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APR - 8 1994

NDA 50-708
NDA 50-709

Fujisawa USA, Inc.
Attn: Hatsuo Aoki, Ph.D.
Chairman and Chief Executive Officer
Parkway North Center
Three Parkway North
Deerfield, IL 60015-2548

Dear Dr. Aoki:

Reference is made to your new drug applications dated July 23, 1993 and August 3, 1993, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Prograf[™] (tacrolimus capsules, NDA 50-708, and tacrolimus injection, NDA 50-709).

We also acknowledge receipt of your additional communications dated as follows:

NDA 50-708

August 5, 1993	November 1, 1993 (2)	January 27, 1994 (2)
August 23, 1993	November 2, 1993 (2)	January 28, 1994
September 1, 1993	November 4, 1993	January 31, 1994
October 1, 1993 (2)	November 17, 1993	February 1, 1994
October 6, 1993	December 2, 1993 (2)	February 2, 1994
October 19, 1993	December 10, 1993	March 4, 1994
October 20, 1993 (2)	December 27, 1993	March 29, 1994
October 21, 1993	January 7, 1994	April 8, 1994 (2)
October 28, 1993	January 21, 1994 (2)	

NDA 50-709

August 23, 1993	October 28, 1993	December 27, 1993
October 1, 1993	November 1, 1993	January 7, 1994
October 4, 1993	November 2, 1993 (2)	January 27, 1994
October 6, 1993	November 4, 1993	March 4, 1994
October 19, 1993	November 16, 1993	March 22, 1994
October 20, 1993	December 2, 1993	April 8, 1994
October 21, 1993	December 10, 1993	

These NDAs provide for the use of Prograf[™] in the prophylaxis of organ rejection in patients receiving allogeneic liver transplants.

We have completed the review of these applications and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the draft labeling dated April 8, 1994, submitted to NDA 50-708. Accordingly, these applications are approved, effective as of the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling. Marketing the products with FPL that is not identical to the draft labeling may render the products misbranded and unapproved new drugs. Please submit 12 copies of the FPL to each NDA as soon as it is available. Seven of the copies must be individually mounted on heavyweight paper or similar material. For administrative purposes these submissions should be designated "FPL Supplement" to the approved NDA 50-708 or NDA 50-709. Approval of these supplements by the FDA is not required before the labeling is used.

Please submit one market package of each drug product when they are available.

Validation of the analytical methods for these applications has not been completed. We will expect your full cooperation in resolving any problems that may arise.

We remind you of your Phase 4 commitments, dated January 31, February 2, and April 8, 1994, regarding the performance of additional clinical, pharmacology/toxicology, and pharmacokinetic studies, collection of certain data, and development of a new dosage form. We also remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Should you have any questions concerning these NDAs, please contact Ms. Carole Broadnax at (301) 443-9553.

Sincerely yours,

 4/8/94

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation
and Research

Concurrences:

HFD-530/Division Director/DFeigal *DFeigal 1-8-94*
HFD-530/SMO/DFreeman/2-1-94
HFD-530/MO/MCavaillé-Coll/1-28-94
HFD-530/SPharm/JFarrelly/1-31-94
HFD-530/Pharm/LBlack/1-31-94
HFD-530/SChem/CWChen/1-31-94
HFD-530/Chem/MSeffel/1-28-94
HFD-530/SBiopharm/JLazor/1-28-94
HFD-530/Biopharm/ADorantes/1-31-94
HFD-715/SStat/LKammerman/1-28-94
HFD-715/Stat/PFlyer/1-28-94
HFD-530/SCSO/ADeCicco/1-28-94
HFD-530/CSO/CBROADNAX/RD 12-14-93/Edit 1-28-94/2-1-94/4-8-94

cc:

HFD-530/Original NDA 50-708 and NDA 50-709
HFD-530/Division File
HFD-530/Division Director/DFeigal
HFD-530/SMO/DFreeman
HFD-530/MO/MCavaillé-Coll
HFD-530/Chem/MSeffel
HFD-530/Pharm/LBlack
HFD-426/Biopharm/ADorantes
HFD-715/Stat/LKammerman
HFD-715/Stat/PFlyer
HFD-530/SCSO/ADeCicco
HFD-530/CSO/CBROADNAX
HF-2 (w/labeling)
HFD-8/PSavino (w/labeling)
HFD-80/KStruble (w/labeling)
HFD-100/LCarter (w/labeling)
HFD-240/EZimney (w/labeling)
HFD-500/LRipper (w/labeling)
HFD-638/OGD (w/labeling)
HFD-735/Biometrics (w/labeling)
District Office (w/labeling)
HFI-20/EAdams (w/labeling)
HF-12/RWykoff/TToigo (w/labeling)
HF-35/PVaccari/EMcNeilly (w/labeling)
PROGRAF.AP
APPROVAL LETTER

PROPOSED LABELING

PrografTM
tacrolimus capsules
tacrolimus injection (for intravenous infusion only)

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.

DESCRIPTION:

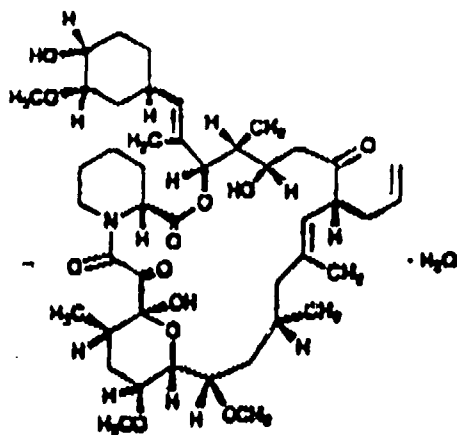
Prograf is available for oral administration as capsules (tacrolimus capsules) containing the equivalent of 1 mg or 5 mg of anhydrous tacrolimus. Inactive ingredients include lactose, hydroxypropyl methylcellulose, croscarmellose sodium, and magnesium stearate. The 1-mg capsule shell contains gelatin and titanium dioxide, and the 5-mg capsule shell contains gelatin, titanium dioxide and ferric oxide.

Prograf is also available as a sterile solution (tacrolimus injection) containing the equivalent of 5 mg anhydrous tacrolimus in 1 mL for

3 administration by intravenous infusion only. Each
 4 mL contains polyoxyl 60 hydrogenated castor oil
 5 (HCO-60), 200 mg, and dehydrated alcohol, USP,
 6 80.0% v/v. Prograf injection must be diluted with
 0.9% Sodium Chloride Injection or 5% Dextrose
 Injection before use.

7 Tacrolimus, previously known as FK506, is the
 8 active ingredient in Prograf. Tacrolimus is a
 9 macrolide immunosuppressant produced by
 10 *Streptomyces tsukubaensis*. Chemically, tacrolimus
 11 is designated as [3*S*-
 12 [3*R*'[*E*(1*S*',3*S*',4*S*')],4*S*',5*R*',8*S*',9*E*,12*R*',14*R*',15
 13 *S*',16*R*',18*S*',19*S*',26*aR*')] -5,6,8,11,12,
 14 13,14,15,16,17,18,19,24,25,26,26*a*-hexadecahydro-
 15 5,19-dihydroxy-3-[2-(4-hydroxy-3-
 16 methoxycyclohexyl)-1-methylethenyl]-14,16-
 17 dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-
 18 15,19-epoxy-3*H*-pyrido[2,1-*c*][1,4]
 19 oxazacyclotricosine-1,7,20,21(4*H*,23*H*)-tetrone,
 20 monohydrate.

-- The chemical structure of tacrolimus is:



22 Tacrolimus has an empirical formula of
 23 $C_{44}H_{69}NO_{12} \cdot H_2O$ and a formula weight of 822.05.
 24 Tacrolimus appears as white crystals or crystalline
 25 powder. It is practically insoluble in water, freely
 soluble in ethanol, and very soluble in methanol and
 chloroform.

CLINICAL PHARMACOLOGY:

Mechanism of Action

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

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

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

Pharmacokinetics

26 Absorption of tacrolimus from the gastrointestinal
27 tract after oral administration is variable. The
28 absorption half-life of tacrolimus in 16 liver
29 transplant patients averaged 5.7 hours (standard
30 deviation 4.6 hours). Peak concentrations (C_{max})
31 in blood and plasma were achieved at approximately
32 1.5-3.5 hours. Mean (standard deviation)
33 pharmacokinetic parameters of tacrolimus in whole
34 blood after oral administration were:
35

Population	No. of Subjects	Dose mg/kg/12h	C _{max} ng/ml	T _{max} hours	AUC ng/ml.h	F%
Healthy Volunteers	27	0.07 (1x5mg)	26.6 (8.6)	1.4 (0.62)	271 (122)	14.4 (6.0)
		0.07 (5x1mg)	36.7 (13.8)	1.3 (0.43)	329 (174)	17.4 (7.0)
Liver transplant patients	17	0.15 (Food)	66.5 (30.0)	2.3 (1.3)	519 (179)	21.8 (6.3)
			27.1 (14.7)	3.2 (1.3)	223 (125)	-
			52.4 (17.0)	1.5 (1.2)	290 (117)	-
			17.0 (17.0)	1.2 (1.2)	117 (117)	-

Mean (SD) C_{max} maximum concentration
 T_{max} time to maximum concentration
 AUC area under the concentration-time curve
 F absolute bioavailability

The disposition of tacrolimus from whole blood was biphasic with a terminal elimination half-life of 11.7 (\pm 3.9) hours in liver transplant patients and 21.2 (\pm 8.5) hours in healthy volunteers. The volume of distribution and total body clearance for tacrolimus following intravenous administration were:

Population	Number of Subjects	Dose (mg/kg/12h)	V _d (l/kg)	Cl (L/h/kg)
Healthy Volunteers	27	0.01	0.88 (0.31)	0.042 (0.016)
Liver Transplant Patients	17	0.05	0.85 (0.3)	0.053 (0.017)

Mean (SD) V_d Volume of distribution
 Cl Total body clearance

Pharmacokinetic data indicate that whole blood rather than plasma may serve as the more appropriate medium to describe the pharmacokinetic characteristics of tacrolimus.

The results of a single-dose bioequivalence study conducted in 27 healthy volunteers indicated that the absolute bioavailability of the 5-mg capsule was 14.4% and that of five 1-mg capsules was 17.4%. This study failed to establish the bioequivalence of these two formulations.

The effect of food was studied in 11 liver transplant patients. Prograf was administered in the fasting state or 15 minutes after a breakfast of measured fat

3 content (34% of 400 total calories). The results
4 indicate that the presence of food reduces the
5 absorption of tacrolimus (decrease in AUC and
6 C_{max}, and increase in T_{max}). The relative oral
7 bioavailability (whole blood) was reduced by 27.0
(± 18.2%) when compared to administration in the
fasting state.

8 The protein-binding of tacrolimus reported in two
9 studies was 75% and 99% over a range of
10 concentrations of 0.1 - 100 ng/mL. Tacrolimus is
11 bound to proteins, mainly albumin and alpha-1-acid
12 glycoprotein, and is highly bound to erythrocytes.
13 The distribution of tacrolimus between whole blood
14 and plasma depends on several factors such as
15 hematocrit, temperature of separation of plasma,
16 drug concentration, and plasma protein
17 concentration. In a U.S. study, the ratio of whole
18 blood concentration to plasma concentration ranged
19 from 12 to 67 (mean 35).

20 Tacrolimus trough concentrations from 10 to 60
21 ng/mL measured at 10-12 hours post-dose (C_{min})
22 correlated well with the area under the plasma or
23 whole blood concentration-time curve (AUC). In
24 28 liver transplant patients, the correlation
25 coefficient was 0.94.

26 Pharmacokinetic studies in pediatric patients have
27 not been conducted. However, trough
28 concentrations obtained from 30 children (less than
29 12 years old) showed that children need higher
30 doses than adults to achieve similar tacrolimus
31 trough concentrations, suggesting that the
32 pharmacokinetic characteristics of tacrolimus are
33 different in children as compared to adults. (see
34 DOSAGE AND ADMINISTRATION).

35 Tacrolimus is extensively metabolized by the
36 mixed-function oxidase system, primarily the
37 cytochrome P-450 enzyme system (P-450 IIIA). In
38 man, less than 1% of the dose administered is
39 excreted unchanged in the urine. The major
40 metabolic pathway has not been determined.
41 Demethylation and hydroxylation were identified as
the primary mechanisms of biotransformation *in*

3 *in vitro*. The major metabolite identified in
4 incubations with human liver microsomes is 13-
5 demethyl tacrolimus. Ten possible metabolites have
6 been identified in human plasma. Two metabolites,
7 a demethylated and a double-demethylated
8 tacrolimus, were shown to retain 10% and 7%,
respectively, of the inhibitory effect of tacrolimus
on T-lymphocyte activation.

9 *Clinical Studies*

10 The safety and efficacy of Prograf-based
11 immunosuppression following orthotopic liver
12 transplantation were assessed in two prospective,
13 randomized, non-blinded multicenter studies. The
14 active control groups were treated with a
15 cyclosporine-based immunosuppressive regimen.
16 Both studies used concomitant adrenal
17 corticosteroids as part of the immunosuppressive
18 regimens. These studies were designed to evaluate
19 whether the two regimens were therapeutically
20 equivalent, with patient and graft survival at 12
21 months following transplantation as the primary
22 endpoints. The Prograf-based immunosuppressive
23 regimen was found to be equivalent to the
24 cyclosporine-based immunosuppressive regimens.

25 In one trial, 529 patients were enrolled at 12
26 clinical sites in the United States; prior to surgery,
27 263 were randomized to the Prograf-based
28 immunosuppressive regimen and 266 to a
29 cyclosporine-based immunosuppressive regimen
30 (CBIR). In 10 of the 12 sites, the same CBIR
31 protocol was used, while 2 sites used different
32 control protocols. This trial excluded patients with
33 renal dysfunction, fulminant hepatic failure with
34 Stage IV encephalopathy, and cancers; pediatric
35 patients (≤ 12 years old) were allowed.

36 In the second trial, 545 patients were enrolled at 8
37 clinical sites in Europe; prior to surgery, 270 were
38 randomized to the Prograf-based
39 immunosuppressive regimen and 275 to a CBIR. In
40 this study, each center used its local standard CBIR
41 protocol in the active-control arm. This trial

3 excluded pediatric patients, but did allow enrollment
4 of subjects with renal dysfunction, fulminant hepatic
failure in Stage IV encephalopathy, and cancers
other than primary hepatic with metastases.

5 One-year patient survival and graft survival in the
6 Prograf-based treatment groups were equivalent to
7 those in the CBIR treatment groups in both studies.
8 The overall one-year patient survival (CBIR and
9 Prograf-based treatment groups combined) was 88%
10 in the U.S. study and 78% in the European study.
11 The overall one-year graft survival (CBIR and
12 Prograf-based treatment groups combined) was 81%
13 in the U.S. study and 73% in the European study.
14 In both studies, the median time to convert from IV
15 to oral Prograf dosing was 2 days.

16 Information on secondary outcomes (incidence of
17 acute rejection, use of OKT3 for steroid-resistant
18 rejection, and incidence of refractory rejection) was
19 also collected. Because of the nature of the study
20 designs, comparisons of differences between the
study arms for these secondary endpoints could not
be reliably assessed.

23 **INDICATIONS AND USAGE:**

24 Prograf is indicated for the prophylaxis of organ
25 rejection in patients receiving allogeneic liver
26 transplants. It is recommended that Prograf be used
27 concomitantly with adrenal corticosteroids. Because
28 of the risk of anaphylaxis, Prograf injection should
29 be reserved for patients unable to take Prograf
30 capsules orally.

31 **CONTRAINDICATIONS:**

32 Prograf is contraindicated in patients with a
33 hypersensitivity to tacrolimus. Prograf injection is
34 contraindicated in patients with a hypersensitivity to
35 HCO-60 (polyoxyl 60 hydrogenated castor oil).

36 **WARNINGS:**

37 (See boxed WARNING)

38 Prograf can cause neurotoxicity and nephrotoxicity,
39 particularly when used in high doses.
Nephrotoxicity has been noted in 40% and 33% of
liver transplantation

3 patients receiving Prograf in the U.S. and European
4 randomized trials, respectively (see ADVERSE
5 REACTIONS). More overt nephrotoxicity is seen
6 early after transplantation, characterized by
7 increasing serum creatinine and a decrease in urine
8 output. Patients with impaired renal function
9 should be monitored closely, and the dosage of
10 Prograf may need to be reduced. In patients with
11 persistent elevations of serum creatinine who are
12 unresponsive to dosage adjustments, consideration
13 should be given to changing to another
14 immunosuppressive therapy. Care should be taken
15 in using tacrolimus with other nephrotoxic drugs.
16 In particular, to avoid excess nephrotoxicity,
17 Prograf should not be used simultaneously with
18 cyclosporine. Prograf or cyclosporine should be
19 discontinued at least 24 hours prior to initiating
20 the other. In the presence of elevated Prograf or
cyclosporine concentrations, dosing with the
other drug usually should be further delayed.

21 Mild to severe hyperkalemia has been noted in 44%
22 and 10% of liver transplant recipients treated with
23 Prograf in the U.S. and European randomized trials
24 and may require treatment (see ADVERSE
25 REACTIONS). Serum potassium levels should be
26 monitored and potassium-sparing diuretics
27 should not be used during Prograf therapy (see
28 PRECAUTIONS).

29 Neurotoxicity, including tremor, headache, and
30 other changes in motor function, mental status, and
31 sensory function were reported in approximately
32 55% of liver transplant recipients in the two
33 randomized studies (see ADVERSE REACTIONS).
34 Tremor and headache have been associated with
35 high whole-blood concentrations of tacrolimus and
36 may respond to dosage adjustment. Seizures have
37 occurred in adult and pediatric patients receiving
38 Prograf (see ADVERSE REACTIONS). Coma and
39 delirium also have been associated with high plasma
40 concentrations of tacrolimus.

41 As in patients receiving other immunosuppressants,
42 patients receiving Prograf are at increased risk of

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3 developing lymphomas and other malignancies,
4 particularly of the skin. The risk appears to be
5 related to the intensity and duration of
6 immunosuppression rather than to the use of any
7 specific agent. A lymphoproliferative disorder
8 (LPD) related to Epstein-Barr Virus (EBV) infection
9 has been reported in immunosuppressed organ
10 transplant recipients. The risk of LPD appears
11 greatest in young children who are at risk for
12 primary EBV infection while immunosuppressed or
13 who are switched to Prograf following long-term
14 immunosuppression therapy. Because of the danger
15 of oversuppression of the immune system, which
16 can increase susceptibility to infection, Prograf
17 should not be administered with other
18 immunosuppressive agents except adrenal
19 corticosteroids. The efficacy and safety of the use
of Prograf in combination with other
immunosuppressive agents has not been determined.

20 A few patients receiving Prograf injection have
21 experienced anaphylactic reactions. Although the
exact cause of these reactions is not known, other
24 drugs with castor oil derivatives in the formulation
25 have been associated with anaphylaxis in a small
26 percentage of patients. Because of this potential
27 risk of anaphylaxis, Prograf injection should be
28 reserved for patients who are unable to take Prograf
capsules.

29 Patients receiving Prograf injection should be
30 under continuous observation for at least the first
31 30 minutes following the start of the infusion and
32 at frequent intervals thereafter. If signs or
33 symptoms of anaphylaxis occur, the infusion
34 should be stopped. An aqueous solution of
35 epinephrine 1:1000 should be available at the
36 bedside as well as a source of oxygen.

37 **PRECAUTIONS:**

38 *General*

39 Hypertension is a common adverse effect of Prograf
40 therapy (see ADVERSE REACTIONS.) Mild or
41 moderate hypertension is more frequently reported

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than severe hypertension. Antihypertensive therapy may be required; the control of blood pressure can be accomplished with any of the common antihypertensive agents. Since tacrolimus may cause hyperkalemia, potassium-sparing diuretics should be avoided. While calcium-channel blocking agents can be effective in treating Prograf-associated hypertension, care should be taken since interference with tacrolimus metabolism may require a dosage reduction (see *Drug Interactions*).

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Hyperglycemia was associated with the use of Prograf in 47% and 29% of liver transplant recipients in the U.S. and European randomized studies, respectively, and may require treatment (see ADVERSE REACTIONS).

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Renally and Hepatically Impaired Patients

For patients with renal insufficiency some evidence suggests that lower doses should be used (see DOSAGE AND ADMINISTRATION).

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

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Information for Patients

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

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Laboratory Tests

Serum creatinine and potassium should be assessed regularly. Routine monitoring of metabolic and hematologic systems should be performed as clinically warranted.

Drug Interactions

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Drug interaction studies with tacrolimus have not been conducted. Due to the potential for additive or synergistic impairment of renal function, care should be taken when administering Prograf with drugs that may be associated with renal dysfunction. These include, but are not limited to, aminoglycosides, amphotericin B, and cisplatin. Initial clinical experience with the co-administration of Prograf and cyclosporine resulted in additive/synergistic nephrotoxicity. Patients switched from cyclosporine to Prograf should receive the first Prograf dose no sooner than 24 hours after the last cyclosporine dose. Dosing may be further delayed in the presence of elevated cyclosporine levels.

Drugs that May Alter Tacrolimus Concentrations

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Since tacrolimus is metabolized mainly by the cytochrome P-450 IIIA enzyme systems, substances known to inhibit these enzymes may decrease the metabolism of tacrolimus with resultant increases in whole blood or plasma levels. Drugs known to induce these enzyme systems may result in an increased metabolism of tacrolimus and decreased whole blood or plasma levels. Monitoring of blood levels and appropriate dosage adjustments are essential when such drugs are used concomitantly.

Drugs That May Increase Tacrolimus Blood Levels:

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<u>Calcium Channel Blockers</u>	<u>Antifungal Agents</u>	<u>Other Drugs</u>
diltiazem	clotrimazole	bromocriptino
nicardipine	fluconazole	cimetidine
verapamil	itraconazole	clarithromycin
	ketoconazole	cyclosporins
		danazol
		erythromycin
		methylprednisolone
		metoclopramide

Drugs That May Decrease Tacrolimus Blood Levels:

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<u>Anticonvulsants</u>	<u>Antibiotics</u>
carbamazepine	rifabutin
phenobarbital	rifampin
phenytoin	

Other Drug Interactions

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

9 Carcinogenesis, Mutagenesis and Impairment of 10 Fertility

11 An increased incidence of malignancy is a
12 recognized complication of immunosuppression in
13 recipients of organ transplants. The most common
14 forms of neoplasms are non-Hodgkin's lymphomas
15 and carcinomas of the skin. As with other
16 immunosuppressive therapies, the risk of
17 malignancies in Prograf recipients may be higher
18 than in the normal, healthy population.
19 Lymphoproliferative disorders associated with
20 Epstein-Barr Virus infection have been seen. It has
21 been reported that reduction or discontinuation of
immunosuppression may cause the lesions to
regress.

24 No evidence of genotoxicity was seen in bacterial
25 (Salmonella and E.coli) or mammalian (Chinese
26 hamster lung-derived cells) *in vitro* assays of
27 mutagenicity, the *in vitro* CHO/HGPRT assay of
28 mutagenicity, or *in vivo* clastogenicity assays
29 performed in mice; tacrolimus did not cause
30 unscheduled DNA synthesis in rodent hepatocytes.

31 Although studies are ongoing, no adequate studies
32 to evaluate the carcinogenic potential of tacrolimus
33 have been completed.

34 No impairment of fertility was demonstrated in
35 studies of male and female rats. Tacrolimus, given
36 orally at 1.0 mg/kg (0.5X the recommended clinical
37 dose based on body surface area corrections) to
38 male and female rats, prior to and during mating, as
39 well as to dams during gestation and lactation, was
40 associated with embryoletality and with adverse
effects on female reproduction. Effects on

3 female reproductive function (parturition) and
4 embryo-lethal effects were indicated by a higher rate
5 of pre-implantation loss and increased numbers of
6 undelivered and nonviable pups. When given at 3.2
7 mg/kg (1.5X the recommended clinical dose based
8 on body surface area correction), tacrolimus
9 was associated with maternal and paternal toxicity
10 as well as reproductive toxicity including marked
adverse effects on estrus cycles, parturition, pup
viability, and pup malformations.

11 *Pregnancy: Category C*

12 In reproduction studies in rats and rabbits, adverse
13 effects on the fetus were observed mainly at dose
14 levels that were toxic to dams. Tacrolimus at oral
15 doses of 0.32 and 1.0 mg/kg during organogenesis
16 in rabbits was associated with maternal toxicity as
17 well as an increase in incidence of abortions; these
18 doses are equivalent to 0.33X and 1.0X (based on
19 body surface area corrections) the recommended
20 clinical dose (0.3 mg/kg). At the higher dose only,
21 an increased incidence of malformations and
22 developmental variations was also seen.
23 Tacrolimus, at oral doses of 3.2 mg/kg during
24 organogenesis in rats, was associated with maternal
25 toxicity and caused an increase in late resorptions,
26 decreased numbers of live births, and decreased pup
27 weight and viability. Tacrolimus, given orally at
28 1.0 and 3.2 mg/kg (equivalent to 0.5X and 1.5X the
29 recommended clinical dose based on body surface
30 area corrections) to pregnant rats after
31 organogenesis and during lactation, was associated
32 with reduced pup weights.

33 No reduction in male or female fertility was
34 evident.

35 There are no adequate and well-controlled studies in
36 pregnant women. Tacrolimus is transferred across
37 the placenta. The use of tacrolimus during
38 pregnancy has been associated with neonatal
39 hyperkalemia and renal dysfunction. Prograf should
40 be used during pregnancy only if the potential
41 benefit to the mother justifies potential risk to the
42 fetus.

Nursing Mothers

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

Pediatric Patients

Successful liver transplants have been performed in pediatric patients (age less than 12 years) using Prograf. One of the two randomized active-controlled trials of Prograf in primary liver transplantation included 51 pediatric patients. Thirty patients were randomized to Prograf-based and 21 to cyclosporine-based therapies. Additionally, 22 pediatric patients were studied in an uncontrolled trial of tacrolimus in living related donor liver transplantation. Pediatric patients generally required higher doses of Prograf to maintain blood trough levels of tacrolimus similar to adult patients (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS:

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

Hyperkalemia, hypomagnesemia and hyperuricemia have occurred in patients receiving Prograf therapy. Hyperglycemia has been noted in many patients; some may require insulin therapy.

The incidence of adverse events was determined in two randomized comparative liver transplant trials among 512 patients receiving tacrolimus and steroids and 511 patients receiving a cyclosporine-based regimen (CBIR). The proportion of patients reporting more than one adverse event was 99.8% in the tacrolimus group and 99.6% in the CBIR group. Precautions must be taken when comparing the incidence of adverse events in the U.S. study to that in the European study. Only adverse events occurring up to 12-months post-transplant in the

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1 U.S. study and up to 6-months in the European
2 study are presented. The two studies also included
3 different patient populations and patients were
4 treated with immunosuppressive regimens of
5 differing intensities. Adverse events reported in
6 >15% in tacrolimus patients (combined study
7 results) are presented below for the two controlled
8 trials in liver transplantation:

	U.S. STUDY (%)		EUROPEAN STUDY (%)		
	Prograf (N=250)	CBIR (N=250)	Prograf (N=262)	CBIR (N=261)	
5	<u>Nervous System</u>				
6					
	Headache (See WARNINGS)	64	60	31	20
7	Tremor (See WARNINGS)	56	46	44	30
8	Insomnia	64	68	29	21
9	Paresthesia	40	30	15	13
10	<u>Gastrointestinal</u>				
11	Diarrhea	72	47	32	23
12	Nausea	46	37	30	22
13	Constipation	24	27	19	20
14	LFT Abnormal	36	30	5	2
15	Anorexia	34	24	6	4
16	Vomiting	27	15	12	9
17	<u>Cardiovascular</u>				
18	Hypertension (see PRECAUTIONS)	47	56	31	35
19	<u>Urogenital</u>				
20	Kidney Function Abnormal (See WARNINGS)	40	27	33	18
21	Creatinine Increased (See WARNINGS)	39	25	19	16
22	BUN Increased (See WARNINGS)	30	22	8	7
23	Urinary Tract Infection	16	18	19	18
	Oliguria	18	15	16	8
24	<u>Metabolic and Nutritional</u>				
26	Hyperkalemia (See WARNINGS)	45	26	10	7
27	Hypokalemia	29	34	11	14
28	Hyperglycemia (see PRECAUTIONS)	47	38	29	16
29	Hypomagnesemia	48	45	15	8
30	<u>Hemic and Lymphatic</u>				
31	Anemia	47	38	4	1
32	Leukocytosis	32	26	8	7
33	Thrombocytopenia	24	20	10	14
34	<u>Miscellaneous</u>				
35	Abdominal Pain	59	54	26	20
36	Pain	63	57	19	14
37	Fever	48	56	15	18
38	Asthenia	52	48	7	4
39	Back Pain	30	29	13	14
40	Ascites	27	22	5	6
41	Peripheral Edema	26	26	10	11
42	<u>Respiratory System</u>				
43	Pleural Effusion	30	32	32	29
44	Atelectasis	28	30	5	4
45	Dyspnea	29	23	3	2

Skin and Appendages

Pruritus	36	20	11	5
Rash	24	19	8	3

4 The following adverse events, not mentioned
5 above, were reported with greater than 3%
6 incidence in tacrolimus-treated patients.
7 **NERVOUS SYSTEM:** (see WARNINGS)
8 abnormal dreams, agitation, anxiety, confusion,
9 convulsion, depression, dizziness, emotional
10 lability, hallucinations, hypertonia,
11 incoordination, myoclonus nervousness,
12 neuropathy, psychosis, somnolence, thinking
13 abnormal; **SPECIAL SENSES:** abnormal vision,
14 amblyopia, tinnitus; **GASTROINTESTINAL:**
15 cholangitis, cholestatic jaundice, dyspepsia,
16 dysphasia, flatulence, gastrointestinal hemorrhage,
17 GGT increase, GI perforation, hepatitis, ileus,
18 increased appetite, jaundice, liver damage, oral
19 moniliasis; **CARDIOVASCULAR:** chest pain,
20 abnormal ECG, hemorrhage, hypotension,
21 tachycardia; **UROGENITAL:** (see WARNINGS)
hematuria, kidney failure; **METABOLIC**
24 **NUTRITIONAL:** acidosis, alkaline phosphatase
25 increased, alkalosis, bilirubinemia, healing
26 abnormal, hyperlipemia, hyperphosphatemia,
27 hyperuricemia, hypocalcemia, hypophosphatemia,
28 hyponatremia, hypoproteinemia, AST (SGOT)
29 increased, ALT (SGPT) increased; **ENDOCRINE:**
30 (see PRECAUTIONS) diabetes mellitus;
31 **HEMIC/LYMPHATIC:** coagulation disorder,
32 ecchymosis, hypochromic anemia, leukopenia,
33 prothrombin decreased; **MISCELLANEOUS:**
34 abdomen enlarged, abscess, chills, hernia,
35 peritonitis, photosensitivity reaction;
36 **MUSCULOSKELETAL:** arthralgia, generalized
37 spasm, leg cramps, myalgia, myasthenia,
38 osteoporosis; **RESPIRATORY:** asthma,
39 bronchitis, cough increased, lung disorder,
40 pulmonary edema, pharyngitis, pneumonia,
41 respiratory disorder, rhinitis, sinusitis, voice
42 alteration; **SKIN:** alopecia, herpes simplex,
hirsutism, skin disorder, sweating.

[Handwritten signature]

OVERDOSAGE:

3 There is minimal experience with overdosage. In
4 patients who have received inadvertent overdosage
5 of Prograf, no adverse reactions different from
6 those reported in patients receiving therapeutic
7 doses have been described. General supportive
8 measures and systemic treatment should be
9 followed in all cases of overdosage. Based on the
10 poor aqueous solubility and extensive erythrocyte
11 and plasma protein binding, it is anticipated that
12 tacrolimus is not dialyzable to any significant
13 extent.

13 In acute oral and intravenous toxicity studies,
14 mortalities were seen at and above the following
15 doses: in adult rats, 52X the recommended
16 human oral dose; in immature rats, 16X the
17 recommended oral dose; and in adult rats, 16X
18 the recommended human intravenous dose (all
19 based on body surface area corrections).

DOSAGE AND ADMINISTRATION:

Prograf injection (tacrolimus injection)

For Intravenous Infusion Only

23 **NOTE:** Anaphylactic reactions have occurred
24 with injectables containing castor oil
25 derivatives. See WARNINGS SECTION.

26 In patients unable to take oral Prograf capsules,
27 therapy may be initiated with Prograf injection.
28 The initial dose of Prograf should be administered
29 no sooner than 6 hours after transplantation. The
30 recommended starting dose of Prograf injection is
31 0.05-0.10 mg/kg/day as a continuous intravenous
32 infusion. Adult patients should receive doses at
33 the lower end of the dosing range. Concomitant
34 *ad.* adrenal corticosteroid therapy is recommended
35 early post transplantation. Continuous
36 intravenous infusion of Prograf injection should
37 be continued only until the patient can tolerate
38 oral administration of Prograf capsules.

Preparation for Administration/Stability

3 Prograf injection must be diluted with 0.9%
4 Sodium Chloride Injection or 5% Dextrose
5 Injection to a concentration between 0.004 mg/mL
6 and 0.02 mg/mL prior to use. Diluted infusion
7 solution should be stored in glass or polyethylene
8 containers and should be discarded after 24 hours.
9 The diluted infusion solution should not be stored
10 in a PVC container due to decreased stability and
11 the potential for extraction of phthalates.
12 Parenteral drug products should be inspected
13 visually for particulate matter and discoloration
14 prior to administration, whenever solution and
container permit.

Prograf capsules (tacrolimus capsules)

15 It is recommended that patients be converted from
16 intravenous to oral Prograf capsules as soon as
17 oral therapy can be tolerated. This usually occurs
18 within 2-3 days. The first dose of oral therapy
19 should be given 8-12 hours after discontinuing the
20 IV infusion. The recommended starting oral dose
21 of Prograf capsules is 0.15-0.30 mg/kg/day
22 administered in two divided daily doses every 12
23 hours. The initial dose of Prograf should be
24 administered no sooner than 6 hours after
25 transplantation. Adult patients should receive
26 doses at the lower end of the dosing range.
27

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

Pediatric Patients

34 Pediatric patients without pre-existing renal or
35 hepatic dysfunction have required and tolerated
36 higher doses than adults to achieve similar blood
37 concentrations. Therefore, it is recommended
38 that therapy be initiated in pediatric patients at the
39 high end of the recommended adult intravenous
40 and oral dosing ranges (0.1mg/kg/day intravenous
41 and 0.3mg/kg/day oral). Dose adjustments may
be required.

Patients with Hepatic or Renal Dysfunction

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

Conversion from one Immunosuppressive Regimen to Another

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

Blood Concentration Monitoring

Most study centers have found tacrolimus blood-concentration monitoring helpful in patient management. While no fixed relationship has been established, such blood monitoring may assist in the clinical evaluation of rejection and toxicity, dose adjustments, and the assessment of compliance.

Various assays have been used to measure blood concentrations of tacrolimus. Comparison of the concentrations in published literature to patient concentrations using current assays must be made with detailed knowledge of the assay methods employed.

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

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HOW SUPPLIED:

3 Prograf capsules (tacrolimus capsules) 1mg
4 Oblong, white, branded with red "1 mg" on the
5 capsule cap and "[E] 617" on the capsule body,
6 supplied in 100-count bottles (NDC 0469-0617-
7 71), containing the equivalent of 1 mg of
anhydrous tacrolimus.

8 Prograf capsules (tacrolimus capsules) 5mg
9 Oblong, grayish/red, branded with white "5 mg"
10 on the capsule cap and "[E] 657" on the capsule
11 body, supplied in 100-count bottles (NDC 0469-
12 0657-71), containing the equivalent of 5 mg of
13 anhydrous tacrolimus.

14 *Store and Dispense*
15 Store at controlled room temperature, 15°C-30°C
16 (59°F-86°F).

17 Prograf injection (tacrolimus injection)
18 5mg (for intravenous infusion only)
19 Supplied as a sterile solution in 1-mL ampules
20 containing the equivalent of 5 mg of anhydrous
tacrolimus per mL, in boxes of 10 ampules (NDC
0469-3016-01).

23 *Store and Dispense*
24 Store between 5°C and 25°C (41°F and 77°F).

25 **CAUTION:**
26 Federal law prohibits dispensing without
27 prescription.

28 Made in Ireland
29 for Fujisawa USA, Inc.
30 Deerfield, IL 60015-2548
31 by Fujisawa Ireland, Ltd.
32 Killorglin, Co. Kerry Ireland

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REFERENCE

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

- 7 Revision J - 4/8/94

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: February 1, 1994

FROM: David W. Feigal, M.D., Director
Division of Antiviral Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

TO: NDA 50-708 and NDA 50-709

DRUG: Prograf™ (tacrolimus)

SUBJECT: Summary Basis of Approval (SBA)

The following documents will serve as the SBA for NDA 50-708 and NDA 50-709.

Medical Review (draft)
Marc Cavaille-Coll, M.D., Ph.D.

Statistical Review - December 30, 1993
Lisa A. Kammerman, Ph.D./Paul Flyer, Ph.D.

Pharmacology Review - December 16, 1993
Lauren E. Black, Ph.D.

Chemistry Review (draft)
Mark R. Seggel, Ph.D.

Biopharmaceutics Review (draft)
Angelica Dorantes, Ph.D.

HFD-530 /Original NDA 50-708 and NDA 50-709
HFD-530/ Division File
HFD-530/Dir/Feigal
HFD-530/SMO/Freeman
HFD-530/MO/Cavaille-Coll
HFD-530/Chem/Seggel
HFD-530/Pharm/Black
HFD-530/SBiopharm/Lazor
HFD-426/Biopharm/Dorantes
HFD-713/Stat/Kammerman/Flyer
HFD-530/SCSO/DeCicco
HFD-530/CSO/Broadnax