

PROPOSED PACKAGE INSERT

1 Revised: January 2001

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 anhydrous
12 tacrolimus. Inactive ingredients include lactose,
13 hydroxypropyl methylcellulose, croscarmellose
14 sodium, and magnesium stearate. The 0.5 mg
15 capsule shell

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

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

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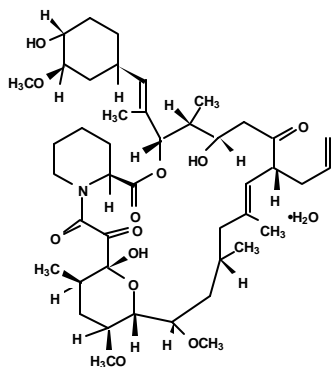
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56 Tacrolimus has an empirical formula of

57 $C_{44}H_{69}NO_{12}CH_2O$ and a formula weight of

58 822.05. Tacrolimus appears as white crystals or

59 crystalline powder. It is practically insoluble in

60 water, freely soluble in ethanol, and very soluble

61 in methanol and chloroform.

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64 **CLINICAL PHARMACOLOGY:**

65 *Mechanism of Action*

66 Tacrolimus prolongs the survival of the host and

67 transplanted graft in animal transplant models of

68 liver, kidney, heart, bone marrow, small bowel

69 and pancreas, lung and trachea, skin, cornea, and

70 limb.

71 In animals, tacrolimus has been

72 demonstrated to suppress some humoral

73 immunity and, to a greater extent, cell-mediated

74 reactions such as allograft rejection, delayed type

75 hypersensitivity, collagen- induced arthritis,

76 experimental allergic encephalomyelitis, and graft

77 versus host disease.

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

94

95 *Pharmacokinetics*

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

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H Corrected for individual bioavailability

* AUC₀₋₁₂₀

** AUC₀₋₇₂

*** AUC_{0-inf}

-- not applicable

not available

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

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116 Pharmacokinetic data indicate that whole

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117 blood concentrations rather than plasma
118 concentrations serve as the more appropriate
119 sampling compartment to describe tacrolimus
120 pharmacokinetics.

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122 Absorption

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

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

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

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

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

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In healthy volunteers (N=16), the time of the meal also affected tacrolimus bioavailability.

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

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

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178 Distribution

179 The plasma protein binding of tacrolimus is
180 approximately 99% and is independent of
181 concentration over a range of 5-50 ng/mL.

182 Tacrolimus is bound mainly to albumin and alpha-
183 1-acid glycoprotein, and has a high level of
184 association with erythrocytes. The distribution of
185 tacrolimus between whole blood and plasma
186 depends on several factors, such as hematocrit,
187 temperature at the time of plasma separation,
188 drug concentration, and plasma protein
189 concentration. In a U.S. study, the ratio of whole
190 blood concentration to plasma concentration
191 averaged 35 (range 12 to 67).

192

193 Metabolism

194 Tacrolimus is extensively metabolized by the
195 mixed-function oxidase system, primarily the
196 cytochrome P-450 system (CYP3A). A
197 metabolic pathway leading to the formation of 8
198 possible metabolites has been proposed.

199 Demethylation and hydroxylation were identified
200 as the primary mechanisms of biotransformation
201 in vitro. The major metabolite identified in
202 incubations with human liver microsomes is 13-
203 demethyl tacrolimus. In in vitro studies, a 31-
204 demethyl metabolite has been reported to have
205 the same activity as tacrolimus.

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208 Excretion

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

215 In a mass balance study of IV
216 administered radiolabeled tacrolimus to 6 healthy
217 volunteers, the mean recovery of radiolabel was
218 77.8% 12.7%. Fecal elimination accounted for
219 92.4% 1.0% and the elimination half-life based on
220 radioactivity was 48.1 15.9 hours whereas it
221 was 43.5 11.6 hours based on tacrolimus
222 concentrations. The mean clearance of radiolabel
223 was 0.029 0.015 L/hr/kg and clearance of
224 tacrolimus was 0.029 0.009 L/hr/kg. When
225 administered PO, the mean recovery of the
226 radiolabel was 94.9% 30.7%. Fecal elimination
227 accounted for 92.6% 30.7%, urinary elimination
228 accounted for 2.3% 1.1% and the elimination half-
229 life based on radioactivity was 31.9 10.5 hours
230 whereas it was 48.4 12.3 hours based on
231 tacrolimus concentrations. The mean clearance
232 of radiolabel was 0.226 0.116 L/hr/kg and
233 clearance of tacrolimus 0.172 0.088 L/hr/kg.

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235 Special Populations

236 Pediatric

237 Pharmacokinetics of tacrolimus have been studied
238 in liver transplantation patients, 0.7 to 13.2 years
239 of age. Following IV administration of a 0.037
240 mg/kg/day dose to 12 pediatric patients, mean
241 terminal half-life, volume of distribution and
242 clearance were 11.5" 3.8 hours, 2.6" 2.1 L/kg
243 and 0.138" 0.071 L/hr/kg, respectively.

244 Following oral administration to 9 patients, mean
245 AUC and C_{max} were 337" 167 ng\$hr/mL and
246 43.4" 27.9 ng/mL, respectively. The absolute
247 bioavailability was 31" 21%.

248 Whole blood trough concentrations from
249 31 patients less than 12 years old showed that
250 pediatric patients needed higher doses than adults
251 to achieve similar tacrolimus trough
252 concentrations. (See **DOSAGE AND**
253 **ADMINISTRATION**).

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255 Renal and Hepatic Insufficiency

256 The mean pharmacokinetic parameters for
257 tacrolimus following single administrations to
258 patients with renal and hepatic impairment are
259 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) | | | |

261 * corrected for bioavailability

262 † 1 patient did not receive the PO dose

263

264 Renal Insufficiency:

265 Tacrolimus pharmacokinetics following a single
 266 IV administration were determined in 12 patients
 267 (7 not on dialysis and 5 on dialysis, serum
 268 creatinine of 3.9" 1.6 and 12.0" 2.4 mg/dL,
 269 respectively) prior to their kidney transplant. The
 270 pharmacokinetic parameters obtained were
 271 similar for both groups.

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272
273 The mean clearance of tacrolimus in
274 patients with renal dysfunction was similar to that
275 in normal volunteers (see previous table).

276
277 Hepatic Insufficiency:
278 Tacrolimus pharmacokinetics have been
279 determined in six patients with mild hepatic
280 dysfunction (mean Pugh score: 6.2) following
281 single IV and oral administrations. The mean
282 clearance of tacrolimus in patients with mild
283 hepatic dysfunction was not substantially different
284 from that in normal volunteers (see previous
285 table). Tacrolimus pharmacokinetics were
286 studied in 6 patients with severe hepatic
287 dysfunction (mean Pugh score: >10). The mean
288 clearance was substantially lower in patients with
289 severe hepatic dysfunction, irrespective of the
290 route of administration.

291
292 Race
293 A formal study to evaluate the pharmacokinetic
294 disposition of tacrolimus in Black transplant
295 patients has not been conducted. However, a
296 retrospective comparison of Black and Caucasian
297 kidney transplant patients indicated that Black
298 patients required higher tacrolimus doses to attain
299 similar trough concentrations. (See **DOSAGE**
300 **AND ADMINISTRATION**).

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302

303 Gender

304 A formal study to evaluate the effect of gender on
305 tacrolimus pharmacokinetics has not been
306 conducted, however, there was no difference in
307 dosing by gender in the kidney transplant trial. A
308 retrospective comparison of pharmacokinetics in
309 healthy volunteers, and in kidney and liver
310 transplant patients indicated no gender-based
311 differences.

312

313 *Clinical Studies*

314 *Liver Transplantation*

315 The safety and efficacy of Prograf-based
316 immunosuppression following orthotopic liver
317 transplantation were assessed in two prospective,
318 randomized, non-blinded multicenter studies. The
319 active control groups were treated with a
320 cyclosporine-based immunosuppressive regimen.
321 Both studies used concomitant adrenal
322 corticosteroids as part of the immunosuppressive
323 regimens. These studies were designed to
324 evaluate whether the two regimens were
325 therapeutically equivalent, with patient and graft
326 survival at 12 months following transplantation as
327 the primary endpoints. The Prograf-based
328 immunosuppressive regimen was found to be
329 equivalent to the cyclosporine-based
330 immunosuppressive regimens.

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332 In one trial, 529 patients were enrolled at
333 12 clinical sites in the United States; prior to
334 surgery, 263 were randomized to the Prograf-
335 based immunosuppressive regimen and 266 to a
336 cyclosporine-based immunosuppressive regimen
337 (CBIR). In 10 of the 12 sites, the same CBIR
338 protocol was used, while 2 sites used different
339 control protocols. This trial excluded patients
340 with renal dysfunction, fulminant hepatic failure
341 with Stage IV encephalopathy, and cancers;
342 pediatric patients (\leq 12 years old) were allowed.

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

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

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361 The overall one-year graft survival (CBIR and
362 Prograf-based treatment groups combined) was
363 81% in the U.S. study and 73% in the European
364 study. In both studies, the median time to convert
365 from IV to oral Prograf dosing was 2 days.

366 Because of the nature of the study design,
367 comparisons of differences in secondary
368 endpoints, such as incidence of acute rejection,
369 refractory rejection or use of OKT3 for steroid-
370 resistant rejection, could not be reliably made.

371

372 ***Kidney Transplantation***

373 Prograf-based immunosuppression following
374 kidney transplantation was assessed in a Phase
375 III randomized, multicenter, non-blinded,
376 prospective study. There were 412 kidney
377 transplant patients enrolled at 19 clinical sites in
378 the United States. Study therapy was initiated
379 when renal function was stable as indicated by a
380 serum creatinine ≤ 4 mg/dL (median of 4 days
381 after transplantation, range 1 to 14 days).
382 Patients less than 6 years of age were excluded.

383 There were 205 patients randomized to
384 Prograf-based immunosuppression and 207
385 patients were randomized to cyclosporine-based
386 immunosuppression. All patients received
387 prophylactic induction therapy consisting of an
388 antilymphocyte antibody preparation,
389 corticosteroids and azathioprine.

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390 Overall one year patient and graft survival was
391 96.1% and 89.6%, respectively and was
392 equivalent between treatment arms.

393 Because of the nature of the study design,
394 comparisons of differences in secondary
395 endpoints, such as incidence of acute rejection,
396 refractory rejection or use of OKT3 for steroid-
397 resistant rejection, could not be reliably made.

398

399 **INDICATIONS AND USAGE:**

400 Prograf is indicated for the prophylaxis of organ
401 rejection in patients receiving allogeneic liver or
402 kidney transplants. It is recommended that
403 Prograf be used concomitantly with adrenal
404 corticosteroids. Because of the risk of
405 anaphylaxis, Prograf injection should be reserved
406 for patients unable to take Prograf capsules
407 orally.

408

409 **CONTRAINDICATIONS:**

410 Prograf is contraindicated in patients with a
411 hypersensitivity to tacrolimus. Prograf injection is
412 contraindicated in patients with a hypersensitivity
413 to HCO-60 (polyoxyl 60 hydrogenated castor
414 oil).

415

416 **WARNINGS:**

417 (See boxed **WARNING**.)

418 Insulin-dependent post-transplant diabetes
419 mellitus (PTDM) was reported in 20% of
420 Prograf-treated kidney transplant patients

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421 without pretransplant history of diabetes mellitus
422 in the Phase III study (See Tables Below). The
423 median time to onset of PTDM was 68 days.
424 Insulin dependence was reversible in 15% of
425 these PTDM patients at one year and in 50% at
426 two years post transplant. Black and Hispanic
427 kidney transplant patients were at an increased
428 risk of development of PTDM.

429

430 **Incidence of Post Transplant Diabetes**
431 **Mellitus and Insulin Use at 2 Years in**
432 **Kidney Transplant Recipients in the Phase**
433 **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%) |

434 *use of insulin for 30 or more consecutive days, with <
435 5 day gap, without a prior history of insulin dependent
436 diabetes mellitus or non insulin dependent diabetes
437 mellitus.

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440 **Development of Post Transplant Diabetes**
 441 **Mellitus by Race and by Treatment Group**
 442 **during First Year Post Kidney**
 443 **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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448 **Insulin-dependent post-transplant diabetes**
 449 **mellitus was reported in 18% and 11% of**
 450 **Prograf-treated liver transplant patients and**
 451 **was reversible in 45% and 31% of these**
 452 **patients at one year post transplant, in the**
 453 **U.S. and European randomized studies,**
 454 **respectively (See Table below).**
 455 Hyperglycemia was associated with the use of
 456 Prograf in 47% and 33% of liver transplant
 457 recipients in the U.S. and European randomized
 458 studies, respectively, and may require treatment
 459 (see **ADVERSE REACTIONS**).

460
 461 **Incidence of Post Transplant Diabetes**
 462 **Mellitus and Insulin Use at One Year in**
 463 **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%) |

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

468 **Patients without pretransplant history of diabetes
 469 mellitus.
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471 Prograf can cause neurotoxicity and
472 nephrotoxicity, particularly when used in high
473 doses. Nephrotoxicity was reported in
474 approximately 52% of kidney transplantation
475 patients and in 40% and 36% of liver
476 transplantation patients receiving Prograf in the
477 U.S. and European randomized trials,
478 respectively (see **ADVERSE REACTIONS**).
479 More overt nephrotoxicity is seen early after
480 transplantation, characterized by increasing serum
481 creatinine and a decrease in urine output.
482 Patients with impaired renal function should be
483 monitored closely as the dosage of Prograf may
484 need to be reduced. In patients with persistent
485 elevations of serum creatinine who are
486 unresponsive to dosage adjustments,
487 consideration should be given to changing to
488 another immunosuppressive therapy. Care
489 should be taken in using tacrolimus with other
490 nephrotoxic drugs. **In particular, to avoid**
491 **excess nephrotoxicity, Prograf should not be**
492 **used simultaneously with cyclosporine.**
493 **Prograf or cyclosporine should be**
494 **discontinued at least 24 hours prior to**
495 **initiating the other. In the presence of**
496 **elevated Prograf or cyclosporine**
497 **concentrations, dosing with the other drug**
498 **usually should be further delayed.**

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500 Mild to severe hyperkalemia was
501 reported in 31% of kidney transplant recipients
502 and in 45% and 13% of liver transplant recipients
503 treated with Prograf in the U.S. and European
504 randomized trials, respectively, and may require
505 treatment (see **ADVERSE REACTIONS**).
506 **Serum potassium levels should be monitored**
507 **and potassium-sparing diuretics should not**
508 **be used during Prograf therapy (see**
509 **PRECAUTIONS).**

510 Neurotoxicity, including tremor,
511 headache, and other changes in motor function,
512 mental status, and sensory function were reported
513 in approximately 55% of liver transplant
514 recipients in the two randomized studies. Tremor
515 occurred more often in Prograf-treated kidney
516 transplant patients (54%) compared to
517 cyclosporine-treated patients. The incidence of
518 other neurological events in kidney transplant
519 patients was similar in the two treatment groups
520 (see **ADVERSE REACTIONS**). Tremor and
521 headache have been associated with high whole-
522 blood concentrations of tacrolimus and may
523 respond to dosage adjustment. Seizures have
524 occurred in adult and pediatric patients receiving
525 Prograf (see **ADVERSE REACTIONS**).
526 Coma and delirium also have been associated
527 with high plasma concentrations of tacrolimus.
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529 As in patients receiving other
530 immunosuppressants, patients receiving Prograf
531 are at increased risk of developing lymphomas
532 and other malignancies, particularly of the skin.
533 The risk appears to be related to the intensity and
534 duration of immunosuppression rather than to the
535 use of any specific agent. A lymphoproliferative
536 disorder (LPD) related to Epstein-Barr Virus
537 (EBV) infection has been reported in
538 immunosuppressed organ transplant recipients.
539 The risk of LPD appears greatest in young
540 children who are at risk for primary EBV
541 infection while immunosuppressed or who are
542 switched to Prograf following long-term
543 immunosuppression therapy. Because of the
544 danger of oversuppression of the immune system
545 which can increase susceptibility to infection,
546 combination immunosuppressant therapy should
547 be used with caution.

548 A few patients receiving Prograf injection
549 have experienced anaphylactic reactions.
550 Although the exact cause of these reactions is not
551 known, other drugs with castor oil derivatives in
552 the formulation have been associated with
553 anaphylaxis in a small percentage of patients.
554 Because of this potential risk of anaphylaxis,
555 Prograf injection should be reserved for patients
556 who are unable to take Prograf capsules.

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558 **Patients receiving Prograf injection**
559 **should be under continuous observation for**
560 **at least the first 30 minutes following the**
561 **start of the infusion and at frequent intervals**
562 **thereafter. If signs or symptoms of**
563 **anaphylaxis occur, the infusion should be**
564 **stopped. An aqueous solution of epinephrine**
565 **should be available at the bedside as well as**
566 **a source of oxygen.**

567
568

569 **PRECAUTIONS:**

570 ***General***

571 Hypertension is a common adverse effect of
572 Prograf therapy (see **ADVERSE**
573 **REACTIONS**). Mild or moderate hypertension
574 is more frequently reported than severe
575 hypertension. Antihypertensive therapy may be
576 required; the control of blood pressure can be
577 accomplished with any of the common
578 antihypertensive agents. Since tacrolimus may
579 cause hyperkalemia, potassium-sparing diuretics
580 should be avoided. While calcium-channel
581 blocking agents can be effective in treating
582 Prograf-associated hypertension, care should be
583 taken since interference with tacrolimus
584 metabolism may require a dosage reduction (see
585 ***Drug Interactions***).

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587 ***Renally and Hepatically Impaired Patients***

588 For patients with renal insufficiency some
589 evidence suggests that lower doses should be
590 used (see **CLINICAL PHARMACOLOGY**
591 and **DOSAGE AND ADMINISTRATION**).

592 The use of Prograf in liver transplant
593 recipients experiencing post-transplant hepatic
594 impairment may be associated with increased risk
595 of developing renal insufficiency related to high
596 whole-blood levels of tacrolimus. These patients
597 should be monitored closely and dosage
598 adjustments should be considered. Some
599 evidence suggests that lower doses should be
600 used in these patients (see **DOSAGE AND**
601 **ADMINISTRATION**).

602

603 ***Myocardial Hypertrophy***

604 Myocardial hypertrophy has been reported in
605 association with the administration of Prograf, and
606 is generally manifested by echocardiographically
607 demonstrated concentric increases in left
608 ventricular posterior wall and interventricular
609 septum thickness. Hypertrophy has been
610 observed in infants, children and adults. This
611 condition appears reversible in most cases
612 following dose reduction or discontinuance of
613 therapy. In a group of 20 patients with pre- and
614 post-treatment echocardiograms who showed
615 evidence of myocardial hypertrophy, mean
616 tacrolimus

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617 whole blood concentrations during the period
618 prior to diagnosis of myocardial hypertrophy
619 ranged from 11 to 53 ng/mL in infants (N=10,
620 age 0.4 to 2 years), 4 to 46 ng/mL in children
621 (N=7, age 2 to 15 years) and 11 to 24 ng/mL in
622 adults (N=3, age 37 to 53 years).

623 In patients who develop renal failure or
624 clinical manifestations of ventricular dysfunction
625 while receiving Prograf therapy,
626 echocardiographic evaluation should be
627 considered. If myocardial hypertrophy is
628 diagnosed, dosage reduction or discontinuation of
629 Prograf should be considered.

630

631 ***Information for Patients***

632 Patients should be informed of the need for
633 repeated appropriate laboratory tests while they
634 are receiving Prograf. They should be given
635 complete dosage instructions, advised of the
636 potential risks during pregnancy, and informed of
637 the increased risk of neoplasia. Patients should
638 be informed that changes in dosage should not be
639 undertaken without first consulting their physician.

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

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645 ***Laboratory Tests***

646 Serum creatinine, potassium, and fasting glucose
647 should be assessed regularly. Routine monitoring
648 of metabolic and hematologic systems should be
649 performed as clinically warranted.

650

651 ***Drug Interactions***

652 Due to the potential for additive or synergistic
653 impairment of renal function, care should be taken
654 when administering Prograf with drugs that may
655 be associated with renal dysfunction. These
656 include, but are not limited to, aminoglycosides,
657 amphotericin B, and cisplatin. Initial clinical
658 experience with the co-administration of Prograf
659 and cyclosporine resulted in additive/synergistic
660 nephrotoxicity. Patients switched from
661 cyclosporine to Prograf should receive the first
662 Prograf dose no sooner than 24 hours after the
663 last cyclosporine dose. Dosing may be further
664 delayed in the presence of elevated cyclosporine
665 levels.

666

667 ***Drugs that May Alter Tacrolimus***
668 ***Concentrations***

669 Since tacrolimus is metabolized mainly by the
670 CYP3A enzyme systems, substances known to
671 inhibit these enzymes may decrease the
672 metabolism or increase bioavailability of
673 tacrolimus as indicated by increased whole blood
674 or plasma concentrations. Drugs known

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675 to induce these enzyme systems may result in an
676 increased metabolism of tacrolimus or decreased
677 bioavailability as indicated by decreased whole
678 blood or plasma concentrations. Monitoring of
679 blood concentrations and appropriate dosage
680 adjustments are essential when such drugs are
681 used concomitantly.

682
683 **Drugs That May Increase Tacrolimus Blood Concentrations:*
684 **Calcium** **Antifungal** **Macrolide**
685 **Channel Blockers** **Agents** **Antibiotics**
686 diltiazem clotrimazole clarithromycin
687 nocardipine fluconazole erythromycin
688 nifedipine itraconazole troleandomycin
689 verapamil ketoconazole

690
691 **Gastrointestinal** **Other**
692 **Prokinetic** **Drugs**
693 **Agents** bromocriptine
694 cisapride cimetidine
695 metoclopramide cyclosporine
696 danazol
697 ethinyl estradiol
698 methylprednisolone
699 omeprazole
700 protease inhibitors
701 nefazodone

702
703 In a study of 6 normal volunteers, a
704 significant increase in tacrolimus oral
705 bioavailability (14±5% vs. 30±8%) was
706 observed with concomitant ketoconazole
707 administration (200 mg). The apparent oral
708 clearance of tacrolimus during ketoconazole
709 administration was significantly decreased

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710 compared to tacrolimus alone (0.430 ± 0.129
711 L/hr/kg vs. 0.148 ± 0.043 L/hr/kg). Overall, IV
712 clearance of tacrolimus was not significantly
713 changed by ketoconazole co-administration,
714 although it was highly variable between patients.

715
716 **Drugs That May Decrease Tacrolimus Blood Concentrations:*

| <u>Anticonvulsants</u> | <u>Antibiotics</u> |
|------------------------|--------------------|
| 717 carbamazepine | rifabutin |
| 718 phenobarbital | rifampin |
| 719 phenytoin | |

720
721
722
723 Herbal Preparations
724 St. John's Wort

725
726 *This table is not all inclusive.
727

728 St. John's Wort (*hypericum perforatum*)
729 induces CYP3A4 and P-glycoprotein. Since
730 tacrolimus is a substrate for CYP3A4, there is the
731 potential that the use of St. John's Wort in
732 patients receiving Prograf could result in reduced
733 tacrolimus levels.

734
735 In a study of 6 normal volunteers, a
736 significant decrease in tacrolimus oral
737 bioavailability ($14 \pm 6\%$ vs. $7 \pm 3\%$) was observed
738 with concomitant rifampin administration (600
739 mg). In addition, there was a significant increase
740 in tacrolimus clearance (0.036 ± 0.008 L/hr/kg vs.
741 0.053 ± 0.010 L/hr/kg) with concomitant rifampin
742 administration.

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743 Interaction studies with drugs used in
744 HIV therapy have not been conducted.
745 However, care should be exercised when drugs
746 that are nephrotoxic (e.g., ganciclovir) or that are
747 metabolized by CYP3A (e.g., ritonavir) are
748 administered concomitantly with tacrolimus.
749 Tacrolimus may affect the pharmacokinetics of
750 other drugs (e.g., phenytoin) and increase their
751 concentration. Grapefruit juice affects CYP3A-
752 mediated metabolism and should be avoided
753 (**See DOSAGE AND ADMINISTRATION**).

754

755 *Other Drug Interactions*

756 Immunosuppressants may affect vaccination.
757 Therefore, during treatment with Prograf,
758 vaccination may be less effective. The use of live
759 vaccines should be avoided; live vaccines may
760 include, but are not limited to measles, mumps,
761 rubella, oral polio, BCG, yellow fever, and TY
762 21a typhoid.¹

763

764 *Carcinogenesis, Mutagenesis and* 765 *Impairment of Fertility*

766 An increased incidence of malignancy is a
767 recognized complication of immunosuppression in
768 recipients of organ transplants. The most
769 common forms of neoplasms are non-Hodgkin's
770 lymphomas and carcinomas of the skin. As with
771 other immunosuppressive therapies, the risk of
772 malignancies in Prograf recipients may be higher
773 than in the normal, healthy

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774 population. Lymphoproliferative disorders
775 associated with Epstein-Barr Virus infection have
776 been seen. It has been reported that reduction or
777 discontinuation of immunosuppression may cause
778 the lesions to regress.

779 No evidence of genotoxicity was seen in
780 bacterial (*Salmonella* and *E. coli*) or mammalian
781 (Chinese hamster lung-derived cells) in vitro
782 assays of mutagenicity, the in vitro CHO/HGPRT
783 assay of mutagenicity, or in vivo clastogenicity
784 assays performed in mice; tacrolimus did not
785 cause unscheduled DNA synthesis in rodent
786 hepatocytes.

787 Carcinogenicity studies were carried out
788 in male and female rats and mice. In the 80-week
789 mouse study and in the 104-week rat study no
790 relationship of tumor incidence to tacrolimus
791 dosage was found. The highest doses used in the
792 mouse and rat studies were 0.8 - 2.5 times (mice)
793 and 3.5 - 7.1 times (rats) the recommended
794 clinical dose range of 0.1 - 0.2 mg/kg/day when
795 corrected for body surface area.

796 No impairment of fertility was
797 demonstrated in studies of male and female rats.
798 Tacrolimus, given orally at 1.0 mg/kg

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799 (0.7 - 1.4X the recommended clinical dose
800 range of 0.1 - 0.2 mg/kg/day based on body
801 surface area corrections) to male and female rats,
802 prior to and during mating, as well as to dams
803 during gestation and lactation, was associated
804 with embryolethality and with adverse effects on
805 female reproduction. Effects on female
806 reproductive function (parturition) and
807 embryolethal effects were indicated by a higher
808 rate of pre-implantation loss and increased
809 numbers of undelivered and nonviable pups.
810 When given at 3.2 mg/kg (2.3 - 4.6X the
811 recommended clinical dose range based on body
812 surface area correction), tacrolimus was
813 associated with maternal and paternal toxicity as
814 well as reproductive toxicity including marked
815 adverse effects on estrus cycles, parturition, pup
816 viability, and pup malformations.

817

818 ***Pregnancy: Category C***

819 In reproduction studies in rats and rabbits,
820 adverse effects on the fetus were observed mainly
821 at dose levels that were toxic to dams.
822 Tacrolimus at oral doses of 0.32 and 1.0 mg/kg
823 during organogenesis in rabbits was associated
824 with maternal toxicity as well as an increase in
825 incidence of abortions; these doses are equivalent
826 to 0.5 - 1X and 1.6 - 3.3X the recommended
827 clinical dose range (0.1 - 0.2 mg/kg) based on
828 body surface area

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829 corrections. At the higher dose only, an
830 increased incidence of malformations and
831 developmental variations was also seen.
832 Tacrolimus, at oral doses of 3.2 mg/kg during
833 organogenesis in rats, was associated with
834 maternal toxicity and caused an increase in late
835 resorptions, decreased numbers of live births, and
836 decreased pup weight and viability. Tacrolimus,
837 given orally at 1.0 and 3.2 mg/kg (equivalent to
838 0.7 - 1.4X and 2.3 - 4.6X the recommended
839 clinical dose range based on body surface area
840 corrections) to pregnant rats after organogenesis
841 and during lactation, was associated with reduced
842 pup weights.

843 No reduction in male or female fertility
844 was evident.

845 There are no adequate and well-
846 controlled studies in pregnant women.
847 Tacrolimus is transferred across the placenta.
848 The use of tacrolimus during pregnancy has been
849 associated with neonatal hyperkalemia and renal
850 dysfunction. Prograf should be used during
851 pregnancy only if the potential benefit to the
852 mother justifies potential risk to the fetus.

853

854 *Nursing Mothers*

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

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858

859 *Pediatric Patients*

860 Experience with Prograf in pediatric kidney
861 transplant patients is limited. Successful liver
862 transplants have been performed in pediatric
863 patients (ages up to 16 years) using Prograf. Two
864 randomized active-controlled trials of Prograf in
865 primary liver transplantation included 56
866 pediatric patients. Thirty-one patients were
867 randomized to Prograf-based and 25 to
868 cyclosporine-based therapies. Additionally, a
869 minimum of 122 pediatric patients were studied in
870 an uncontrolled trial of tacrolimus in living related
871 donor liver transplantation. Pediatric patients
872 generally required higher doses of Prograf to
873 maintain blood trough concentrations of
874 tacrolimus similar to adult patients (see
875 **DOSAGE AND ADMINISTRATION**).

876

877 **ADVERSE REACTIONS:**

878 *Liver Transplantation*

879 The principal adverse reactions of Prograf are
880 tremor, headache, diarrhea, hypertension, nausea,
881 and renal dysfunction. These occur with oral and
882 IV administration of Prograf and may respond to
883 a reduction in dosing. Diarrhea was sometimes
884 associated with other gastrointestinal complaints
885 such as nausea and vomiting.

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887 Hyperkalemia and hypomagnesemia have
888 occurred in patients receiving Prograf therapy.
889 Hyperglycemia has been noted in many patients;
890 some may require insulin therapy (see
891 **WARNINGS**).

892 The incidence of adverse events was
893 determined in two randomized comparative liver
894 transplant trials among 514 patients receiving
895 tacrolimus and steroids and 515 patients receiving
896 a cyclosporine-based regimen (CBIR). The
897 proportion of patients reporting more than one
898 adverse event was 99.8% in the tacrolimus
899 group and 99.6% in the CBIR group.

900 Precautions must be taken when comparing the
901 incidence of adverse events in the U.S. study to
902 that in the European study. The 12-month
903 posttransplant information from the U.S. study
904 and from the European study is presented below.

905 The two studies also included different patient
906 populations and patients were treated with
907 immunosuppressive regimens of differing
908 intensities. Adverse events reported in 15% in
909 tacrolimus patients (combined study results) are
910 presented below for the two controlled trials in
911 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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|-----|---------------------------------------------------|----|----|----|----|
| 951 | | | | | |
| 952 | | | | | |
| 953 | | | | | |
| 954 | <u>Hemic and Lymphatic</u> | | | | |
| 955 | Anemia | 47 | 38 | 5 | 1 |
| 956 | Leukocytosis | 32 | 26 | 8 | 8 |
| 957 | Thrombocytopenia | 24 | 20 | 14 | 19 |
| 958 | | | | | |
| 959 | <u>Miscellaneous</u> | | | | |
| 960 | Abdominal Pain | 59 | 54 | 29 | 22 |
| 961 | Pain | 63 | 57 | 24 | 22 |
| 962 | Fever | 48 | 56 | 19 | 22 |
| 963 | Asthenia | 52 | 48 | 11 | 7 |
| 964 | Back Pain | 30 | 29 | 17 | 17 |
| 965 | Ascites | 27 | 22 | 7 | 8 |
| 966 | Peripheral Edema | 26 | 26 | 12 | 14 |
| 967 | | | | | |
| 968 | <u>Respiratory System</u> | | | | |
| 969 | Pleural Effusion | 30 | 32 | 36 | 35 |
| 970 | Atelectasis | 28 | 30 | 5 | 4 |
| 971 | Dyspnea | 9 | 23 | 5 | 4 |
| 972 | | | | | |
| 973 | <u>Skin and Appendages</u> | | | | |
| 974 | Pruritus | 36 | 20 | 15 | 7 |
| 975 | Rash | 24 | 19 | 10 | 4 |
| 976 | | | | | |
| 977 | Less frequently observed adverse reactions in | | | | |
| 978 | both liver transplantation and kidney | | | | |
| 979 | transplantation patient are described under the | | | | |
| 980 | subsection Less Frequently Reported | | | | |
| 981 | Adverse Reactions below. | | | | |
| 982 | | | | | |
| 983 | <i>Kidney Transplantation</i> | | | | |
| 984 | The most common adverse reactions reported | | | | |
| 985 | were infection, tremor, hypertension, decreased | | | | |
| 986 | renal function, constipation, diarrhea, headache, | | | | |
| 987 | abdominal pain and insomnia. | | | | |

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988
 989 Adverse events that occurred in \$ 15
 990 % of Prograf-treated kidney transplant patients
 991 are presented below:

992
 993 **KIDNEY**
 994 **TRANSPLANTATION:**
 995 **ADVERSE EVENTS**
 996 **OCCURRING IN \$ 15%**
 997 **OF PROGRAF-**
 998 **TREATED PATIENTS**

| 1000 | | Prograf (N=205) | CBIR (N=207) |
|------|--------------------------------|--------------------|-----------------|
| 1003 | <u>Nervous System</u> | | |
| 1004 | Tremor (See | | |
| 1005 | WARNINGS) | 54 | 34 |
| 1006 | Headache (See | | |
| 1007 | WARNINGS) | 44 | 38 |
| 1008 | Insomnia | 32 | 30 |
| 1009 | Paresthesia | 23 | 16 |
| 1010 | Dizziness | 19 | 16 |
| 1011 | | | |
| 1012 | <u>Gastrointestinal</u> | | |
| 1013 | Diarrhea | 44 | 41 |
| 1014 | Nausea | 38 | 36 |
| 1015 | Constipation | 35 | 43 |
| 1016 | Vomiting | 29 | 23 |
| 1017 | Dyspepsia | 28 | 20 |
| 1018 | | | |
| 1019 | <u>Cardiovascular</u> | | |
| 1020 | Hypertension (See | | |
| 1021 | PRECAUTIONS) | 50 | 52 |
| 1022 | Chest pain | 19 | 13 |

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|------|-----------------------------------------|----|----|
| 1023 | | | |
| 1024 | <u>Urogenital</u> | | |
| 1025 | Creatinine increased | | |
| 1026 | (See WARNINGS) | 45 | 42 |
| 1027 | Urinary tract infection | 34 | 35 |
| 1028 | | | |
| 1029 | <u>Metabolic and Nutritional</u> | | |
| 1030 | Hypophosphatemia | 49 | 53 |
| 1031 | Hypomagnesemia | 34 | 17 |
| 1032 | Hyperlipemia | 31 | 38 |
| 1033 | Hyperkalemia (See | | |
| 1034 | WARNINGS) | 31 | 32 |
| 1035 | Diabetes mellitus | | |
| 1036 | (See WARNINGS) | 24 | 9 |
| 1037 | Hypokalemia | 22 | 25 |
| 1038 | Hyperglycemia (See | | |
| 1039 | WARNINGS) | 22 | 16 |
| 1040 | Edema | 18 | 19 |
| 1041 | | | |
| 1042 | <u>Hemic and Lymphatic</u> | | |
| 1043 | Anemia | 30 | 24 |
| 1044 | Leukopenia | 15 | 17 |
| 1045 | | | |
| 1046 | <u>Miscellaneous</u> | | |
| 1047 | Infection | 45 | 49 |
| 1048 | Peripheral edema | 36 | 48 |
| 1049 | Asthenia | 34 | 30 |
| 1050 | Abdominal pain | 33 | 31 |
| 1051 | Pain | 32 | 30 |
| 1052 | Fever | 29 | 29 |
| 1053 | Back pain | 24 | 20 |

PROPOSED PACKAGE INSERT

| | | | |
|------|----------------------------------|----|----|
| 1054 | | | |
| 1055 | | | |
| 1056 | <u>Respiratory System</u> | | |
| 1057 | Dyspnea | 22 | 18 |
| 1058 | Cough increased | 18 | 15 |
| 1059 | | | |
| 1060 | <u>Musculoskeletal</u> | | |
| 1061 | Arthralgia | 25 | 24 |
| 1062 | | | |
| 1063 | <u>Skin</u> | | |
| 1064 | Rash | 17 | 12 |
| 1065 | Pruritis | 15 | 7 |
| 1066 | | | |

1067 Less frequently observed adverse reactions in
1068 both liver transplantation and kidney
1069 transplantation patients are described under the
1070 subsection **Less Frequently Reported**
1071 **Adverse Reactions** shown below.

1072
1073 **Less Frequently Reported Adverse**
1074 **Reactions**

1075 The following adverse events were reported in
1076 the range of 3% to less than 15% incidence in
1077 either liver or kidney transplant recipients who
1078 were treated with tacrolimus in the Phase 3
1079 comparative trials.

1080 **NERVOUS SYSTEM:** (see
1081 **WARNINGS**) abnormal dreams, agitation,
1082 amnesia, anxiety, confusion, convulsion,
1083 depression, dizziness, emotional lability,
1084 encephalopathy, hallucinations, hypertonia,
1085 incoordination, myoclonus, nervousness,
1086 neuropathy, psychosis, somnolence, thinking

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1087 abnormal; SPECIAL SENSES: abnormal vision,
1088 amblyopia, ear pain, otitis media, tinnitus;
1089 GASTROINTESTINAL: anorexia, cholangitis,
1090 cholestatic jaundice, dyspepsia, dysphagia,
1091 esophagitis, flatulence, gastritis, gastrointestinal
1092 hemorrhage, GGT increase, GI perforation,
1093 hepatitis, ileus, increased appetite, jaundice, liver
1094 damage, liver function test abnormal, oral
1095 moniliasis, rectal disorder, stomatitis;
1096 CARDIOVASCULAR: angina pectoris, chest
1097 pain, deep thrombophlebitis, abnormal ECG,
1098 hemorrhage, hypotension, postural hypotension,
1099 peripheral vascular disorder, phlebitis,
1100 tachycardia, thrombosis, vasodilatation;
1101 UROGENITAL: (see **WARNINGS**)
1102 albuminuria, cystitis, dysuria, hematuria,
1103 hydronephrosis, kidney failure, kidney tubular
1104 necrosis, nocturia, pyuria, toxic nephropathy,
1105 oliguria, urinary frequency, urinary incontinence,
1106 vaginitis; METABOLIC/NUTRITIONAL:
1107 acidosis, alkaline phosphatase increased, alkalosis,
1108 ALT (SGPT) increased, AST (SGOT) increased,
1109 bicarbonate decreased, bilirubinemia, BUN
1110 increased, dehydration, GGT increased, healing
1111 abnormal, hypercalcemia, hypercholesterolemia,
1112 hyperlipemia, hyperphosphatemia, hyperuricemia,
1113 hypervolemia, hypocalcemia, hypoglycemia,
1114 hyponatremia, hypophosphatemia,
1115 hypoproteinemia, lactic dehydrogenase

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1116 increase, weight gain; ENDOCRINE: (see
1117 **PRECAUTIONS**) Cushing's syndrome, diabetes
1118 mellitus; HEMIC/LYMPHATIC: coagulation
1119 disorder, ecchymosis, hypochromic anemia,
1120 leukocytosis, leukopenia, polycythemia,
1121 prothrombin decreased, serum iron decreased,
1122 thrombocytopenia; MISCELLANEOUS:
1123 abdomen enlarged, abscess, accidental injury,
1124 allergic reaction, cellulitis, chills, flu syndrome,
1125 generalized edema, hernia, peritonitis,
1126 photosensitivity reaction, sepsis;
1127 MUSCULOSKELETAL: arthralgia, cramps,
1128 generalized spasm, joint disorder, leg cramps,
1129 myalgia, myasthenia, osteoporosis;
1130 RESPIRATORY: asthma, bronchitis, cough
1131 increased, lung disorder, pneumothorax,
1132 pulmonary edema, pharyngitis, pneumonia,
1133 respiratory disorder, rhinitis, sinusitis, voice
1134 alteration; SKIN: acne, alopecia, exfoliative
1135 dermatitis, fungal dermatitis, herpes simplex,
1136 hirsutism, skin discoloration, skin disorder, skin
1137 ulcer, sweating.

1138 The overall safety profile of the Prograf-
1139 mycophenolate mofetil Phase IV study did not
1140 differ from the safety profile of the Phase III
1141 kidney study.

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1144 **Post Marketing**

1145 The following have been reported: increased
1146 amylase including pancreatitis, hearing loss
1147 including deafness, leukoencephalopathy,
1148 thrombocytopenic purpura, hemolytic-uremic
1149 syndrome, acute renal failure, Stevens-Johnson
1150 syndrome, stomach ulcer, glycosuria, cardiac
1151 arrhythmia and gastroenteritis.

1152 There have been rare spontaneous reports
1153 of myocardial hypertrophy associated with
1154 clinically manifested ventricular dysfunction in
1155 patients receiving Prograf therapy (see
1156 **PRECAUTIONS-Myocardial Hypertrophy**).

1157

1158 **OVERDOSAGE:**

1159 Limited overdose experience is available. Acute
1160 overdoses of up to 30 times the intended dose
1161 have been reported. Almost all cases have been
1162 asymptomatic and all patients recovered with no
1163 sequelae. Occasionally, acute overdose has
1164 been followed by adverse reactions consistent with
1165 those listed in the **ADVERSE REACTIONS**
1166 section except in one case where transient urticaria
1167 and lethargy were observed. Based on the poor
1168 aqueous solubility and extensive erythrocyte and
1169 plasma protein binding, it is anticipated that
1170 tacrolimus is not dialyzable to any significant
1171 extent; there is no experience with charcoal
1172 hemoperfusion.

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1173 The oral use of activated charcoal has been
1174 reported in treating acute overdoses, but
1175 experience has not been sufficient to warrant
1176 recommending its use. General supportive
1177 measures and treatment of specific symptoms
1178 should be followed in all cases of overdose.

1179 In acute oral and IV toxicity studies,
1180 mortalities were seen at or above the following
1181 doses: in adult rats, 52X the recommended human
1182 oral dose; in immature rats, 16X the
1183 recommended oral dose; and in adult rats, 16X
1184 the recommended human IV dose (all based on
1185 body surface area corrections).

1186

1187 **DOSAGE AND ADMINISTRATION:**

1188 *Prograf injection (tacrolimus injection)*

1189

1190 *For IV Infusion Only*

1191

1192 **NOTE: Anaphylactic reactions have**
1193 **occurred with injectables containing castor oil**
1194 **derivatives. See WARNINGS.**

1195

1196 In patients unable to take oral Prograf capsules,
1197 therapy may be initiated with Prograf injection.

1198 The initial dose of Prograf should be administered
1199 no sooner than 6 hours after transplantation. The
1200 recommended starting dose of Prograf injection is
1201 0.03-0.05 mg/kg/day as a continuous IV infusion.
1202 Adult patients should receive doses at the lower
1203 end

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1204 of the dosing range. Concomitant adrenal
1205 corticosteroid therapy is recommended early post-
1206 transplantation. Continuous IV infusion of Prograf
1207 injection should be continued only until the patient
1208 can tolerate oral administration of Prograf
1209 capsules.

1210

1211

1212

1213 ***Preparation for Administration/Stability***

1214 Prograf injection must be diluted with 0.9%
1215 Sodium Chloride Injection or 5% Dextrose
1216 Injection to a concentration between 0.004
1217 mg/mL and 0.02 mg/mL prior to use. Diluted
1218 infusion solution should be stored in glass or
1219 polyethylene containers and should be discarded
1220 after 24 hours. The diluted infusion solution
1221 should not be stored in a PVC container due to
1222 decreased stability and the potential for extraction
1223 of phthalates. In situations where more dilute
1224 solutions are utilized (e.g., pediatric dosing, etc.),
1225 PVC-free tubing should likewise be used to
1226 minimize the potential for significant drug
1227 adsorption onto the tubing. Parenteral drug
1228 products should be inspected visually for
1229 particulate matter and discoloration prior to
1230 administration, whenever solution and container
1231 permit. Due to the chemical instability of
1232 tacrolimus in alkaline media, Prograf injection
1233 should not be mixed or co-infused with solutions
1234 of pH 9 or greater (e.g., ganciclovir or acyclovir).

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1235

1236

1237 ***Prograf capsules (tacrolimus capsules)-***

1238

1239 ***Summary of Initial Oral Dosage***

1240 ***Recommendations and Typical Whole Blood***

1241 ***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 |

1242

*Note: two divided doses, q12h

1243

1244 ***Liver Transplantation***

1245 It is recommended that patients initiate oral
1246 therapy with Prograf capsules if possible. If IV
1247 therapy is necessary, conversion from IV to oral
1248 Prograf is recommended as soon as oral therapy
1249 can be tolerated. This usually occurs within 2-3
1250 days. The initial dose of Prograf should be
1251 administered no sooner than 6 hours after
1252 transplantation. In a patient receiving an IV
1253 infusion, the first dose of oral therapy should be
1254 given 8-12 hours after discontinuing the IV
1255 infusion. The recommended starting oral dose of
1256 Prograf capsules is 0.10-0.15 mg/kg/day
1257 administered in two divided daily

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1258 doses every 12 hours. Co-administered
1259 grapefruit juice has been reported to increase
1260 tacrolimus blood trough concentrations in liver
1261 transplant patients. (See *Drugs that May Alter*
1262 *Tacrolimus Concentrations*.)

1263 Dosing should be titrated based on
1264 clinical assessments of rejection and tolerability.

1265 Lower Prograf dosages may be sufficient as
1266 maintenance therapy. Adjunct therapy with
1267 adrenal corticosteroids is recommended early
1268 post transplant.

1269 Dosage and typical tacrolimus whole
1270 blood trough concentrations are shown in the
1271 table above; blood concentration details are
1272 described in **Blood Concentration Monitoring:**
1273 *Liver Transplantation* below.

1274

1275 *Kidney Transplantation*

1276 The recommended starting oral dose of Prograf
1277 is 0.2 mg/kg/day administered every 12 hours in
1278 two divided doses. The initial dose of Prograf
1279 may be administered within 24 hours of
1280 transplantation, but should be delayed until renal
1281 function has recovered (as indicated for example
1282 by a serum creatinine \leq 4 mg/dL). Black patients
1283 may require higher doses to achieve comparable
1284 blood concentrations. Dosage and typical
1285 tacrolimus whole blood trough concentrations are
1286 shown in the table above; blood concentration
1287 details are described in **Blood Concentration**
1288 **Monitoring: Kidney Transplantation** below.

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1289
 1290 The data in kidney transplant patients
 1291 indicate that the Black patients required a higher
 1292 dose to attain comparable trough concentrations
 1293 compared to Caucasian patients.
 1294

| 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 |

1295
 1296 ***Pediatric Patients***
 1297 Pediatric liver transplantation patients without
 1298 pre-existing renal or hepatic dysfunction have
 1299 required and tolerated higher doses than adults to
 1300 achieve similar blood concentrations. Therefore,
 1301 it is recommended that therapy be initiated in
 1302 pediatric patients at a starting IV dose of 0.03-
 1303 0.05 mg/kg/day and a starting oral dose of 0.15-
 1304 0.20 mg/kg/day. Dose adjustments may be
 1305 required. Experience in pediatric kidney
 1306 transplantation patients is limited.

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1308

1309 ***Patients with Hepatic or Renal Dysfunction***

1310 Due to the reduced clearance and prolonged half-
1311 life, patients with severe hepatic impairment (Pugh
1312 ≥ 10) may require lower doses of Prograf. Close
1313 monitoring of blood concentrations is warranted.

1314 Due to the potential for nephrotoxicity, patients
1315 with renal or hepatic impairment should receive
1316 doses at the lowest value of the recommended IV
1317 and oral dosing ranges. Further reductions in
1318 dose below these ranges may be required.

1319 Prograf therapy usually should be delayed up to
1320 48 hours or longer in patients with post-operative
1321 oliguria.

1322

1323

1324 ***Conversion from One Immunosuppressive***
1325 ***Regimen to Another***

1326 Prograf should not be used simultaneously with
1327 cyclosporine. Prograf or cyclosporine should be
1328 discontinued at least 24 hours before initiating the
1329 other. In the presence of elevated Prograf or
1330 cyclosporine concentrations, dosing with the
1331 other drug usually should be further delayed.

1332

1333 **Blood Concentration Monitoring**

1334 Monitoring of tacrolimus blood concentrations in
1335 conjunction with other laboratory and clinical
1336 parameters is considered an essential

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1337 aid to patient management for the evaluation of
1338 rejection, toxicity, dose adjustments and
1339 compliance. Factors influencing frequency of
1340 monitoring include but are not limited to hepatic
1341 or renal dysfunction, the addition or
1342 discontinuation of potentially interacting drugs and
1343 the posttransplant time. Blood concentration
1344 monitoring is not a replacement for renal and liver
1345 function monitoring and tissue biopsies.

1346 Two methods have been used for the
1347 assay of tacrolimus, a microparticle enzyme
1348 immunoassay (MEIA) and an ELISA. Both
1349 methods have the same monoclonal antibody for
1350 tacrolimus. Comparison of the concentrations in
1351 published literature to patient concentrations using
1352 the current assays must be made with detailed
1353 knowledge of the assay methods and biological
1354 matrices employed. Whole blood is the matrix of
1355 choice and specimens should be collected into
1356 tubes containing ethylene diamine tetraacetic acid
1357 (EDTA) anti-coagulant. Heparin anti-coagulation
1358 is not recommended because of the tendency to
1359 form clots on storage. Samples which are not
1360 analyzed immediately should be stored at room
1361 temperature or in a refrigerator and assayed
1362 within 7 days; if samples are to be kept longer
1363 they should be deep frozen at -20E C for up to
1364 12 months.

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1365

1366

1367 ***Liver Transplantation***

1368 Although there is a lack of direct correlation
1369 between tacrolimus concentrations and drug
1370 efficacy, data from Phase II and III studies of
1371 liver transplant patients have shown an increasing
1372 incidence of adverse events with increasing trough
1373 blood concentrations. Most patients are stable
1374 when trough whole blood concentrations are
1375 maintained between 5 to 20 ng/mL. Long term
1376 posttransplant patients often are maintained at the
1377 low end of this target range.

1378 Data from the U.S. clinical trial show that
1379 tacrolimus whole blood concentrations, as
1380 measured by ELISA, were most variable during
1381 the first week post-transplantation. After this
1382 early period, the median trough blood
1383 concentrations, measured at intervals from the
1384 second week to one year post-transplantation,
1385 ranged from 9.8 ng/mL to 19.4 ng/mL.

1386 *Therapeutic Drug Monitoring*, 1995,
1387 Volume 17, Number 6 contains a consensus
1388 document and several position papers regarding
1389 the therapeutic monitoring of tacrolimus from the
1390 1995 International Consensus Conference on
1391 Immunosuppressive Drugs. Refer to these
1392 manuscripts for further discussions of tacrolimus
1393 monitoring.

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1394

1395

1396 ***Kidney Transplantation***

1397 Data from the Phase III study indicates that
1398 trough concentrations of tacrolimus in whole
1399 blood, as measured by IMx7, were most variable
1400 during the first week of dosing. During the first
1401 three months, 80% of the patients maintained
1402 trough concentrations between 7-20 ng/mL, and
1403 then between 5-15 ng/mL, through one-year.

1404 The relative risk of toxicity is increased
1405 with higher trough concentrations. Therefore,
1406 monitoring of whole blood trough concentrations
1407 is recommended to assist in the clinical evaluation
1408 of toxicity.

1409

1410 **HOW SUPPLIED:**

1411 **Prograf capsules (tacrolimus capsules)**

1412 **0.5 mg**

1413 Oblong, light yellow, branded with red “0.5 mg”
1414 on the capsule cap and “f607” on the
1415 capsule body, supplied in 60-count bottles (NDC
1416 0469-0607-67) and 10 blister cards of 10
1417 capsules (NDC 0469-0607-10), containing the
1418 equivalent of 0.5 mg anhydrous tacrolimus.

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1419

1420

1421 **Prograf capsules (tacrolimus capsules)**

1422 **1 mg**

1423 Oblong, white, branded with red "1 mg" on the
1424 capsule cap and " f 7" on the capsule
1425 body, supplied in 100-count bottles (NDC 0469-
1426 0617-71) and 10 blister cards of 10 capsules
1427 (NDC 0469-0617-10), containing the equivalent
1428 of 1 mg anhydrous tacrolimus.

1429

1430 **Prograf capsules (tacrolimus capsules)**

1431 **5 mg**

1432 Oblong, grayish/red, branded with white "5 mg"
1433 on the capsule cap and " f 657" on the
1434 capsule body, supplied in 100-count bottles
1435 (NDC 0469-0657-71) and 10 blister cards of 10
1436 capsules (NDC 0469-0657-10), containing the
1437 equivalent of 5 mg anhydrous tacrolimus.

1438

1439 *Store and Dispense*

1440 Store at 25°C (77°F); excursions permitted to
1441 15EC-30EC (59EF-86EF) [see USP Controlled
1442 Room Temperature].

1443

1444 **Prograf injection (tacrolimus injection) 5mg**
1445 **(for IV infusion only)**

1446 Supplied as a sterile solution in 1 mL ampules
1447 containing the equivalent of 5 mg of anhydrous
1448 tacrolimus per mL, in boxes of 10 ampules (NDC
1449 0469-3016-01).

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1450
1451
1452 *Store and Dispense*
1453 Store between 5EC and 25EC (41EF and 77EF).
1454
1455 Rx only
1456
1457 Made in Ireland
1458 for Fujisawa Healthcare, Inc.
1459 Deerfield, IL 60015-2548
1460 by Fujisawa Ireland, Ltd.
1461 Killorglin, Co. Kerry Ireland
1462

1463 **REFERENCE:**
1464 1. CDC: Recommendations of the Advisory
1465 Committee on Immunization Practices: Use of
1466 vaccines and immune globulins in persons
1467 with altered immunocompetence. MMWR
1468 1993;42(RR-4):1-18.
1469
1470 1/23/01

1471
1472 **Patient Information**

1473
1474 **PROGRAF**
1475 *(tacrolimus capsules)*
1476

1477
1478 **Read this important information before you**
1479 **start using PROGRAF [PRO-graf] and**
1480 **each time you refill your prescription. This**
1481 **summary does not take the place of talking**
1482 **with your transplant team.**

1483
1484 **Talk with your transplant team if you have**
1485 **any questions or want more information**

PROPOSED PACKAGE INSERT

1486 **about PROGRAF. You can also visit the**
1487 **Fujisawa Internet site at www.fujisawa.com.**

1488

1489 **What Is PROGRAF?**

1490

1491 PROGRAF is a medicine that slows down the
1492 body's immune system. For this reason, it
1493 works as an anti-rejection medicine.

1494 PROGRAF helps patients who have had a liver
1495 or kidney transplant protect their new organ
1496 and prevent it from being rejected by the body.

1497

1498 **How Does PROGRAF Protect My New**
1499 **Organ?**

1500

1501 **The body's immune system protects the**
1502 **body against anything that it does not**
1503 **recognize as part of the body. For**
1504 **example, when the immune system detects**
1505 **a virus or bacteria it tries to get rid of it to**
1506 **prevent infection. When a person has a**
1507 **liver or kidney transplant, the immune**
1508 **system does not recognize the new organ**
1509 **as a part of the body and tries to get rid of**
1510 **it, too. This is called "rejection."**

1511 **PROGRAF protects your new organ by**
1512 **slowing down the body's immune system.**

1513

1514 **Who Should Not Take PROGRAF?**

1515

1516 Do not take PROGRAF if you are allergic to
1517 any of the ingredients in PROGRAF. The
1518 active ingredient is tacrolimus. Ask your doctor
1519 or pharmacist about the inactive ingredients.

1520

1521 Tell your transplant team about all your health

PROPOSED PACKAGE INSERT

1522 conditions, including kidney and/or liver
1523 problems. Discuss with your transplant team
1524 the use of any other prescription and non-
1525 prescription medications, including any herbal
1526 or over-the-counter remedies that you may take
1527 while on Prograf. In very rare cases you may
1528 not be able to take Prograf.
1529
1530 Tell your transplant team if you are pregnant,
1531 planning to have a baby or are breastfeeding.
1532 Talk with your transplant doctor about possible
1533 effects PROGRAF could have on your child.
1534 Do not nurse a baby while taking PROGRAF
1535 since the medicine will be in the breast milk.

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1536

1537

1538 **How Should I Take PROGRAF?**

1539

1540 PROGRAF can protect your new kidney or
1541 liver only if you take the medicine correctly.

1542

1543 Your new organ needs around-the-clock
1544 protection so your body does not reject it. The
1545 success of your transplant depends a great deal
1546 upon how well you help PROGRAF do its job.
1547 Here is what you can do to help.

1548

1549

1550 **\$ Take PROGRAF exactly as**
1551 **prescribed**

1552

1553 It is important to take
1554 PROGRAF capsules exactly as
1555 your transplant team tells you
1556 to.

1557

1558 PROGRAF comes in several
1559 different strength capsules--0.5
1560 mg, 1 mg and 5 mg. Your
1561 transplant team will tell you
1562 what dose to take and how
1563 often to take it. Your transplant
1564 team may adjust your dose until
1565 they find what works best for
1566 you.

1567

1568 Never change your dose on
1569 your own. Never stop taking
1570 PROGRAF even if you are
1571 feeling well. However, if you

PROPOSED PACKAGE INSERT

1572 feel poorly on Prograf, discuss
1573 this with your transplant team.

1574

1575

1576 **\$ Take PROGRAF two times**
1577 **a day, 12 hours apart**

1578

1579 Try to pick times that will be
1580 easy for you. For example, if
1581 you take your first dose at 7:00
1582 a.m. you should take your
1583 second dose at 7:00 p.m. Do
1584 not vary the times. You must
1585 take PROGRAF at the same
1586 times every day. If you decide
1587 to take PROGRAF at 7:00
1588 a.m. and 7:00 p.m., take it at
1589 these same times every day.

1590 This will make sure you always
1591 have enough medicine in your
1592 body to give your new organ
1593 the around-the-clock protection
1594 it needs.

1595

1596

1597 **\$ Take PROGRAF the same**
1598 **way each day**

1599

1600 Some people prefer to take
1601 PROGRAF with food to help
1602 reduce possible stomach upset.

1603 Whether you take PROGRAF
1604 with or without food, it is
1605 important to take PROGRAF
1606 the same way every day. For
1607 example, if you take

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1608 PROGRAF with food, you
1609 should always take it with food.
1610 Do not eat grapefruit or drink
1611 grapefruit juice in combination
1612 with your medicine unless your
1613 transplant teams approves. Do
1614 not change the way you take
1615 this medicine without telling
1616 your transplant team, since this
1617 could change the amount of
1618 protection you get from
1619 PROGRAF.

1620
1621
1622

\$ Take all your doses

1624
1625 It is important to take your
1626 doses twice a day exactly as
1627 prescribed by your doctor. If
1628 you miss even two doses, your
1629 new liver or kidney could lose
1630 the protection it needs to
1631 defend itself against rejection by
1632 your body.

1633
1634 If you miss one dose, do not try
1635 to catch up on your own. Call
1636 your transplant team right away
1637 for instructions on what to do.

1638
1639 If you travel and change time
1640 zones, be sure to ask your
1641 transplant team how to adjust
1642 your dosage schedule so your
1643 new organ does not lose its

PROPOSED PACKAGE INSERT

1644 protection.

1645

1646

1647 • **Plan ahead so that you do**
1648 **not run out of PROGRAF**

1649

1650 Make sure you have your
1651 prescription for PROGRAF
1652 refilled and at home before you
1653 need it. Circle the date on a
1654 calendar when you need to
1655 order your refill. Allow extra
1656 time if you receive your
1657 medicines through the mail.

1658

1659 Your transplant team will follow your progress
1660 and watch for early signs of side effects. This is
1661 why you will have blood tests done often after
1662 your transplant. On the days you are going to
1663 have a blood test to measure the amount of
1664 PROGRAF in your body, your transplant team
1665 may ask you not to take your morning dose
1666 until after the blood sample is taken. Check
1667 with your transplant team before skipping this
1668 dose.

1669

1670

1671 **Can Other Medicines Affect How**
1672 **PROGRAF Works?**

1673

1674 Some medicines and alcohol can affect how
1675 well PROGRAF works. After you start taking
1676 PROGRAF:

1677

1678 \$ Be sure to tell your transplant
1679 team, family doctor, dentist,

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1680 pharmacist and any other health
1681 care professional treating you
1682 the names of **all** the medicines
1683 you are taking. This includes
1684 PROGRAF as well as all other
1685 prescription medicines and non-
1686 prescription medicines, natural
1687 or herbal remedies, nutritional
1688 supplements, and vitamins. This
1689 is the only way that your health
1690 care team can help prevent
1691 drug interactions that could be
1692 serious.

1693
1694 \$ Always check with your
1695 transplant team before you start
1696 taking any new medicine.

1697
1698 \$ While you are taking
1699 PROGRAF, **do not get any**
1700 **vaccinations without your**
1701 **transplant team’s approval.**
1702 The vaccination may not work
1703 as well as it should.

1704
1705 \$ Liver transplant patients,
1706 including those taking
1707 PROGRAF, should not drink
1708 alcohol.

1709
1710 **What Are the Possible Side Effects of**
1711 **PROGRAF?**
1712
1713
1714
1715 Tell your transplant team right away if you think

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1716 you might be having a side effect. Your
1717 transplant team will decide if it is a medicine
1718 side effect or a sign that has nothing to do with
1719 the medicine but needs to be treated. Infection
1720 or reduced urine can be signs of serious
1721 problems that you should discuss with your
1722 transplant team.

1723
1724 Your transplant team will also follow your
1725 progress and watch for the early signs of any
1726 side effects. This is why you will have blood
1727 tests done often during the first few months after
1728 your transplant. On the days you are going to
1729 have a blood test to measure the amount of
1730 PROGRAF in your body, your transplant team
1731 may ask you not to take your morning dose
1732 until after the blood sample is taken. Check
1733 with your transplant team before skipping this
1734 dose.

1735
1736
1737

For Kidney Transplant Patients:

1738
1739
1740 The most common side effects of
1741 PROGRAF for kidney transplant
1742 patients are infection, headache,
1743 tremors (shaking of the body), diarrhea,
1744 constipation, nausea, high blood
1745 pressure, changes in the amount of
1746 urine, and trouble sleeping.

1747
1748 Less common side effects are
1749 abdominal pain (stomach pain),
1750 numbness or tingling in your hands or
1751 feet; loss of appetite; indigestion or

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1752 “upset stomach”; vomiting; urinary tract
1753 infections; fever; pain; swelling of the
1754 hands, ankles or legs; shortness of
1755 breath or trouble breathing; cough; leg
1756 cramps; heart “fluttering”, palpitations
1757 or chest pain; unusual weakness or
1758 tiredness; dizziness; confusion; changes
1759 in mood or emotions; itchy skin, skin
1760 rash, and diabetes.

1761
1762

For Liver Transplant Patients:

1763
1764
1765 The most common side effects of
1766 PROGRAF for liver transplant patients
1767 are headache, tremors (shaking of the
1768 body), diarrhea, high blood pressure,
1769 nausea and changes in the amount of
1770 urine.

1771
1772 Less common side effects are
1773 numbness or tingling in your hands or
1774 feet; trouble sleeping; constipation; loss
1775 of appetite; vomiting; urinary tract
1776 infections; fever; pain (especially in the
1777 back or abdomen [stomach area]);
1778 swelling of the hands, ankles, legs or
1779 abdomen; shortness of breath or
1780 trouble breathing; cough; unusual
1781 bruising; leg cramps; heart “fluttering”
1782 or palpitations; unusual weakness or
1783 tiredness; confusion; changes in mood
1784 or emotions; itchy skin, and skin rash.

1785
1786
1787

Be sure to tell your transplant team right

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1788 **away if you notice that you are thirstier**
1789 **than usual, have to urinate more often,**
1790 **have blurred vision or seem to get**
1791 **confused. These may be the early signs of**
1792 **high blood sugar or diabetes.**

1793
1794 All anti-rejection medicines, including
1795 PROGRAF, suppress your body's immune
1796 system. As a result, they may increase your
1797 chances of getting infections and some kinds of
1798 cancer, including skin and lymph gland cancer
1799 (lymphoma). As usual for patients with
1800 increased risk for skin cancer, exposure to
1801 sunlight and UV light should be limited by
1802 wearing protective clothing and using a
1803 sunscreen with a high sun protection factor
1804 (SPF \$ 15). However, getting cancer from
1805 taking an anti-rejection medicine is not
1806 common. Talk with your transplant team about
1807 any concerns or questions you have.

1808
1809

1810 **How Should I Store PROGRAF?**

1811
1812 Store PROGRAF in a dry area at room
1813 temperature (77° F/25° C). Do not let the
1814 medicine get colder than 59° F (15° C) or
1815 hotter than 86° F (30° C). For instance, do not
1816 leave PROGRAF in the glove compartment of
1817 your car in the summer or winter. Do not keep
1818 PROGRAF capsules in a hot or moist place
1819 such as the medicine cabinet in the bathroom.

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1820

1821

1822

1823

1824

1825 **General Advice about Prescription**

1826 **Medicines**

1827

1828 Medicines are sometimes prescribed for
1829 conditions that are not mentioned in patient
1830 information leaflets. Do not use PROGRAF for
1831 a condition for which it was not prescribed. Do
1832 not give PROGRAF to other people.

1833

1834 This leaflet summarizes the most important
1835 information about PROGRAF. If you would
1836 like more information, talk with your doctor.
1837 You can ask your pharmacist or doctor for
1838 information about PROGRAF that is written for
1839 health professionals. You can also visit the
1840 Fujisawa Internet site at www.fujisawa.com.

1841

1842

1843 **Fujisawa logotype**

1844 **[address, copyright, date, code, etc.]**

1845

1846