and C_{max} (50" 19%), as
compared to a fasted state.

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184 Distribution

185 The plasma protein binding of tacrolimus is
186 approximately 99% and is independent of
187 concentration over a range of 5-50 ng/mL.

188 Tacrolimus is bound mainly to albumin and
189 alpha-1-acid glycoprotein, and has a high level
190 of association with erythrocytes. The
191 distribution of tacrolimus between whole
192 blood and plasma depends on several factors,
193 such as hematocrit, temperature at the time of
194 plasma separation, drug concentration, and
195 plasma protein concentration. In a U.S. study,
196 the ratio of whole blood concentration to
197 plasma concentration averaged 35 (range 12 to
198 67).

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200 Metabolism

201 Tacrolimus is extensively metabolized by the
202 mixed-function oxidase system, primarily the
203 cytochrome P-450 system (CYP3A). A
204 metabolic pathway leading to the formation of
205 8 possible metabolites has been proposed.

206 Demethylation and hydroxylation were
207 identified as the primary mechanisms of
208 biotransformation in vitro. The major
209 metabolite identified in incubations with human
210 liver microsomes is 13-demethyl tacrolimus.

211 In in vitro studies, a 31-demethyl metabolite
212 has been reported to have the same activity as
213 tacrolimus.

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216 Excretion

217 The mean clearance following IV
218 administration of tacrolimus is 0.040, 0.083
219 and 0.053 L/hr/kg in healthy volunteers, adult
220 kidney transplant patients and adult liver
221 transplant patients, respectively. In man, less
222 than 1% of the dose administered is excreted
223 unchanged in urine.

224 In a mass balance study of IV
225 administered radiolabeled tacrolimus to 6
226 healthy volunteers, the mean recovery of
227 radiolabel was 77.8%±12.7%. Fecal
228 elimination accounted for 92.4%±1.0% and the
229 elimination half-life based on radioactivity
230 was 48.1±15.9 hours whereas it was
231 43.5±11.6 hours based on tacrolimus
232 concentrations. The mean clearance of
233 radiolabel was 0.029±0.015 L/hr/kg and
234 clearance of tacrolimus was 0.029±0.009
235 L/hr/kg. When administered PO, the mean
236 recovery of the radiolabel was 94.9%±30.7%.

237 Fecal elimination accounted for 92.6%±30.7%,
238 urinary elimination accounted for 2.3%±1.1%
239 and the elimination half-life based on
240 radioactivity was 31.9±10.5 hours whereas it
241 was 48.4±12.3 hours based on tacrolimus
242 concentrations. The mean clearance of
243 radiolabel was 0.226±0.116 L/hr/kg and
244 clearance of tacrolimus 0.172±0.088 L/hr/kg.
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247 Special Populations

248 Pediatric

249 Pharmacokinetics of tacrolimus have been
250 studied in liver transplantation patients, 0.7 to
251 13.2 years of age. Following IV administration
252 of a 0.037 mg/kg/day dose to 12 pediatric
253 patients, mean terminal half-life, volume of
254 distribution and clearance were 11.5"3.8
255 hours, 2.6"2.1 L/kg and 0.138"0.071 L/hr/kg,
256 respectively. Following oral administration to
257 9 patients, mean AUC and C_{max} were 337"167
258 ng\$hr/mL and 43.4"27.9 ng/mL, respectively.
259 The absolute bioavailability was 31" 21%.

260 Whole blood trough concentrations
261 from 31 patients less than 12 years old showed
262 that pediatric patients needed higher doses than
263 adults to achieve similar tacrolimus trough
264 concentrations. (See **DOSAGE AND**
265 **ADMINISTRATION**).

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267 Renal and Hepatic Insufficiency

268 The mean pharmacokinetic parameters for
269 tacrolimus following single administrations to
270 patients with renal and hepatic impairment are
271 given in the following table.

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Population (No. of Patients)	Dose	AUC _{0-t} (ng · hr/mL)	t _{1/2} (hr)	V (L/kg)	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)			

273 * corrected for bioavailability

274 † 1 patient did not receive the PO dose

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276 Renal Insufficiency:

277 Tacrolimus pharmacokinetics following a
 278 single IV administration were determined in 12
 279 patients (7 not on dialysis and 5 on dialysis,
 280 serum creatinine of 3.9" 1.6 and 12.0" 2.4
 281 mg/dL, respectively) prior to their kidney
 282 transplant. The pharmacokinetic parameters
 283 obtained were similar for both groups.

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284
285 The mean clearance of tacrolimus in
286 patients with renal dysfunction was similar to
287 that in normal volunteers (see previous table).

288
289 Hepatic Insufficiency:
290 Tacrolimus pharmacokinetics have been
291 determined in six patients with mild hepatic
292 dysfunction (mean Pugh score: 6.2) following
293 single IV and oral administrations. The mean
294 clearance of tacrolimus in patients with mild
295 hepatic dysfunction was not substantially
296 different from that in normal volunteers (see
297 previous table). Tacrolimus pharmacokinetics
298 were studied in 6 patients with severe hepatic
299 dysfunction (mean Pugh score:>10). The mean
300 clearance was substantially lower in patients
301 with severe hepatic dysfunction, irrespective
302 of the route of administration.

303
304 Race
305 A formal study to evaluate the pharmacokinetic
306 disposition of tacrolimus in Black transplant
307 patients has not been conducted. However, a
308 retrospective comparison of Black and
309 Caucasian kidney transplant patients indicated
310 that Black patients required higher tacrolimus
311 doses to attain similar trough concentrations.
312 **(See DOSAGE AND ADMINISTRATION).**

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316 Gender

317 A formal study to evaluate the effect of gender
318 on tacrolimus pharmacokinetics has not been
319 conducted, however, there was no difference in
320 dosing by gender in the kidney transplant trial.

321 A retrospective comparison of
322 pharmacokinetics in healthy volunteers, and in
323 kidney and liver transplant patients indicated
324 no gender-based differences.

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326 *Clinical Studies*

327 *Liver Transplantation*

328 The safety and efficacy of Prograf-based
329 immunosuppression following orthotopic liver
330 transplantation were assessed in two
331 prospective, randomized, non-blinded
332 multicenter studies. The active control groups
333 were treated with a cyclosporine-based
334 immunosuppressive regimen. Both studies used
335 concomitant adrenal corticosteroids as part of
336 the immunosuppressive regimens. These
337 studies were designed to evaluate whether the
338 two regimens were therapeutically equivalent,
339 with patient and graft survival at 12 months
340 following transplantation as the primary
341 endpoints. The Prograf-based
342 immunosuppressive regimen was found to be
343 equivalent to the cyclosporine-based
344 immunosuppressive regimens.

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

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

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One-year patient survival and graft survival in the Prograf-based treatment groups were equivalent to those in the CBIR treatment groups in both studies. The overall one-year patient survival (CBIR and Prograf-based treatment groups combined) was 88% in the U.S. study and 78% in the European study.

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376 The overall one-year graft survival (CBIR and
377 Prograf-based treatment groups combined) was
378 81% in the U.S. study and 73% in the
379 European study. In both studies, the median
380 time to convert from IV to oral Prograf dosing
381 was 2 days.

382 Because of the nature of the study
383 design, comparisons of differences in
384 secondary endpoints, such as incidence of
385 acute rejection, refractory rejection or use of
386 OKT3 for steroid-resistant rejection, could not
387 be reliably made.

388

389 ***Kidney Transplantation***

390 Prograf-based immunosuppression following
391 kidney transplantation was assessed in a Phase
392 III randomized, multicenter, non-blinded,
393 prospective study. There were 412 kidney
394 transplant patients enrolled at 19 clinical sites
395 in the United States. Study therapy was
396 initiated when renal function was stable as
397 indicated by a serum creatinine ≤ 4 mg/dL
398 (median of 4 days after transplantation, range
399 1 to 14 days). Patients less than 6 years of age
400 were excluded.

401 There were 205 patients randomized to
402 Prograf-based immunosuppression and 207
403 patients were randomized to cyclosporine-
404 based immunosuppression. All patients
405 received prophylactic induction therapy
406 consisting of an antilymphocyte antibody
407 preparation, corticosteroids and azathioprine.

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408 Overall one year patient and graft survival
409 was 96.1% and 89.6%, respectively and was
410 equivalent between treatment arms.

411 Because of the nature of the study
412 design, comparisons of differences in
413 secondary endpoints, such as incidence of
414 acute rejection, refractory rejection or use of
415 OKT3 for steroid-resistant rejection, could not
416 be reliably made.

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420 **INDICATIONS AND USAGE:**

421 Prograf is indicated for the prophylaxis of
422 organ rejection in patients receiving allogeneic
423 liver or kidney transplants. It is recommended
424 that Prograf be used concomitantly with
425 adrenal corticosteroids. Because of the risk of
426 anaphylaxis, Prograf injection should be
427 reserved for patients unable to take Prograf
428 capsules orally.

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430 **CONTRAINDICATIONS:**

431 Prograf is contraindicated in patients with a
432 hypersensitivity to tacrolimus. Prograf
433 injection is contraindicated in patients with a
434 hypersensitivity to HCO-60 (polyoxyl 60
435 hydrogenated castor oil).

436

437 **WARNINGS:**

438 (See boxed **WARNING**.)

439 Insulin-dependent post-transplant diabetes
440 mellitus (PTDM) was reported in 20% of
441 Prograf-treated kidney transplant patients
442 without pretransplant history of diabetes
443 mellitus in the Phase III study (See Tables
444 Below). The median time to onset of PTDM
445 was 68 days. Insulin dependence was
446 reversible in 15% of these PTDM patients at

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447 one year and in 50% at two years post
448 transplant. Black and Hispanic kidney
449 transplant patients were at an increased risk of
450 development of PTDM.

451

452 **Incidence of Post Transplant Diabetes**
453 **Mellitus and Insulin Use at 2 Years in**
454 **Kidney Transplant Recipients in the Phase**
455 **III Study**

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

456 *use of insulin for 30 or more consecutive days, with <
457 5 day gap, without a prior history of insulin dependent
458 diabetes mellitus or non insulin dependent diabetes
459 mellitus.

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

Patient Race	Prograf		CBIR	
	No. of Patients at Risk	Patients Who Developed PTDM*	No. of Patients At Risk	Patients Who Developed PTDM*
Black	41	15 (37%)	36	3 (8%)
Hispanic	17	5 (29%)	18	1 (6%)
Caucasian	82	10 (12%)	87	1 (1%)
Other	11	0 (0%)	10	1 (10%)
Total	151	30 (20%)	151	6 (4%)

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

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474 **Insulin-dependent post-transplant diabetes**
475 **mellitus was reported in 18% and 11% of**
476 **Prograf-treated liver transplant patients and**
477 **was reversible in 45% and 31% of these**
478 **patients at one year post transplant, in the**
479 **U.S. and European randomized studies,**
480 **respectively (See Table below).**
481 Hyperglycemia was associated with the use of
482 Prograf in 47% and 33% of liver transplant
483 recipients in the U.S. and European
484 randomized studies, respectively, and may
485 require treatment (see **ADVERSE**
486 **REACTIONS**).

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Incidence of Post Transplant Diabetes Mellitus and Insulin Use at One Year in Liver Transplant Recipients

Status of PTDM*	US Study		European Study	
	Prograf	CBIR	Prograf	CBIR
Patients at risk **	239	236	239	249
New Onset PTDM*	42 (18%)	30 (13%)	26 (11%)	12(5%)
Patients still on insulin at 1 year	23 (10%)	19 (8%)	18 (8%)	6 (2%)

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

**Patients without pretransplant history of diabetes mellitus.

Prograf can cause neurotoxicity and nephrotoxicity, particularly when used in high doses. Nephrotoxicity was reported in approximately 52% of kidney transplantation patients and in 40% and 36% of liver transplantation patients receiving Prograf in the U.S. and European randomized trials, respectively (see **ADVERSE REACTIONS**). More overt nephrotoxicity is seen early after transplantation, characterized by increasing serum creatinine and a decrease in urine output. Patients with impaired renal function

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511 should be monitored closely as the dosage of
512 Prograf may need to be reduced. In patients
513 with persistent elevations of serum creatinine
514 who are unresponsive to dosage adjustments,
515 consideration should be given to changing to
516 another immunosuppressive therapy. Care
517 should be taken in using tacrolimus with other
518 nephrotoxic drugs. **In particular, to avoid
519 excess nephrotoxicity, Prograf should not be
520 used simultaneously with cyclosporine.
521 Prograf or cyclosporine should be
522 discontinued at least 24 hours prior to
523 initiating the other. In the presence of
524 elevated Prograf or cyclosporine
525 concentrations, dosing with the other drug
526 usually should be further delayed.**

527 Mild to severe hyperkalemia was
528 reported in 31% of kidney transplant recipients
529 and in 45% and 13% of liver transplant
530 recipients treated with Prograf in the U.S. and
531 European randomized trials, respectively, and
532 may require treatment (see **ADVERSE
533 REACTIONS**). **Serum potassium levels
534 should be monitored and potassium-sparing
535 diuretics should not be used during Prograf
536 therapy (see PRECAUTIONS).**

537 Neurotoxicity, including tremor,
538 headache, and other changes in motor function,
539 mental status, and sensory function were
540 reported in approximately 55% of liver
541 transplant recipients in the two randomized

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542 studies. Tremor occurred more often in
543 Prograf-treated kidney transplant patients
544 (54%) compared to cyclosporine-treated
545 patients. The incidence of other neurological
546 events in kidney transplant patients was similar
547 in the two treatment groups (see **ADVERSE**
548 **REACTIONS**). Tremor and headache have
549 been associated with high whole-blood
550 concentrations of tacrolimus and may respond
551 to dosage adjustment. Seizures have occurred
552 in adult and pediatric patients receiving
553 Prograf (see **ADVERSE REACTIONS**).

554 Coma and delirium also have been associated
555 with high plasma concentrations of tacrolimus.

556 As in patients receiving other
557 immunosuppressants, patients receiving
558 Prograf are at increased risk of developing
559 lymphomas and other malignancies,
560 particularly of the skin. The risk appears to be
561 related to the intensity and duration of
562 immunosuppression rather than to the use of
563 any specific agent. A lymphoproliferative
564 disorder (LPD) related to Epstein-Barr Virus
565 (EBV) infection has been reported in
566 immunosuppressed organ transplant recipients.

567 The risk of LPD appears greatest in young
568 children who are at risk for primary EBV
569 infection while immunosuppressed or who are
570 switched to Prograf following long-term
571 immunosuppression therapy. Because of the
572 danger of oversuppression of the immune

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573 system which can increase susceptibility to
574 infection, combination immunosuppressant
575 therapy should be used with caution.

576 A few patients receiving Prograf
577 injection have experienced anaphylactic
578 reactions. Although the exact cause of these
579 reactions is not known, other drugs with castor
580 oil derivatives in the formulation have been
581 associated with anaphylaxis in a small
582 percentage of patients. Because of this
583 potential risk of anaphylaxis, Prograf injection
584 should be reserved for patients who are unable
585 to take Prograf capsules.

586 **Patients receiving Prograf injection**
587 **should be under continuous observation for**
588 **at least the first 30 minutes following the**
589 **start of the infusion and at frequent**
590 **intervals thereafter. If signs or symptoms of**
591 **anaphylaxis occur, the infusion should be**
592 **stopped. An aqueous solution of epinephrine**
593 **should be available at the bedside as well as**
594 **a source of oxygen.**

595
596

597 **PRECAUTIONS:**

598 *General*

599 Hypertension is a common adverse effect of
600 Prograf therapy (see **ADVERSE**
601 **REACTIONS**). Mild or moderate
602 hypertension is more frequently reported than
603 severe hypertension. Antihypertensive therapy
604 may be required; the control of blood

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605 pressure can be accomplished with any of the
606 common antihypertensive agents. Since
607 tacrolimus may cause hyperkalemia,
608 potassium-sparing diuretics should be avoided.
609 While calcium-channel blocking agents can be
610 effective in treating Prograf-associated
611 hypertension, care should be taken since
612 interference with tacrolimus metabolism may
613 require a dosage reduction (see ***Drug***
614 ***Interactions***).

615
616 ***Renally and Hepatically Impaired Patients***
617 For patients with renal insufficiency some
618 evidence suggests that lower doses should be
619 used (see **CLINICAL PHARMACOLOGY**
620 and **DOSAGE AND ADMINISTRATION**).

621 The use of Prograf in liver transplant
622 recipients experiencing post-transplant hepatic
623 impairment may be associated with increased
624 risk of developing renal insufficiency related
625 to high whole-blood levels of tacrolimus.
626 These patients should be monitored closely and
627 dosage adjustments should be considered.
628 Some evidence suggests that lower doses
629 should be used in these patients (see
630 **DOSAGE AND ADMINISTRATION**).

631
632 ***Myocardial Hypertrophy***
633 Myocardial hypertrophy has been reported in
634 association with the administration of Prograf,
635 and is generally manifested by
636 echocardiographically demonstrated

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637 concentric increases in left ventricular
638 posterior wall and interventricular septum
639 thickness. Hypertrophy has been observed in
640 infants, children and adults. This condition
641 appears reversible in most cases following
642 dose reduction or discontinuance of therapy. In
643 a group of 20 patients with pre- and post-
644 treatment echocardiograms who showed
645 evidence of myocardial hypertrophy, mean
646 tacrolimus whole blood concentrations during
647 the period prior to diagnosis of myocardial
648 hypertrophy ranged from 11 to 53 ng/mL in
649 infants (N=10, age 0.4 to 2 years), 4 to 46
650 ng/mL in children (N=7, age 2 to 15 years) and
651 11 to 24 ng/mL in adults (N=3, age 37 to 53
652 years).

653 In patients who develop renal failure or
654 clinical manifestations of ventricular
655 dysfunction while receiving Prograf therapy,
656 echocardiographic evaluation should be
657 considered. If myocardial hypertrophy is
658 diagnosed, dosage reduction or discontinuation
659 of Prograf should be considered.

660

661 *Information for Patients*

662 Patients should be informed of the need for
663 repeated appropriate laboratory tests while
664 they are receiving Prograf. They should be
665 given complete dosage instructions, advised of
666 the potential risks during pregnancy, and
667 informed of the increased risk of neoplasia.

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668 Patients should be informed that changes in
669 dosage should not be undertaken without first
670 consulting their physician.

671 Patients should be informed that
672 Prograf can cause diabetes mellitus and should
673 be advised of the need to see their physician if
674 they develop frequent urination, increased
675 thirst or hunger.

676

677 *Laboratory Tests*

678 Serum creatinine, potassium, and fasting
679 glucose should be assessed regularly. Routine
680 monitoring of metabolic and hematologic
681 systems should be performed as clinically
682 warranted.

683

684 *Drug Interactions*

685 Due to the potential for additive or synergistic
686 impairment of renal function, care should be
687 taken when administering Prograf with drugs
688 that may be associated with renal dysfunction.
689 These include, but are not limited to,
690 aminoglycosides, amphotericin B, and
691 cisplatin. Initial clinical experience with the
692 co-administration of Prograf and cyclosporine
693 resulted in additive/synergistic nephrotoxicity.

694 Patients switched from cyclosporine to
695 Prograf should receive the first Prograf dose
696 no sooner than 24 hours after the last
697 cyclosporine dose. Dosing may be further
698 delayed in the presence of elevated
699 cyclosporine levels.

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Drugs that May Alter Tacrolimus Concentrations

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

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

Calcium Channel Blockers	Antifungal Agents	Macrolide Antibiotics	
diltiazem	clotrimazole	clarithromycin	
nicardipine		fluconazole	erythromycin
nifedipine	itraconazole	troleandomycin	
verapamil	ketoconazole		

Gastrointestinal Prokinetic Agents	Other Drugs
cisapride	bromocriptine
metoclopramide	cimetidine
	cyclosporine
	danazol
	ethinyl estradiol
	methylprednisolone
	omeprazole
	protease inhibitors
	nefazodone

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739 In a study of 6 normal volunteers, a
740 significant increase in tacrolimus oral
741 bioavailability ($14\pm 5\%$ vs. $30\pm 8\%$) was
742 observed with concomitant ketoconazole
743 administration (200 mg). The apparent oral
744 clearance of tacrolimus during ketoconazole
745 administration was significantly decreased
746 compared to tacrolimus alone (0.430 ± 0.129
747 L/hr/kg vs. 0.148 ± 0.043 L/hr/kg). Overall, IV
748 clearance of tacrolimus was not significantly
749 changed by ketoconazole co-administration,
750 although it was highly variable between
751 patients.

752
753 **Drugs That May Decrease Tacrolimus Blood Concentrations:*

<u>Anticonvulsants</u>	<u>Antibiotics</u>
754 carbamazepine	754 rifabutin
755 phenobarbital	755 rifampin
756 phenytoin	

757
758
759 *This table is not all inclusive.

760
761 In a study of 6 normal volunteers, a
762 significant decrease in tacrolimus oral
763 bioavailability ($14\pm 6\%$ vs. $7\pm 3\%$) was
764 observed with concomitant rifampin
765 administration (600 mg). In addition, there
766 was a significant increase in tacrolimus
767 clearance (0.036 ± 0.008 L/hr/kg vs.
768 0.053 ± 0.010 L/hr/kg) with concomitant
769 rifampin administration.

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770 Interaction studies with drugs used in
771 HIV therapy have not been conducted.
772 However, care should be exercised when
773 drugs that are nephrotoxic (e.g., ganciclovir) or
774 that are metabolized by CYP3A (e.g.,
775 ritonavir) are administered concomitantly with
776 tacrolimus. Tacrolimus may affect the
777 pharmacokinetics of other drugs (e.g.,
778 phenytoin) and increase their concentration.
779 Grapefruit juice affects CYP3A-mediated
780 metabolism and should be avoided (**See**
781 **DOSAGE AND ADMINISTRATION**).

782

783 *Other Drug Interactions*

784 Immunosuppressants may affect vaccination.
785 Therefore, during treatment with Prograf,
786 vaccination may be less effective. The use of
787 live vaccines should be avoided; live vaccines
788 may include, but are not limited to measles,
789 mumps, rubella, oral polio, BCG, yellow
790 fever, and TY 21a typhoid.¹

791

792 *Carcinogenesis, Mutagenesis and* 793 *Impairment of Fertility*

794 An increased incidence of malignancy is a
795 recognized complication of
796 immunosuppression in recipients of organ
797 transplants. The most common forms of

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798 neoplasms are non-Hodgkin's lymphomas and
799 carcinomas of the skin. As with other
800 immunosuppressive therapies, the risk of
801 malignancies in Prograf recipients may be
802 higher than in the normal, healthy population.
803 Lymphoproliferative disorders associated
804 with Epstein-Barr Virus infection have been
805 seen. It has been reported that reduction or
806 discontinuation of immunosuppression may
807 cause the lesions to regress.

808 No evidence of genotoxicity was seen
809 in bacterial (*Salmonella* and *E. coli*) or
810 mammalian (Chinese hamster lung-derived
811 cells) in vitro assays of mutagenicity, the in
812 vitro CHO/HGPRT assay of mutagenicity, or in
813 vivo clastogenicity assays performed in mice;
814 tacrolimus did not cause unscheduled DNA
815 synthesis in rodent hepatocytes.

816 Carcinogenicity studies were carried
817 out in male and female rats and mice. In the 80-
818 week mouse study and in the 104-week rat
819 study no relationship of tumor incidence to
820 tacrolimus dosage was found. The highest
821 doses used in the mouse and rat studies were
822 0.8 - 2.5 times (mice) and 3.5 - 7.1 times (rats)
823 the recommended clinical dose range of 0.1 -
824 0.2 mg/kg/day when corrected for body surface
825 area.

826 No impairment of fertility was
827 demonstrated in studies of male and female
828 rats. Tacrolimus, given orally at 1.0 mg/kg

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829 (0.7 - 1.4X the recommended clinical dose
830 range of 0.1 - 0.2 mg/kg/day based on body
831 surface area corrections) to male and female
832 rats, prior to and during mating, as well as to
833 dams during gestation and lactation, was
834 associated with embryoletality and with
835 adverse effects on female reproduction.
836 Effects on female reproductive function
837 (parturition) and embryoletal effects were
838 indicated by a higher rate of pre-implantation
839 loss and increased numbers of undelivered and
840 nonviable pups. When given at 3.2 mg/kg (2.3
841 - 4.6X the recommended clinical dose range
842 based on body surface area correction),
843 tacrolimus was associated with maternal and
844 paternal toxicity as well as reproductive
845 toxicity including marked adverse effects on
846 estrus cycles, parturition, pup viability, and
847 pup malformations.

848

849 ***Pregnancy: Category C***

850 In reproduction studies in rats and rabbits,
851 adverse effects on the fetus were observed
852 mainly at dose levels that were toxic to dams.
853 Tacrolimus at oral doses of 0.32 and 1.0
854 mg/kg during organogenesis in rabbits was
855 associated with maternal toxicity as well as an
856 increase in incidence of abortions; these doses
857 are equivalent to 0.5 - 1X and 1.6 - 3.3X the
858 recommended clinical dose range (0.1 - 0.2
859 mg/kg) based on body surface area

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860 corrections. At the higher dose only, an
861 increased incidence of malformations and
862 developmental variations was also seen.
863 Tacrolimus, at oral doses of 3.2 mg/kg during
864 organogenesis in rats, was associated with
865 maternal toxicity and caused an increase in late
866 resorptions, decreased numbers of live births,
867 and decreased pup weight and viability.
868 Tacrolimus, given orally at 1.0 and 3.2 mg/kg
869 (equivalent to 0.7 - 1.4X and 2.3 - 4.6X the
870 recommended clinical dose range based on
871 body surface area corrections) to pregnant rats
872 after organogenesis and during lactation, was
873 associated with reduced pup weights.

874 No reduction in male or female fertility
875 was evident.

876 There are no adequate and well-
877 controlled studies in pregnant women.
878 Tacrolimus is transferred across the placenta.
879 The use of tacrolimus during pregnancy has
880 been associated with neonatal hyperkalemia
881 and renal dysfunction. Prograf should be used
882 during pregnancy only if the potential benefit to
883 the mother justifies potential risk to the fetus.

884 *Nursing Mothers*

885 Since tacrolimus is excreted in human milk,
886 nursing should be avoided.
887

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890 ***Pediatric Patients***

891 Experience with Prograf in pediatric kidney
892 transplant patients is limited. Successful liver
893 transplants have been performed in pediatric
894 patients (ages up to 16 years) using Prograf.
895 Two randomized active-controlled trials of
896 Prograf in primary liver transplantation
897 included 56 pediatric patients. Thirty-one
898 patients were randomized to Prograf-based and
899 25 to cyclosporine-based therapies.

900 Additionally, a minimum of 122 pediatric
901 patients were studied in an uncontrolled trial of
902 tacrolimus in living related donor liver
903 transplantation. Pediatric patients generally
904 required higher doses of Prograf to maintain
905 blood trough concentrations of tacrolimus
906 similar to adult patients (see **DOSAGE AND**
907 **ADMINISTRATION**).

908

909 **ADVERSE REACTIONS:**

910 ***Liver Transplantation***

911 The principal adverse reactions of Prograf are
912 tremor, headache, diarrhea, hypertension,
913 nausea, and renal dysfunction. These occur
914 with oral and IV administration of Prograf and
915 may respond to a reduction in dosing.

916 Diarrhea was sometimes associated with other
917 gastrointestinal complaints such as nausea and
918 vomiting.

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919

920 Hyperkalemia and hypomagnesemia
921 have occurred in patients receiving Prograf
922 therapy. Hyperglycemia has been noted in
923 many patients; some may require insulin
924 therapy (see **WARNINGS**).

925 The incidence of adverse events was
926 determined in two randomized comparative
927 liver transplant trials among 514 patients
928 receiving tacrolimus and steroids and 515
929 patients receiving a cyclosporine-based
930 regimen (CBIR). The proportion of patients
931 reporting more than one adverse event was
932 99.8% in the tacrolimus group and 99.6% in
933 the CBIR group. Precautions must be taken
934 when comparing the incidence of adverse
935 events in the U.S. study to that in the European
936 study. The 12-month posttransplant
937 information from the U.S. study and from the
938 European study is presented below. The two
939 studies also included different patient
940 populations and patients were treated with
941 immunosuppressive regimens of differing
942 intensities. Adverse events reported in 15%
943 in tacrolimus patients (combined study results)
944 are presented below for the two controlled
945 trials in liver transplantation:

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**LIVER TRANSPLANTATION: ADVERSE
EVENTS OCCURRING IN \$ 15% OF
PROGRAF-TREATED PATIENTS**

U.S. STUDY (%)		EUROPEAN STUDY (%)		
Prograf (N=250)	CBIR (N=250)	Prograf (N=264)	CBIR (N=265)	
<u>Nervous System</u>				
Headache (See WARNINGS)	64	60	37	26
Tremor (See WARNINGS)	56	46	48	32
Insomnia	64	68	32	23
Paresthesia	40	30	17	17
<u>Gastrointestinal</u>				
Diarrhea	72	47	37	27
Nausea	46	37	32	27
Constipation	24	27	23	21
LFT Abnormal	36	30	6	5
Anorexia	34	24	7	5
Vomiting	27	15	14	11
<u>Cardiovascular</u>				
Hypertension (See PRECAUTIONS)	47	56	38	43
<u>Urogenital</u>				
Kidney Function Abnormal (See WARNINGS)	40	27	36	23
Creatinine Increased (See WARNINGS)	39	25	24	19
BUN Increased (See WARNINGS)	30	22	12	9
Urinary Tract Infection 16	18	21	19	
Oliguria	18	15	19	12
<u>Metabolic and Nutritional</u>				
Hyperkalemia (See WARNINGS)	45	26	13	9
Hypokalemia	29	34	13	16
Hyperglycemia (See WARNINGS)	47	38	33	22
Hypomagnesemia	48	45	16	9

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986					
987					
988	<u>Hemic and Lymphatic</u>				
989	Anemia	47	38	5	1
990	Leukocytosis	32	26	8	8
991	Thrombocytopenia	24	20	14	19
992					
993	<u>Miscellaneous</u>				
994	Abdominal Pain	59	54	29	22
995	Pain	63	57	24	22
996	Fever	48	56	19	22
997	Asthenia	52	48	11	7
998	Back Pain	30	29	17	17
999	Ascites	27	22	7	8
1000	Peripheral Edema	26	26	12	14
1001					
1002	<u>Respiratory System</u>				
1003	Pleural Effusion	30	32	36	35
1004	Atelectasis	28	30	5	4
1005	Dyspnea	9	23	5	4
1006					
1007	<u>Skin and Appendages</u>				
1008	Pruritus	36	20	15	7
1009	Rash	24	19	10	4
1010					
1011	Less frequently observed adverse reactions				
1012	in both liver transplantation and kidney				
1013	transplantation patient are described under				
1014	the subsection Less Frequently Reported				
1015	Adverse Reactions below.				
1016					
1017	<i>Kidney Transplantation</i>				
1018	The most common adverse reactions reported				
1019	were infection, tremor, hypertension,				
1020	decreased renal function, constipation,				
1021	diarrhea, headache, abdominal pain and				
1022	insomnia.				

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1023
 1024 Adverse events that occurred in \$ 15
 1025 % of Prograf-treated kidney transplant
 1026 patients are presented below:

1027
 1028 **KIDNEY**
 1029 **TRANSPLANTATION:**
 1030 **ADVERSE EVENTS**
 1031 **OCCURRING IN \$**
 1032 **15% OF PROGRAF-**
 1033 **TREATED PATIENTS**
 1034
 1035

1036	Prograf	CBIR
1037	<u>(N=205)</u>	<u>(N=207)</u>
1038 <u>Nervous System</u>		
1039 Tremor (See		
1040 WARNINGS)	54	34
1041 Headache (See		
1042 WARNINGS)	44	38
1043 Insomnia	32	30
1044 Paresthesia	23	16
1045 Dizziness	19	16
1046		
1047 <u>Gastrointestinal</u>		
1048 Diarrhea	44	41
1049 Nausea	38	36
1050 Constipation	35	43
1051 Vomiting	29	23
1052 Dyspepsia	28	20
1053		
1054 <u>Cardiovascular</u>		
1055 Hypertension (See		
1056 PRECAUTIONS)	50	52
1057 Chest pain	19	13

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1058			
1059	<u>Urogenital</u>		
1060	Creatinine increased		
1061	(See WARNINGS)	45	42
1062	Urinary tract infection	34	35
1063			
1064	<u>Metabolic and Nutritional</u>		
1065	Hypophosphatemia	49	53
1066	Hypomagnesemia	34	17
1067	Hyperlipemia	31	38
1068	Hyperkalemia (See		
1069	WARNINGS)	31	32
1070	Diabetes mellitus		
1071	(See WARNINGS)	24	9
1072	Hypokalemia	22	25
1073	Hyperglycemia (See		
1074	WARNINGS)	22	16
1075	Edema	18	19
1076			
1077	<u>Hemic and Lymphatic</u>		
1078	Anemia	30	24
1079	Leukopenia	15	17
1080			
1081	<u>Miscellaneous</u>		
1082	Infection	45	49
1083	Peripheral edema	36	48
1084	Asthenia	34	30
1085	Abdominal pain	33	31
1086	Pain	32	30
1087	Fever	29	29
1088	Back pain	24	20

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1089			
1090			
1091	<u>Respiratory System</u>		
1092	Dyspnea	22	18
1093	Cough increased	18	15
1094			
1095	<u>Musculoskeletal</u>		
1096	Arthralgia	25	24
1097			
1098	<u>Skin</u>		
1099	Rash	17	12
1100	Pruritis	15	7

1101
1102 Less frequently observed adverse reactions in
1103 both liver transplantation and kidney
1104 transplantation patients are described under the
1105 subsection **Less Frequently Reported**
1106 **Adverse Reactions** shown below.

1107
1108 **Less Frequently Reported Adverse**
1109 **Reactions**

1110 The following adverse events were reported in
1111 the range of 3% to less than 15% incidence in
1112 either liver or kidney transplant recipients who
1113 were treated with tacrolimus in the Phase 3
1114 comparative trials.

1115 **NERVOUS SYSTEM:** (see
1116 **WARNINGS**) abnormal dreams, agitation,
1117 amnesia, anxiety, confusion, convulsion,
1118 depression, dizziness, emotional lability,
1119 encephalopathy, hallucinations, hypertonia,
1120 incoordination, myoclonus, nervousness,
1121 neuropathy, psychosis, somnolence, thinking

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1122 abnormal; SPECIAL SENSES: abnormal
1123 vision, amblyopia, ear pain, otitis media,
1124 tinnitus; GASTROINTESTINAL: anorexia,
1125 cholangitis, cholestatic jaundice, dyspepsia,
1126 dysphagia, esophagitis, flatulence, gastritis,
1127 gastrointestinal hemorrhage, GGT increase, GI
1128 perforation, hepatitis, ileus, increased appetite,
1129 jaundice, liver damage, liver function test
1130 abnormal, oral moniliasis, rectal disorder,
1131 stomatitis; CARDIOVASCULAR: angina
1132 pectoris, chest pain, deep thrombophlebitis,
1133 abnormal ECG, hemorrhage, hypotension,
1134 postural hypotension, peripheral vascular
1135 disorder, phlebitis, tachycardia, thrombosis,
1136 vasodilatation; UROGENITAL: (see
1137 **WARNINGS**) albuminuria, cystitis, dysuria,
1138 hematuria, hydronephrosis, kidney failure,
1139 kidney tubular necrosis, nocturia, pyuria, toxic
1140 nephropathy, oliguria, urinary frequency, urinary
1141 incontinence, vaginitis;
1142 METABOLIC/NUTRITIONAL: acidosis,
1143 alkaline phosphatase increased, alkalosis, ALT
1144 (SGPT) increased, AST (SGOT) increased,
1145 bicarbonate decreased, bilirubinemia, BUN
1146 increased, dehydration, GGT increased, healing
1147 abnormal, hypercalcemia,
1148 hypercholesterolemia, hyperlipemia,
1149 hyperphosphatemia, hyperuricemia,
1150 hypervolemia, hypocalcemia, hypoglycemia,
1151 hyponatremia, hypophosphatemia,
1152 hypoproteinemia, lactic dehydrogenase

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1153 increase, weight gain; ENDOCRINE: (see
1154 **PRECAUTIONS**) Cushing's syndrome,
1155 diabetes mellitus; HEMIC/LYMPHATIC:
1156 coagulation disorder, ecchymosis, hypochromic
1157 anemia, leukocytosis, leukopenia, polycythemia,
1158 prothrombin decreased, serum iron decreased,
1159 thrombocytopenia; MISCELLANEOUS:
1160 abdomen enlarged, abscess, accidental injury,
1161 allergic reaction, cellulitis, chills, flu syndrome,
1162 generalized edema, hernia, peritonitis,
1163 photosensitivity reaction, sepsis;
1164 MUSCULOSKELETAL: arthralgia, cramps,
1165 generalized spasm, joint disorder, leg cramps,
1166 myalgia, myasthenia, osteoporosis;
1167 RESPIRATORY: asthma, bronchitis, cough
1168 increased, lung disorder, pneumothorax,
1169 pulmonary edema, pharyngitis, pneumonia,
1170 respiratory disorder, rhinitis, sinusitis, voice
1171 alteration; SKIN: acne, alopecia, exfoliative
1172 dermatitis, fungal dermatitis, herpes simplex,
1173 hirsutism, skin discoloration, skin disorder, skin
1174 ulcer, sweating.

1175 The overall safety profile of the Prograf-
1176 mycophenolate mofetil Phase IV study did not
1177 differ from the safety profile of the Phase III
1178 kidney study.

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1181 **Post Marketing**

1182 The following have been reported: increased
1183 amylase including pancreatitis, hearing loss
1184 including deafness, leukoencephalopathy,
1185 thrombocytopenic purpura, hemolytic-uremic
1186 syndrome, acute renal failure, Stevens-Johnson
1187 syndrome, stomach ulcer, glycosuria and
1188 cardiac arrhythmia.

1189 There have been rare spontaneous
1190 reports of myocardial hypertrophy associated
1191 with clinically manifested ventricular
1192 dysfunction in patients receiving Prograf therapy
1193 (see **PRECAUTIONS-Myocardial**
1194 **Hypertrophy**).

1195

1196 **OVERDOSAGE:**

1197 Limited overdose experience is available.

1198 Acute overdoses of up to 30 times the
1199 intended dose have been reported. Almost all
1200 cases have been asymptomatic and all patients
1201 recovered with no sequelae. Occasionally,
1202 acute overdose has been followed by adverse
1203 reactions consistent with those listed in the

1204 **ADVERSE REACTIONS** section except in
1205 one case where transient urticaria and lethargy
1206 were observed. Based on the poor aqueous
1207 solubility and extensive erythrocyte and plasma
1208 protein binding, it is anticipated that tacrolimus
1209 is not dialyzable to any significant extent; there
1210 is no experience with charcoal hemoperfusion.

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1211 The oral use of activated charcoal has been
1212 reported in treating acute overdoses, but
1213 experience has not been sufficient to warrant
1214 recommending its use. General supportive
1215 measures and treatment of specific symptoms
1216 should be followed in all cases of overdosage.

1217 In acute oral and IV toxicity studies,
1218 mortalities were seen at or above the following
1219 doses: in adult rats, 52X the recommended
1220 human oral dose; in immature rats, 16X the
1221 recommended oral dose; and in adult rats, 16X
1222 the recommended human IV dose (all based on
1223 body surface area corrections).

1224

1225 **DOSAGE AND ADMINISTRATION:**

1226 *Prograf injection (tacrolimus injection)*

1227

1228 **For IV Infusion Only**

1229

1230 **NOTE: Anaphylactic reactions have**
1231 **occurred with injectables containing castor**
1232 **oil derivatives. See WARNINGS.**

1233

1234 In patients unable to take oral Prograf capsules,
1235 therapy may be initiated with Prograf injection.

1236 The initial dose of Prograf should be
1237 administered no sooner than 6 hours after
1238 transplantation. The recommended starting dose
1239 of Prograf injection is 0.03-0.05 mg/kg/day as a
1240 continuous IV infusion. Adult patients should
1241 receive doses at the lower end

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1242 of the dosing range. Concomitant adrenal
1243 corticosteroid therapy is recommended early
1244 post-transplantation. Continuous IV infusion of
1245 Prograf injection should be continued only until
1246 the patient can tolerate oral administration of
1247 Prograf capsules.

1248

1249

1250

1251 ***Preparation for Administration/Stability***

1252 Prograf injection must be diluted with 0.9%
1253 Sodium Chloride Injection or 5% Dextrose
1254 Injection to a concentration between 0.004
1255 mg/mL and 0.02 mg/mL prior to use. Diluted
1256 infusion solution should be stored in glass or
1257 polyethylene containers and should be
1258 discarded after 24 hours. The diluted infusion
1259 solution should not be stored in a PVC
1260 container due to decreased stability and the
1261 potential for extraction of phthalates. In
1262 situations where more dilute solutions are
1263 utilized (e.g., pediatric dosing, etc.), PVC-free
1264 tubing should likewise be used to minimize the
1265 potential for significant drug adsorption onto
1266 the tubing. Parenteral drug products should be
1267 inspected visually for particulate matter and
1268 discoloration prior to administration,
1269 whenever solution and container permit. Due
1270 to the chemical instability of tacrolimus in
1271 alkaline media, Prograf injection should not be
1272 mixed or co-infused with solutions of pH 9 or
1273 greater (e.g., ganciclovir or acyclovir).

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1276 ***Prograf capsules (tacrolimus capsules)-***

1277

1278 ***Summary of Initial Oral Dosage***

1279 ***Recommendations and Typical Whole Blood***

1280 ***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

1281

*Note: two divided doses, q12h

1282

1283 ***Liver Transplantation***

1284

1285 It is recommended that patients initiate oral

1286 therapy with Prograf capsules if possible. If

1287 IV therapy is necessary, conversion from IV to

1288 oral Prograf is recommended as soon as oral

1289 therapy can be tolerated. This usually occurs

1290 within 2-3 days. The initial dose of Prograf

1291 should be administered no sooner than 6 hours

1292 after transplantation. In a patient receiving an

1293 IV infusion, the first dose of oral therapy

1294 should be given 8-12 hours after discontinuing

1295 the IV infusion. The recommended starting

1296 oral dose of Prograf capsules is 0.10-0.15

mg/kg/day administered in two divided daily

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1297 doses every 12 hours. Co-administered
1298 grapefruit juice has been reported to increase
1299 tacrolimus blood trough concentrations in liver
1300 transplant patients. (See *Drugs that May*
1301 *Alter Tacrolimus Concentrations.*)

1302 Dosing should be titrated based on
1303 clinical assessments of rejection and
1304 tolerability. Lower Prograf dosages may be
1305 sufficient as maintenance therapy. Adjunct
1306 therapy with adrenal corticosteroids is
1307 recommended early post transplant.

1308 Dosage and typical tacrolimus whole
1309 blood trough concentrations are shown in the
1310 table above; blood concentration details are
1311 described in **Blood Concentration**
1312 **Monitoring: Liver Transplantation** below.

1313

1314 *Kidney Transplantation*

1315 The recommended starting oral dose of Prograf
1316 is 0.2 mg/kg/day administered every 12 hours
1317 in two divided doses. The initial dose of
1318 Prograf may be administered within 24 hours
1319 of transplantation, but should be delayed until
1320 renal function has recovered (as indicated for
1321 example by a serum creatinine \leq 4 mg/dL).

1322 Black patients may require higher doses to
1323 achieve comparable blood concentrations.
1324 Dosage and typical tacrolimus whole blood
1325 trough concentrations are shown in the table
1326 above; blood concentration details are
1327 described in **Blood Concentration**
1328 **Monitoring: Kidney Transplantation** below.

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1329
 1330 The data in kidney transplant patients
 1331 indicate that the Black patients required a
 1332 higher dose to attain comparable trough
 1333 concentrations compared to Caucasian patients.
 1334

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

1335
 1336 ***Pediatric Patients***
 1337 Pediatric liver transplantation patients without
 1338 pre-existing renal or hepatic dysfunction have
 1339 required and tolerated higher doses than adults
 1340 to achieve similar blood concentrations.
 1341 Therefore, it is recommended that therapy be
 1342 initiated in pediatric patients at a starting IV
 1343 dose of 0.03-0.05 mg/kg/day and a starting oral
 1344 dose of 0.15-0.20 mg/kg/day. Dose adjustments
 1345 may be required. Experience in pediatric
 1346 kidney transplantation patients is limited.

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1349 ***Patients with Hepatic or Renal Dysfunction***

1350 Due to the reduced clearance and prolonged
1351 half-life, patients with severe hepatic
1352 impairment (Pugh \geq 10) may require lower
1353 doses of Prograf. Close monitoring of blood
1354 concentrations is warranted. Due to the
1355 potential for nephrotoxicity, patients with renal
1356 or hepatic impairment should receive doses at
1357 the lowest value of the recommended IV and
1358 oral dosing ranges. Further reductions in dose
1359 below these ranges may be required. Prograf
1360 therapy usually should be delayed up to 48
1361 hours or longer in patients with post-operative
1362 oliguria.

1363

1364

1365 ***Conversion from One Immunosuppressive***
1366 ***Regimen to Another***

1367 Prograf should not be used simultaneously with
1368 cyclosporine. Prograf or cyclosporine should
1369 be discontinued at least 24 hours before
1370 initiating the other. In the presence of elevated
1371 Prograf or cyclosporine concentrations, dosing
1372 with the other drug usually should be further
1373 delayed.

1374

1375 **Blood Concentration Monitoring**

1376 Monitoring of tacrolimus blood concentrations
1377 in conjunction with other laboratory and
1378 clinical parameters is considered an essential

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1379 aid to patient management for the evaluation of
1380 rejection, toxicity, dose adjustments and
1381 compliance. Factors influencing frequency of
1382 monitoring include but are not limited to
1383 hepatic or renal dysfunction, the addition or
1384 discontinuation of potentially interacting drugs
1385 and the posttransplant time. Blood
1386 concentration monitoring is not a replacement
1387 for renal and liver function monitoring and
1388 tissue biopsies.

1389 Two methods have been used for the
1390 assay of tacrolimus, a microparticle enzyme
1391 immunoassay (MEIA) and an ELISA. Both
1392 methods have the same monoclonal antibody
1393 for tacrolimus. Comparison of the
1394 concentrations in published literature to patient
1395 concentrations using the current assays must be
1396 made with detailed knowledge of the assay
1397 methods and biological matrices employed.
1398 Whole blood is the matrix of choice and
1399 specimens should be collected into tubes
1400 containing ethylene diamine tetraacetic acid
1401 (EDTA) anti-coagulant. Heparin anti-
1402 coagulation is not recommended because of the
1403 tendency to form clots on storage. Samples
1404 which are not analyzed immediately should be
1405 stored at room temperature or in a refrigerator
1406 and assayed within 7 days; if samples are to be
1407 kept longer they should be deep frozen at -20E
1408 C for up to 12 months.

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1409

1410

1411 ***Liver Transplantation***

1412 Although there is a lack of direct correlation
1413 between tacrolimus concentrations and drug
1414 efficacy, data from Phase II and III studies of
1415 liver transplant patients have shown an
1416 increasing incidence of adverse events with
1417 increasing trough blood concentrations. Most
1418 patients are stable when trough whole blood
1419 concentrations are maintained between 5 to 20
1420 ng/mL. Long term posttransplant patients often
1421 are maintained at the low end of this target
1422 range.

1423 Data from the U.S. clinical trial show
1424 that tacrolimus whole blood concentrations, as
1425 measured by ELISA, were most variable
1426 during the first week post-transplantation.
1427 After this early period, the median trough
1428 blood concentrations, measured at intervals
1429 from the second week to one year post-
1430 transplantation, ranged from 9.8 ng/mL to 19.4
1431 ng/mL.

1432 *Therapeutic Drug Monitoring*, 1995,
1433 Volume 17, Number 6 contains a consensus
1434 document and several position papers
1435 regarding the therapeutic monitoring of
1436 tacrolimus from the 1995 International
1437 Consensus Conference on Immunosuppressive
1438 Drugs. Refer to these manuscripts for further
1439 discussions of tacrolimus monitoring.

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1441

1442 ***Kidney Transplantation***

1443 Data from the Phase III study indicates that
1444 trough concentrations of tacrolimus in whole
1445 blood, as measured by IMx7, were most
1446 variable during the first week of dosing.

1447 During the first three months, 80% of the
1448 patients maintained trough concentrations
1449 between 7-20 ng/mL, and then between 5-15
1450 ng/mL, through one-year.

1451 The relative risk of toxicity is
1452 increased with higher trough concentrations.


1453 Therefore, monitoring of whole blood trough
1454 concentrations is recommended to assist in the
1455 clinical evaluation of toxicity.

1456

1457 **HOW SUPPLIED:**

1458 **Prograf capsules (tacrolimus capsules)**

1459 **0.5 mg**

1460 Oblong, light yellow, branded with red “0.5
1461 mg” on the capsule cap and “ 607” on the
1462 capsule body, supplied in 60-count bottles
1463 (NDC 0469-0607-67) and 10 blister cards of
1464 10 capsules (NDC 0469-0607-10), containing
1465 the equivalent of 0.5 mg anhydrous tacrolimus.

PROPOSED PACKAGE INSERT


1466

1467

1468 **Prograf capsules (tacrolimus capsules)**

1469 **1 mg**

1470 Oblong, white, branded with red "1 mg" on the

1471 capsule cap and "  7" on the capsule

1472 body, supplied in 100-count bottles (NDC

1473 0469-0617-71) and 10 blister cards of 10

1474 capsules (NDC 0469-0617-10), containing the


1475 equivalent of 1 mg anhydrous tacrolimus.

1476

1477 **Prograf capsules (tacrolimus capsules)**

1478 **5 mg**

1479 Oblong, grayish/red, branded with white "5

1480 mg" on the capsule cap and "  657" on the

1481 capsule body, supplied in 100-count bottles

1482 (NDC 0469-0657-71) and 10 blister cards of

1483 10 capsules (NDC 0469-0657-10), containing

1484 the equivalent of 5 mg anhydrous tacrolimus.

1485

1486 *Store and Dispense*

1487 Store at 25°C (77°F); excursions permitted to

1488 15EC-30EC (59EF-86EF) [see USP Controlled

1489 Room Temperature].

1490

1491 **Prograf injection (tacrolimus injection) 5mg**

1492 **(for IV infusion only)**

1493 Supplied as a sterile solution in 1 mL ampules

1494 containing the equivalent of 5 mg of anhydrous

1495 tacrolimus per mL, in boxes of 10 ampules

1496 (NDC 0469-3016-01).

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1497
1498
1499 *Store and Dispense*
1500 Store between 5EC and 25EC (41EF and
1501 77EF).
1502
1503 Rx only
1504
1505 Made in Ireland
1506 for Fujisawa Healthcare, Inc.
1507 Deerfield, IL 60015-2548
1508 by Fujisawa Ireland, Ltd.
1509 Killorglin, Co. Kerry Ireland
1510
1511 **REFERENCE:**
1512 1. CDC: Recommendations of the Advisory
1513 Committee on Immunization Practices: Use
1514 of vaccines and immune globulins in
1515 persons with altered immunocompetence.
1516 MMWR 1993;42(RR-4):1-18.
1517
1518 5/15/00a

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/s/

Renata Albrecht
9/4/01 03:52:01 PM
NDA 50-708/S-013, NDA 50-709/S-010