

Active Ingredient Search Results from "Rx" table for query on "cyclosporine."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
065003	AB1	No	CYCLOSPORINE	Capsule; Oral	100MG	GENGRAF	ABBOTT
065003	AB1	No	CYCLOSPORINE	Capsule; Oral	25MG	GENGRAF	ABBOTT
065003	BX	No	CYCLOSPORINE	Capsule; Oral	50MG	GENGRAF	ABBOTT
065017	AB1	No	CYCLOSPORINE	Capsule; Oral	100MG	CYCLOSPORINE	EON
065017	AB1	No	CYCLOSPORINE	Capsule; Oral	25MG	CYCLOSPORINE	EON
050625	AB2	Yes	CYCLOSPORINE	Capsule; Oral	100MG	SANDIMMUNE	NOVARTIS
050715	AB1	Yes	CYCLOSPORINE	Capsule; Oral	100MG	NEORAL	NOVARTIS
050715	AB1	No	CYCLOSPORINE	Capsule; Oral	25MG	NEORAL	NOVARTIS
050625	AB2	No	CYCLOSPORINE	Capsule; Oral	25MG	SANDIMMUNE	NOVARTIS
050625	BX	No	CYCLOSPORINE	Capsule; Oral	50MG	SANDIMMUNE	NOVARTIS
065044	AB1	No	CYCLOSPORINE	Capsule; Oral	100MG	CYCLOSPORINE	PLIVA
065044	AB1	No	CYCLOSPORINE	Capsule; Oral	25MG	CYCLOSPORINE	PLIVA
065040	AB2	No	CYCLOSPORINE	Capsule; Oral	100MG	CYCLOSPORINE	TORPHARM
065040	AB2	No	CYCLOSPORINE	Capsule; Oral	25MG	CYCLOSPORINE	TORPHARM
050790		Yes	CYCLOSPORINE	Emulsion; Ophthalmic	0.05%	RESTASIS	ALLERGAN
065004	AP	No	CYCLOSPORINE	Injectable; Injection	50MG/ML	CYCLOSPORINE	BEDFORD
050573	AP	Yes	CYCLOSPORINE	Injectable; Injection	50MG/ML	SANDIMMUNE	NOVARTIS
065025	AB	No	CYCLOSPORINE	Solution; Oral	100MG/ML	CYCLOSPORINE	ABBOTT
050574	BX	Yes	CYCLOSPORINE	Solution; Oral	100MG/ML	SANDIMMUNE	NOVARTIS
050716	AB	Yes	CYCLOSPORINE	Solution; Oral	100MG/ML	NEORAL	NOVARTIS
065054	AB	No	CYCLOSPORINE	Solution; Oral	100MG/ML	CYCLOSPORINE	PLIVA

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T2001-50
89005205

Sandimmune[®] Soft Gelatin Capsules
(cyclosporine capsules, USP)

Sandimmune[®] Oral Solution
(cyclosporine oral solution, USP)

Sandimmune[®] Injection
(cyclosporine injection, USP)
FOR INFUSION ONLY

Rx only

WARNING: Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Sandimmune[®] (cyclosporine). 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.

Sandimmune[®] (cyclosporine) should be administered with adrenal corticosteroids but not with other immunosuppressive agents. Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression.

Sandimmune[®] soft gelatin capsules (cyclosporine capsules, USP) and Sandimmune[®] oral solution (cyclosporine oral solution, USP) have decreased bioavailability in comparison to Neoral[®] soft gelatin capsules (cyclosporine capsules, USP) MODIFIED and Neoral[®] oral solution (cyclosporine oral solution, USP) MODIFIED.

Sandimmune[®] and Neoral[®] are not bioequivalent and cannot be used interchangeably without physician supervision.

The absorption of cyclosporine during chronic administration of Sandimmune[®] soft gelatin capsules and oral solution was found to be erratic. It is recommended that patients taking the soft gelatin capsules or oral solution over a period of time be monitored at repeated intervals for cyclosporine blood levels and subsequent dose adjustments be made in order to avoid toxicity due to high levels and possible organ rejection due to low absorption of cyclosporine. This is of special importance in liver transplants. Numerous assays are being developed to measure blood levels of cyclosporine. Comparison of levels in published literature to patient levels using current assays must be done with detailed knowledge of the assay methods employed. (See *Blood Level Monitoring under DOSAGE AND ADMINISTRATION*)

DESCRIPTION: Cyclosporine, the active principle in Sandimmune[®] (cyclosporine) is a cyclic polypeptide immunosuppressant agent consisting of 11 amino acids. It is produced as a metabolite by the fungus species *Beauveria nivea*.

Chemically, cyclosporine is designated as [R-[R*,R*-(E)]]-cyclic(L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-3-hydroxy-N,4-dimethyl-L-2-amino-6-octenoyl-L- α -amino-butyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl).

Sandimmune[®] Soft Gelatin Capsules (cyclosporine capsules, USP) are available in 25 mg and 100 mg strengths.

Each 25 mg capsule contains:

cyclosporine, USP 25 mg
alcohol, USP dehydrated max 12.7% by volume

Each 100 mg capsule contains:

cyclosporine, USP 100 mg
alcohol, USP dehydrated max 12.7% by volume

Inactive Ingredients: corn oil, gelatin, glycerol, Labrafil M 2125 CS (polyoxyethylated glycolysed glycerides), red iron oxide (25 mg and 100 mg capsule only), sorbitol, titanium dioxide, and other ingredients.

Sandimmune[®] Oral Solution (cyclosporine oral solution, USP) is available in 50 mL bottles.

Each mL contains:

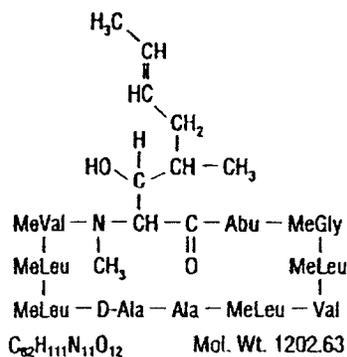
cyclosporine, USP 100 mg
alcohol, Ph. Helv. 12.5% by volume
dissolved in an olive oil, Ph. Helv./Labrafil M 1944 CS (polyoxyethylated oleic glycerides)
vehicle which must be further diluted with milk, chocolate milk, or orange juice before oral administration.

Sandimmune[®] Injection (cyclosporine injection, USP) is available in a 5 mL sterile ampul for I.V. administration.

Each mL contains:

cyclosporine, USP 50 mg
*Cremophor[®] EL (polyoxyethylated castor oil) 650 mg
alcohol, Ph. Helv. 32.9% by volume
nitrogen qs
which must be diluted further with 0.9% Sodium Chloride Injection or 5% Dextrose Injection before use.

The chemical structure of cyclosporine (also known as cyclosporin A) is:



CLINICAL PHARMACOLOGY: Sandimmune® (cyclosporine) is a potent immunosuppressive agent which in animals prolongs survival of allogeneic transplants involving skin, heart, kidney, pancreas, bone marrow, small intestine, and lung. Sandimmune® (cyclosporine) has been demonstrated to suppress some humoral immunity and to a greater extent, cell-mediated reactions such as allograft rejection, delayed hypersensitivity, experimental allergic encephalomyelitis, Freund's adjuvant arthritis, and graft vs. host disease in many animal species for a variety of organs.

Successful kidney, liver, and heart allogeneic transplants have been performed in man using Sandimmune® (cyclosporine).

The exact mechanism of action of Sandimmune® (cyclosporine) is not known. Experimental evidence suggests that the effectiveness of cyclosporine is due to specific and reversible inhibition of immunocompetent lymphocytes in the G₀- or G₁-phase of the cell cycle. T-lymphocytes are preferentially inhibited. The T-helper cell is the main target, although the T-suppressor cell may also be suppressed. Sandimmune® (cyclosporine) also inhibits lymphokine production and release including interleukin-2 or T-cell growth factor (TCGF).

No functional effects on phagocytic (changes in enzyme secretions not altered, chemotactic migration of granulocytes, macrophage migration, carbon clearance *in vivo*) or tumor cells (growth rate, metastasis) can be detected in animals. Sandimmune® (cyclosporine) does not cause bone marrow suppression in animal models or man.

The absorption of cyclosporine from the gastrointestinal tract is incomplete and variable. Peak concentrations (C_{max}) in blood and plasma are achieved at about 3.5 hours. C_{max} and area under the plasma or blood concentration/time curve (AUC) increase with the administered dose; for blood the relationship is curvilinear (parabolic) between 0 and 1400 mg. As determined by a specific assay, C_{max} is approximately 1.0 ng/mL/mg of dose for plasma and 2.7-1.4 ng/mL/mg of dose for blood (for low to high doses). Compared to an intravenous infusion, the absolute bioavailability of the oral solution is approximately 30% based upon the results in 2 patients. The bioavailability of Sandimmune® soft gelatin capsules (cyclosporine capsules, USP) is equivalent to Sandimmune® oral solution, (cyclosporine oral solution, USP).

Cyclosporine is distributed largely outside the blood volume. In blood the distribution is concentration dependent. Approximately 33%-47% is in plasma, 4%-9% in lymphocytes, 5%-12% in granulocytes, and 41%-58% in erythrocytes. At high concentrations, the uptake by leukocytes and erythrocytes becomes saturated. In plasma, approximately 90% is bound to proteins, primarily lipoproteins.

The disposition of cyclosporine from blood is biphasic with a terminal half-life of approximately 19 hours (range: 10-27 hours). Elimination is primarily biliary with only 6% of the dose excreted in the urine.

Cyclosporine is extensively metabolized but there is no major metabolic pathway. Only 0.1% of the dose is excreted in the urine as unchanged drug. Of 15 metabolites characterized in human urine, 9 have been assigned structures. The major pathways consist of hydroxylation of the C_γ-carbon of 2 of the leucine residues, C_η-carbon hydroxylation, and cyclic ether formation (with oxidation of the double bond) in the side chain of the amino acid 3-hydroxyl-

N,4-dimethyl-L-2-amino-6-octenoic acid and *N*-demethylation of *N*-methyl leucine residues. Hydrolysis of the cyclic peptide chain or conjugation of the aforementioned metabolites do not appear to be important biotransformation pathways.

INDICATIONS AND USAGE: Sandimmune® (cyclosporine) is indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. It is always to be used with adrenal corticosteroids. The drug may also be used in the treatment of chronic rejection in patients previously treated with other immunosuppressive agents.

Because of the risk of anaphylaxis, Sandimmune® injection (cyclosporine injection, USP) should be reserved for patients who are unable to take the soft gelatin capsules or oral solution.

CONTRAINDICATIONS: Sandimmune® injection (cyclosporine injection, USP) is contraindicated in patients with a hypersensitivity to Sandimmune® (cyclosporine) and/or Cremophor® EL (polyoxyethylated castor oil).

WARNINGS: (See boxed *WARNINGS*): Sandimmune® (cyclosporine), when used in high doses, can cause hepatotoxicity and nephrotoxicity.

It is not unusual for serum creatinine and BUN levels to be elevated during Sandimmune® (cyclosporine) therapy. These elevations in renal transplant patients do not necessarily indicate rejection, and each patient must be fully evaluated before dosage adjustment is initiated.

Nephrotoxicity has been noted in 25% of cases of renal transplantation, 38% of cases of cardiac transplantation, and 37% of cases of liver transplantation. Mild nephrotoxicity was generally noted 2-3 months after transplant and consisted of an arrest in the fall of the preoperative elevations of BUN and creatinine at a range of 35-45 mg/dl and 2.0-2.5 mg/dl respectively. These elevations were often responsive to dosage reduction.

More overt nephrotoxicity was seen early after transplantation and was characterized by a rapidly rising BUN and creatinine. Since these events are similar to rejection episodes care must be taken to differentiate between them. This form of nephrotoxicity is usually responsive to Sandimmune® (cyclosporine) dosage reduction.

Although specific diagnostic criteria which reliably differentiate renal graft rejection from drug toxicity have not been found, a number of parameters have been significantly associated to one or the other. It should be noted however, that up to 20% of patients may have simultaneous nephrotoxicity and rejection.

Parameter	Nephrotoxicity vs Rejection	
	Nephrotoxicity	Rejection
History	Donor > 50 years old or hypotensive Prolonged kidney preservation Prolonged anastomosis time Concomitant nephrotoxic drugs	Antidonor immune response Retransplant patient
Clinical	Often > 6 weeks postop ^b Prolonged initial nonfunction (acute tubular necrosis)	Often < 4 weeks postop ^b Fever > 37.5°C Weight gain > 0.5 kg

		Graft swelling and tenderness Decrease in daily urine volume > 500 mL (or 50%)
Laboratory	CyA serum trough level > 200 ng/mL Gradual rise in Cr (< 0.15 mg/dl/day) ^a Cr plateau < 25% above baseline BUN/Cr ≥ 20	CyA serum trough level < 150 ng/mL Rapid rise in Cr (> 0.3 mg/dl/day) ^a Cr > 25% above baseline BUN/Cr < 20
Biopsy	Arteriopathy (medial hypertrophy ^a , hyalinosis, nodular deposits, intimal thickening, endothelial vacuolization, progressive scarring) Tubular atrophy, isometric vacuolization, isolated calcifications Minimal edema Mild focal infiltrates ^c Diffuse interstitial fibrosis, often striped form	Endovasculitis ^c (proliferation ^a , intimal arteritis ^b , necrosis, sclerosis) Tubulitis with RBC ^b and WBC ^b casts, Some irregular vacuolization Interstitial edema ^c and hemorrhage ^b Diffuse moderate to severe mononuclear infiltrates ^d Glomerulitis (mononuclear cells) ^c
Aspiration Cytology	CyA deposits in tubular and endothelial cells Fine isometric vacuolization of tubular cells	Inflammatory infiltrate with mononuclear phagocytes, macrophages, lymphoblastoid cells, and activated T-cells These strongly express HLA-DR antigens
Urine Cytology	Tubular cells with vacuolization and granularization	Degenerative tubular cells, plasma cells, and hocyuria > 20% of sediment
Manometry	Intracapsular pressure < 40 mm Hg ^b	Intracapsular pressure > 40 mm Hg ^b
Ultra-sonography	Unchanged graft cross sectional area	Increase in graft cross sectional area AP diameter ≥ Transverse diameter
Magnetic Resonance Imagery	Normal appearance	Loss of distinct corticomedullary junction, swelling, image intensity of parachyma approaching that of psoas, loss of hilar fat
Radionuclide Scan	Normal or generally decreased perfusion Decrease in tubular function (¹³¹ I-hippuran) > decrease in perfusion (^{99m} Tc DTPA)	Patchy arterial flow Decrease in perfusion > decrease in tubular function Increased uptake of Indium 111 labeled platelets or Tc-99m in colloid
Therapy	Responds to decreased Sandimmune [®] (cyclosporine)	Responds to increased steroids or antilymphocyte globulin

^ap < 0.05, ^bp < 0.01, ^cp < 0.001, ^dp < 0.0001

A form of chronic progressive cyclosporine-associated nephrotoxicity is characterized by serial deterioration in renal function and morphologic changes in the kidneys. From 5%-15% of transplant recipients will fail to show a reduction in a rising serum creatinine despite a decrease or discontinuation of cyclosporine therapy. Renal biopsies from these patients will demonstrate an interstitial fibrosis with tubular atrophy. In addition, toxic tubulopathy,

peritubular capillary congestion, arteriopathy, and a striped form of interstitial fibrosis with tubular atrophy may be present. Though none of these morphologic changes is entirely specific, a histologic diagnosis of chronic progressive cyclosporine-associated nephrotoxicity requires evidence of these.

When considering the development of chronic nephrotoxicity it is noteworthy that several authors have reported an association between the appearance of interstitial fibrosis and higher cumulative doses or persistently high circulating trough levels of cyclosporine. This is particularly true during the first 6 posttransplant months when the dosage tends to be highest and when, in kidney recipients, the organ appears to be most vulnerable to the toxic effects of cyclosporine. Among other contributing factors to the development of interstitial fibrosis in these patients must be included, prolonged perfusion time, warm ischemia time, as well as episodes of acute toxicity, and acute and chronic rejection. The reversibility of interstitial fibrosis and its correlation to renal function have not yet been determined.

Impaired renal function at any time requires close monitoring, and frequent dosage adjustment may be indicated. In patients with persistent high elevations of BUN and creatinine who are unresponsive to dosage adjustments, consideration should be given to switching to other immunosuppressive therapy. In the event of severe and unremitting rejection, it is preferable to allow the kidney transplant to be rejected and removed rather than increase the Sandimmune® (cyclosporine) dosage to a very high level in an attempt to reverse the rejection.

Occasionally patients have developed a syndrome of thrombocytopenia and microangiopathic hemolytic anemia which may result in graft failure. The vasculopathy can occur in the absence of rejection and is accompanied by avid platelet consumption within the graft as demonstrated by Indium 111 labeled platelet studies. Neither the pathogenesis nor the management of this syndrome is clear. Though resolution has occurred after reduction or discontinuation of Sandimmune® (cyclosporine) and 1) administration of streptokinase and heparin or 2) plasmapheresis, this appears to depend upon early detection with Indium 111 labeled platelet scans. (*See ADVERSE REACTIONS*)

Significant hyperkalemia (sometimes associated with hyperchloremic metabolic acidosis) and hyperuricemia have been seen occasionally in individual patients.

Hepatotoxicity has been noted in 4% of cases of renal transplantation, 7% of cases of cardiac transplantation, and 4% of cases of liver transplantation. This was usually noted during the first month of therapy when high doses of Sandimmune® (cyclosporine) were used and consisted of elevations of hepatic enzymes and bilirubin. The chemistry elevations usually decreased with a reduction in dosage.

As in patients receiving other immunosuppressants, those patients receiving Sandimmune® (cyclosporine) are at increased risk for development of lymphomas and other malignancies, particularly those of the skin. The increased risk appears related to the intensity and duration of immunosuppression rather than to the use of specific agents. Because of the danger of oversuppression of the immune system, which can also increase susceptibility to infection, Sandimmune® (cyclosporine) should not be administered with other immunosuppressive agents except adrenal corticosteroids. The efficacy and safety of cyclosporine in combination with other immunosuppressive agents have not been determined.

There have been reports of convulsions in adult and pediatric patients receiving cyclosporine, particularly in combination with high dose methylprednisolone.

Encephalopathy has been described both in post-marketing reports and in the literature. Manifestations include impaired consciousness, convulsions, visual disturbances (including blindness), loss of motor function, movement disorders and psychiatric disturbances. In many cases, changes in the white matter have been detected using imaging techniques and pathologic specimens. Predisposing factors such as hypertension, hypomagnesemia, hypocholesterolemia, high-dose corticosteroids, high cyclosporine blood concentrations, and graft-versus-host disease have been noted in many but not all of the reported cases. The changes in most cases have been reversible upon discontinuation of cyclosporine, and in some cases improvement was noted after reduction of dose. It appears that patients receiving liver transplant are more susceptible to encephalopathy than those receiving kidney transplant.

Rarely (approximately 1 in 1000), patients receiving Sandimmune® injection (cyclosporine injection, USP) have experienced anaphylactic reactions. Although the exact cause of these reactions is unknown, it is believed to be due to the Cremophor® EL (polyoxyethylated castor oil) used as the vehicle for the I.V. formulation. These reactions have consisted of flushing of the face and upper thorax, acute respiratory distress with dyspnea and wheezing, blood pressure changes, and tachycardia. One patient died after respiratory arrest and aspiration pneumonia. In some cases, the reaction subsided after the infusion was stopped.

Patients receiving Sandimmune® Injection (cyclosporine injection, USP) should be under continuous observation for at least the first 30 minutes following the start of the infusion and at frequent intervals thereafter. If anaphylaxis occurs, the infusion should be stopped. An aqueous solution of epinephrine 1:1000 should be available at the bedside as well as a source of oxygen.

Anaphylactic reactions have not been reported with the soft gelatin capsules or oral solution which lack Cremophor® EL (polyoxyethylated castor oil). In fact, patients experiencing anaphylactic reactions have been treated subsequently with the soft gelatin capsules or oral solution without incident.

Care should be taken in using Sandimmune® (cyclosporine) with nephrotoxic drugs. (*See PRECAUTIONS*)

Because Sandimmune® is not bioequivalent to Neoral®, conversion from Neoral® to Sandimmune® using a 1:1 ratio (mg/kg/day) may result in a lower cyclosporine blood concentration. Conversion from Neoral® to Sandimmune® should be made with increased blood concentration monitoring to avoid the potential of underdosing.

PRECAUTIONS: General: Patients with malabsorption may have difficulty in achieving therapeutic levels with Sandimmune® soft gelatin capsules or oral solution.

Hypertension is a common side effect of Sandimmune® (cyclosporine) therapy. (*See ADVERSE REACTIONS*) Mild or moderate hypertension is more frequently encountered than severe hypertension and the incidence decreases over time. Antihypertensive therapy may be required. Control of blood pressure can be accomplished with any of the common antihypertensive agents. However, since cyclosporine may cause hyperkalemia, potassium-sparing diuretics should not be used. While calcium antagonists can be effective agents in

treating cyclosporine-associated hypertension, care should be taken since interference with cyclosporine metabolism may require a dosage adjustment. (*See Drug Interactions*)

During treatment with Sandimmune® (cyclosporine), vaccination may be less effective; and the use of live attenuated vaccines should be avoided.

Information for Patients: Patients should be advised that any change of cyclosporine formulation should be made cautiously and only under physician supervision because it may result in the need for a change in dosage.

Patients should be informed of the necessity of repeated laboratory tests while they are receiving the drug. They should be given careful dosage instructions, advised of the potential risks during pregnancy, and informed of the increased risk of neoplasia.

Patients using cyclosporine oral solution with its accompanying syringe for dosage measurement should be cautioned not to rinse the syringe either before or after use. Introduction of water into the product by any means will cause variation in dose.

Laboratory Tests: Renal and liver functions should be assessed repeatedly by measurement of BUN, serum creatinine, serum bilirubin, and liver enzymes.

Drug Interactions: All of the individual drugs cited below are well substantiated to interact with cyclosporine. In addition, concomitant non-steroidal anti-inflammatory drugs, particularly in the setting of dehydration, may potentiate renal dysfunction.

Drugs That May Potentiate Renal Dysfunction

<u>Antibiotics</u>	<u>Antineoplastic</u>	<u>Anti-Inflammatory Drugs</u>	<u>Gastrointestinal Agents</u>
gentamicin	melphalan	azapropazon	cimetidine
tobramycin		diclofenac	ranitidine
vancomycin		naproxen	
trimethoprim	<u>Antifungals</u>	sulindac	<u>Immunosuppressives</u>
with sulfamethoxazole	amphotericin B	colchicine	tacrolimus
	ketoconazole		

Drugs That Alter Cyclosporine Concentrations:

Compounds that decrease cyclosporine absorption such as orlistat should be avoided. Cyclosporine is extensively metabolized by cytochrome P-450 3A. Substances that inhibit this enzyme could decrease metabolism and increase cyclosporine concentrations. Substances that are inducers of cytochrome P-450 activity could increase metabolism and decrease cyclosporine concentrations. Monitoring of circulating cyclosporine concentrations and appropriate Sandimmune[®] dosage adjustment are essential when these drugs are used concomitantly. (See Blood Concentration Monitoring)

Drugs That Increase Cyclosporine Concentrations

<u>Calcium Channel Blockers</u>	<u>Antifungals</u>	<u>Antibiotics</u>	<u>Glucocorticoids</u>	<u>Other Drugs</u>
diltiazem	fluconazole	clarithromycin	methylprednisolone	allopurinol
nicardipine	itraconazole	erythromycin		bromocriptine
verapamil	ketoconazole	quinupristin/ dalfopristin		danazol
				metoclopramide
				colchicine
				amiodarone

The HIV protease inhibitors (e.g., indinavir, nelfinavir, ritonavir, and saquinavir) are known to inhibit cytochrome P-450 3A and thus could potentially increase the concentrations of cyclosporine, however no formal studies of the interaction are available. Care should be exercised when these drugs are administered concomitantly.

Grapefruit and grapefruit juice affect metabolism, increasing blood concentrations of cyclosporine, thus should be avoided.

Drugs/Dietary Supplements That Decrease Cyclosporine Concentrations

<u>Antibiotics</u>	<u>Anticonvulsants</u>	<u>Other Drugs/Dietary Supplements</u>
nafcillin	carbamazepine	octreotide
rifampin	phenobarbital	ticlopidine
	phenytoin	orlistat
		St. John's Wort

There have been reports of a serious drug interaction between cyclosporine and the herbal dietary supplement, St. John's Wort. This interaction has been reported to produce a marked reduction in the blood concentrations of cyclosporine, resulting in subtherapeutic levels, rejection of transplanted organs, and graft loss.

Rifabutin is known to increase the metabolism of other drugs metabolized by the cytochrome P-450 system. The interaction between rifabutin and cyclosporine has not been studied. Care should be exercised when these two drugs are administered concomitantly.

Nonsteroidal Anti-inflammatory Drug (NSAID) Interactions: Clinical status and serum creatinine should be closely monitored when cyclosporine is used with nonsteroidal anti-inflammatory agents in rheumatoid arthritis patients. (See *WARNINGS*)

Pharmacodynamic interactions have been reported to occur between cyclosporine and both naproxen and sulindac, in that concomitant use is associated with additive decreases in renal function, as determined by ^{99m}Tc -diethylenetriaminepentaacetic acid (DTPA) and (*p*-aminohippuric acid) PAH clearances. Although concomitant administration of diclofenac does not affect blood levels of cyclosporine, it has been associated with approximate doubling of diclofenac blood levels and occasional reports of reversible decreases in renal function. Consequently, the dose of diclofenac should be in the lower end of the therapeutic range.

Methotrexate Interaction: Preliminary data indicate that when methotrexate and cyclosporine were co-administered to rheumatoid arthritis patients (N=20), methotrexate concentrations (AUCs) were increased approximately 30% and the concentrations (AUCs) of its metabolite, 7-hydroxy methotrexate, were decreased by approximately 80%. The clinical significance of this interaction is not known. Cyclosporine concentrations do not appear to have been altered (N=6).

Other Drug Interactions: Reduced clearance of prednisolone, digoxin, and lovastatin has been observed when these drugs are administered with cyclosporine. In addition, a decrease in the apparent volume of distribution of digoxin has been reported after cyclosporine administration. Severe digitalis toxicity has been seen within days of starting cyclosporine in several patients taking digoxin. Cyclosporine should not be used with potassium-sparing diuretics because hyperkalemia can occur.

During treatment with cyclosporine, vaccination may be less effective. The use of live vaccines should be avoided. Myositis has occurred with concomitant lovastatin, frequent gingival hyperplasia with nifedipine, and convulsions with high dose methylprednisolone.

Psoriasis patients receiving other immunosuppressive agents or radiation therapy (including PUVA and UVB) should not receive concurrent cyclosporine because of the possibility of excessive immunosuppression.

For additional information on Cyclosporine Drug Interactions please contact Novartis Medical Affairs Department at 888-NOW-NOVA (888-669-6682).

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Cyclosporine gave no evidence of mutagenic or teratogenic effects in appropriate test systems. Only at dose levels toxic to dams, were adverse effects seen in reproduction studies in rats. (See *Pregnancy*)

Carcinogenicity studies were carried out in male and female rats and mice. In the 78-week mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value. In the 24-month rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related.

No impairment in fertility was demonstrated in studies in male and female rats.

Cyclosporine has not been found mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A recent study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes *in vitro* gave indication of a positive effect (i.e., induction of SCE), at high concentrations in this system.

An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants. The most common forms of neoplasms are non-Hodgkin's lymphoma and carcinomas of the skin. The risk of malignancies in cyclosporine recipients is higher than in the normal, healthy population but similar to that in patients receiving other immunosuppressive therapies. It has been reported that reduction or discontinuance of immunosuppression may cause the lesions to regress.

Pregnancy: *Pregnancy Category C.* Sandimmune® oral solution (cyclosporine oral solution, USP) has been shown to be embryo- and fetotoxic in rats and rabbits when given in doses 2-5 times the human dose. At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day), Sandimmune® oral solution (cyclosporine oral solution, USP) was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations. In the well-tolerated dose range (rats at up to 17 mg/kg/day and rabbits at up to 30 mg/kg/day), Sandimmune® oral solution (cyclosporine oral solution, USP) proved to be without any embryolethal or teratogenic effects.

There are no adequate and well-controlled studies in pregnant women. Sandimmune® (cyclosporine) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The following data represent the reported outcomes of 116 pregnancies in women receiving Sandimmune® (cyclosporine) during pregnancy, 90% of whom were transplant patients, and most of whom received Sandimmune® (cyclosporine) throughout the entire gestational period. Since most of the patients were not prospectively identified, the results are likely to be biased toward negative outcomes. The only consistent patterns of abnormality were premature birth (gestational period of 28 to 36 weeks) and low birth weight for gestational age. It is not possible to separate the effects of Sandimmune® (cyclosporine) on these pregnancies from the effects of the other immunosuppressants, the underlying maternal disorders, or other aspects of the transplantation milieu. Sixteen fetal losses occurred. Most of the pregnancies (85 of 100) were complicated by disorders; including, pre-eclampsia, eclampsia, premature labor, abruptio placentae, oligohydramnios, Rh incompatibility and fetoplacental dysfunction. Preterm delivery occurred in 47%. Seven malformations were reported in 5 viable infants and in 2 cases of fetal loss. Twenty-eight percent of the infants were small for gestational age. Neonatal complications occurred in 27%. In a report of 23 children followed up to 4 years, postnatal development was said to be normal. More information on cyclosporine use in pregnancy is available from Novartis Pharmaceuticals Corporation.

Nursing Mothers: Since Sandimmune® (cyclosporine) is excreted in human milk, nursing should be avoided.

Pediatric Use: Although no adequate and well controlled studies have been conducted in children, patients as young as 6 months of age have received the drug with no unusual adverse effects.

ADVERSE REACTIONS: The principal adverse reactions of Sandimmune® (cyclosporine) therapy are renal dysfunction, tremor, hirsutism, hypertension, and gum hyperplasia.

Hypertension, which is usually mild to moderate, may occur in approximately 50% of patients following renal transplantation and in most cardiac transplant patients.

Glomerular capillary thrombosis has been found in patients treated with cyclosporine and may progress to graft failure. The pathologic changes resemble those seen in the hemolytic-uremic syndrome and include thrombosis of the renal microvasculature, with platelet-fibrin thrombi occluding glomerular capillaries and afferent arterioles, microangiopathic hemolytic anemia, thrombocytopenia, and decreased renal function. Similar findings have been observed when other immunosuppressives have been employed posttransplantation.

Hypomagnesemia has been reported in some, but not all, patients exhibiting convulsions while on cyclosporine therapy. Although magnesium-depletion studies in normal subjects suggest that hypomagnesemia is associated with neurologic disorders, multiple factors, including hypertension, high dose methylprednisolone, hypocholesterolemia, and nephrotoxicity associated with high plasma concentrations of cyclosporine appear to be related to the neurological manifestations of cyclosporine toxicity.

The following reactions occurred in 3% or greater of 892 patients involved in clinical trials of kidney, heart, and liver transplants:

Body System/ Adverse Reactions	Randomized Kidney Patients		All Sandimmune® (cyclosporine) Patients		
	Sandimmune® (N=227) %	Azathioprine (N=228) %	Kidney (N=705) %	Heart (N=112) %	Liver (N=75) %
Genitourinary					
Renal Dysfunction	32	6	25	38	37
Cardiovascular					
Hypertension	26	18	13	53	27
Cramps	4	< 1	2	< 1	0
Skin					
Hirsutism	21	< 1	21	28	45
Acne	6	8	2	2	1
Central Nervous System					
Tremor	12	0	21	31	55
Convulsions	3	1	1	4	5
Headache	2	< 1	2	15	4
Gastrointestinal					
Gum Hyperplasia	4	0	9	5	16
Diarrhea	3	< 1	3	4	8
Nausea/Vomiting	2	< 1	4	10	4
Hepatotoxicity	< 1	< 1	4	7	4
Abdominal Discomfort	< 1	0	< 1	7	0
Autonomic Nervous System					

Paresthesia	3	0	1	2	1
Flushing	< 1	0	4	0	4
Hematopoietic					
Leukopenia	2	19	< 1	6	0
Lymphoma	< 1	0	1	6	1
Respiratory					
Sinusitis	< 1	0	4	3	7
Miscellaneous					
Gynecomastia	< 1	0	< 1	4	3

The following reactions occurred in 2% or less of patients: allergic reactions, anemia, anorexia, confusion, conjunctivitis, edema, fever, brittle fingernails, gastritis, hearing loss, hiccups, hyperglycemia, muscle pain, peptic ulcer, thrombocytopenia, tinnitus.

The following reactions occurred rarely: anxiety, chest pain, constipation, depression, hair breaking, hematuria, joint pain, lethargy, mouth sores, myocardial infarction, night sweats, pancreatitis, pruritus, swallowing difficulty, tingling, upper GI bleeding, visual disturbance, weakness, weight loss.

Reason for Discontinuation	Renal Transplant Patients in Whom Therapy Was Discontinued		
	Randomized Patients		All Sandimmune® Patients
	Sandimmune® (N=227) %	Azathioprine (N=228) %	(N=705) %
Renal Toxicity	5.7	0	5.4
Infection	0	0.4	0.9
Lack of Efficacy	2.6	0.9	1.4
Acute Tubular Necrosis	2.6	0	1.0
Lymphoma/Lymphoproliferative Disease	0.4	0	0.3
Hypertension	0	0	0.3
Hematological Abnormalities	0	0.4	0
Other	0	0	0.7

Sandimmune® (cyclosporine) was discontinued on a temporary basis and then restarted in 18 additional patients.

Infectious Complications in the Randomized Renal Transplant Patients		
	Sandimmune® Treatment (N=227)	Standard Treatment* (N=228)
Complication	% of Complications	% of Complications
Septicemia	5.3	4.8
Abscesses	4.4	5.3
Systemic Fungal Infection	2.2	3.9
Local Fungal Infection	7.5	9.6
Cytomegalovirus	4.8	12.3
Other Viral Infections	15.9	18.4
Urinary Tract Infections	21.1	20.2
Wound and Skin Infections	7.0	10.1
Pneumonia	6.2	9.2

*Some patients also received ALG.

Cremophor® EL (polyoxyethylated castor oil) is known to cause hyperlipemia and electrophoretic abnormalities of lipoproteins. These effects are reversible upon discontinuation of treatment but are usually not a reason to stop treatment.

OVERDOSAGE: There is a minimal experience with overdosage. Because of the slow absorption of Sandimmune® soft gelatin capsules or oral solution, forced emesis would be of value up to 2 hours after administration. Transient hepatotoxicity and nephrotoxicity may occur which should resolve following drug withdrawal. General supportive measures and symptomatic treatment should be followed in all cases of overdosage. Sandimmune® (cyclosporine) is not dialyzable to any great extent, nor is it cleared well by charcoal hemoperfusion. The oral LD₅₀ is 2329 mg/kg in mice, 1480 mg/kg in rats, and > 1000 mg/kg in rabbits. The I.V. LD₅₀ is 148 mg/kg in mice, 104 mg/kg in rats, and 46 mg/kg in rabbits.

DOSAGE AND ADMINISTRATION: Sandimmune® Soft Gelatin Capsules (cyclosporine capsules, USP) and Sandimmune® Oral Solution (cyclosporine oral solution, USP): Sandimmune® soft gelatin capsules (cyclosporine capsules, USP) and Sandimmune® oral solution (cyclosporine oral solution, USP) have decreased bioavailability in comparison to Neoral® soft gelatin capsules (cyclosporine capsules, USP) MODIFIED and Neoral® oral solution (cyclosporine oral solution, USP) MODIFIED. Sandimmune® and Neoral® are not bioequivalent and cannot be used interchangeably without physician supervision.

The initial oral dose of Sandimmune® (cyclosporine) should be given 4-12 hours prior to transplantation as a single dose of 15 mg/kg. Although a daily single dose of 14-18 mg/kg was used in most clinical trials, few centers continue to use the highest dose, most favoring the lower end of the scale. There is a trend towards use of even lower initial doses for renal transplantation in the ranges of 10-14 mg/kg/day. The initial single daily dose is continued postoperatively for 1-2 weeks and then tapered by 5% per week to a maintenance dose of 5-10 mg/kg/day. Some centers have successfully tapered the maintenance dose to as low as 3 mg/kg/day in selected renal transplant patients without an apparent rise in rejection rate.

(See Blood Level Monitoring below)

In pediatric usage, the same dose and dosing regimen may be used as in adults although in several studies children have required and tolerated higher doses than those used in adults.

Adjunct therapy with adrenal corticosteroids is recommended. Different tapering dosage schedules of prednisone appear to achieve similar results. A dosage schedule based on the patient's weight started with 2.0 mg/kg/day for the first 4 days tapered to 1.0 mg/kg/day by 1 week, 0.6 mg/kg/day by 2 weeks, 0.3 mg/kg/day by 1 month, and 0.15 mg/kg/day by 2 months and thereafter as a maintenance dose. Another center started with an initial dose of 200 mg tapered by 40 mg/day until reaching 20 mg/day. After 2 months at this dose, a further reduction to 10 mg/day was made. Adjustments in dosage of prednisone must be made according to the clinical situation.

To make Sandimmune® oral solution (cyclosporine oral solution, USP) more palatable, the oral solution may be diluted with milk, chocolate milk, or orange juice preferably at room temperature. Patients should avoid switching diluents frequently. Sandimmune® soft gelatin capsules and oral solution should be administered on a consistent schedule with regard to time of day and relation to meals.

Take the prescribed amount of Sandimmune® (cyclosporine) from the container using the dosage syringe supplied after removal of the protective cover, and transfer the solution to a glass of milk, chocolate milk, or orange juice. Stir well and drink at once. Do not allow to stand before drinking. It is best to use a glass container and rinse it with more diluent to ensure that the total dose is taken. After use, replace the dosage syringe in the protective cover. Do not rinse the dosage syringe with water or other cleaning agents either before or after use. If the dosage syringe requires cleaning, it must be completely dry before resuming use. Introduction of water into the product by any means will cause variation in dose.

Sandimmune® Injection (cyclosporine injection, USP) FOR INFUSION ONLY

Note: Anaphylactic reactions have occurred with Sandimmune® injection (cyclosporine injection, USP). (See *WARNINGS*)

Patients unable to take Sandimmune® soft gelatin capsules or oral solution pre- or postoperatively may be treated with the I.V. concentrate. **Sandimmune® Injection (cyclosporine injection, USP) is administered at 1/3 the oral dose.** The initial dose of Sandimmune® injection (cyclosporine injection, USP) should be given 4-12 hours prior to transplantation as a single I.V. dose of 5-6 mg/kg/day. This daily single dose is continued postoperatively until the patient can tolerate the soft gelatin capsules or oral solution. Patients should be switched to Sandimmune® soft gelatin capsules or oral solution as soon as possible after surgery. In pediatric usage, the same dose and dosing regimen may be used, although higher doses may be required.

Adjunct steroid therapy is to be used. (See *aforementioned*)

Immediately before use, the I.V. concentrate should be diluted 1 mL Sandimmune® injection (cyclosporine injection, USP) in 20 mL-100 mL 0.9% Sodium Chloride Injection or 5% Dextrose Injection and given in a slow intravenous infusion over approximately 2-6 hours.

Diluted infusion solutions should be discarded after 24 hours.

The Cremophor[®] EL (polyoxyethylated castor oil) contained in the concentrate for intravenous infusion can cause phthalate stripping from PVC.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Blood Level Monitoring: Several study centers have found blood level monitoring of cyclosporine useful in patient management. While no fixed relationships have yet been established, in one series of 375 consecutive cadaveric renal transplant recipients, dosage was adjusted to achieve specific whole blood 24-hour trough levels of 100-200 ng/mL as determined by high-pressure liquid chromatography (HPLC).

Of major importance to blood level analysis is the type of assay used. The above levels are specific to the parent cyclosporine molecule and correlate directly to the new monoclonal specific radioimmunoassays (mRIA-sp). Nonspecific assays are also available which detect the parent compound molecule and various of its metabolites. Older studies often cited levels using a nonspecific assay which were roughly twice those of specific assays. Assay results are not interchangeable and their use should be guided by their approved labeling. If plasma specimens are employed, levels will vary with the temperature at the time of separation from whole blood. Plasma levels may range from 1/2-1/5 of whole blood levels. Refer to individual assay labeling for complete instructions. In addition, *Transplantation Proceedings* (June 1990) contains position papers and a broad consensus generated at the Cyclosporine-Therapeutic Drug Monitoring conference that year. Blood level monitoring is not a replacement for renal function monitoring or tissue biopsies.

HOW SUPPLIED: Sandimmune[®] Soft Gelatin Capsules (cyclosporine capsules, USP)

25 mg: Oblong, pink, branded “ 78/240”. Unit dose packages of 30 capsules, 3 blister cards of 10 capsules (NDC 0078-0240-15).

100 mg: Oblong, dusty rose, branded “ 78/241”. Unit dose packages of 30 capsules, 3 blister cards of 10 capsules (NDC 0078-0241-15).

Store and Dispense: Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). [See USP Controlled Room Temperature] An odor may be detected upon opening the unit dose container, which will dissipate shortly thereafter. This odor does not affect the quality of the product.

Sandimmune[®] Oral Solution (cyclosporine oral solution, USP): Supplied in 50 mL bottles containing 100 mg of cyclosporine per mL (NDC 0078-0110-22). A dosage syringe is provided for dispensing.

Store and Dispense: In the original container at temperatures below 86°F (30°C). Do not store in the refrigerator. Protect from freezing. Once opened, the contents must be used within 2 months.

**Sandimmune® Injection (cyclosporine injection, USP)
FOR INTRAVENOUS INFUSION**

Supplied as a 5 mL sterile ampul containing 50 mg of cyclosporine per mL, in boxes of 10 ampuls (NDC 0078-0109-01).

Store and Dispense: At temperatures below 86°F (30°C) and protected from light.

Sandimmune® Soft Gelatin Capsules (cyclosporine capsules, USP)

Manufactured by
R.P. Scherer GmbH, EBERBACH/BADEN, GERMANY

Manufactured for
Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936

**Sandimmune® Oral Solution (cyclosporine oral solution, USP) and
Sandimmune® Injection (cyclosporine injection, USP)
FOR INFUSION ONLY**

Manufactured by
NOVARTIS PHARMA AG, Basle, Switzerland

Manufactured for
Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

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Active Ingredient Search Results from "Rx" table for query on "tacrolimus."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
050708		No	TACROLIMUS	Capsule; Oral	EQ 0.5MG BASE	PROGRAF	FUJISAWA HLTHCARE
050708		No	TACROLIMUS	Capsule; Oral	EQ 1MG BASE	PROGRAF	FUJISAWA HLTHCARE
050708		Yes	TACROLIMUS	Capsule; Oral	EQ 5MG BASE	PROGRAF	FUJISAWA HLTHCARE
050709		Yes	TACROLIMUS	Injectable; Injection	EQ 5MG BASE/ML	PROGRAF	FUJISAWA HLTHCARE
050777		No	TACROLIMUS	Ointment; Topical	0.03%	PROTOPIC	FUJISAWA HLTHCARE
050777		Yes	TACROLIMUS	Ointment; Topical	0.1%	PROTOPIC	FUJISAWA HLTHCARE

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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

PROPOSED PACKAGE INSERT

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.

20

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.

44

PROPOSED PACKAGE INSERT

45 The chemical structure of tacrolimus is:

46

47

48

49

50

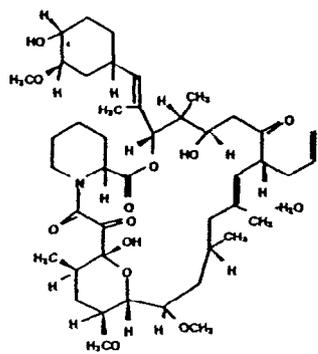
51

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55



56 Tacrolimus has an empirical formula of

57 $C_{44}H_{69}NO_{12} \cdot H_2O$ 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.

62

63

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.

PROPOSED PACKAGE INSERT

78
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.)

PROPOSED PACKAGE INSERT

103
104

Population	N	Route (Dose)	Parameters					
			C _{max} (ng/mL)	T _{max} (hr)	AUC (ng•hr/mL)	t _{1/2} (hr)	Cl (L/hr/kg)	V (L/kg)
Healthy Volunteers	8	IV (0.025 mg/kg/4hr)	--	--	598* • 125	34.2 • 7.7	0.040 • 0.009	1.91 • 0.31
	16	PO (5 mg)	29.7 • 7.2	1.6 • 0.7	243** • 73	34.8 • 11.4	0.041• • 0.008	1.94• • 0.53
Kidney Transplant Pts	26	IV (0.02 mg/kg/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	#	#	#

105
106
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114
115

- 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

PROPOSED PACKAGE INSERT

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

121

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• 10% in adult kidney
127 transplant patients (N=26), 22• 6% in adult liver
128 transplant patients (N=17), and 18• 5% 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.

PROPOSED PACKAGE INSERT

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149

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.

155

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.

162

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

164

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.

171

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.

175

PROPOSED PACKAGE INSERT

176

177

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.

PROPOSED PACKAGE INSERT

206

207

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.

PROPOSED PACKAGE INSERT

234

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**).

254

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.

PROPOSED PACKAGE INSERT

260

Population (No. of Patients)	Dose	AUC ₀₋₄ (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.

PROPOSED PACKAGE INSERT

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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301

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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331

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 (≤ 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 \leq 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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439

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%)

444

445

446

447

* 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.

470

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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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499

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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557
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*).

586

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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.

644

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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 <u>Channel Blockers</u>	<u>Agents</u>	<u>Antibiotics</u>
686 diltiazem	clotrimazole	clarithromycin
687 nifedipine	fluconazole	erythromycin
688 nifedipine	itraconazole	troleanomycin
689 verapamil	ketoconazole	

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

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:*

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

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 embryoletality and with adverse effects on
805 female reproduction. Effects on female
806 reproductive function (parturition) and
807 embryoletal 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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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>			
64	60	37	26
56	46	48	32
64	68	32	23
40	30	17	17
<u>Gastrointestinal</u>			
72	47	37	27
46	37	32	27
24	27	23	21
36	30	6	5
34	24	7	5
27	15	14	11
<u>Cardiovascular</u>			
47	56	38	43
<u>Urogenital</u>			
40	27	36	23
39	25	24	19
30	22	12	9
16	18	21	19
18	15	19	12
<u>Metabolic and Nutritional</u>			
45	26	13	9
29	34	13	16
47	38	33	22
48	45	16	9

PROPOSED PACKAGE INSERT

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 ***Kidney Transplantation***
 984 The most common adverse reactions reported
 985 were infection, tremor, hypertension, decreased
 986 renal function, constipation, diarrhea, headache,
 987 abdominal pain and insomnia.

PROPOSED PACKAGE INSERT

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)
1001			
1002			
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

PROPOSED PACKAGE INSERT

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

PROPOSED PACKAGE INSERT

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

PROPOSED PACKAGE INSERT

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.

PROPOSED PACKAGE INSERT

1142

1143

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 overdosages 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 overdosage.

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

PROPOSED PACKAGE INSERT

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 pII 9 or greater (e.g., ganciclovir or acyclovir).

PROPOSED PACKAGE INSERT

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

1246

1247

1248

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1257

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

PROPOSED PACKAGE INSERT

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.

PROPOSED PACKAGE INSERT

1289

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1291

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1294

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

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

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1306

Pediatric Patients

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

PROPOSED PACKAGE INSERT

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 -20° 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.

PROPOSED PACKAGE INSERT

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 IMx[®], 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 " 607" 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.

PROPOSED PACKAGE INSERT

1419

1420

1421 **Prograf capsules (tacrolimus capsules)**

1422 **1 mg**

1423 Oblong, white, branded with red "1 mg" on the

1424 capsule cap and "  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 "  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 15°C-30°C (59°F-86°F) [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).

PROPOSED PACKAGE INSERT

1450
1451
1452 *Store and Dispense*
1453 Store between 5• C and 25• C (41• F and 77• F).
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.

PROPOSED PACKAGE INSERT

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 team 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

1623 • **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

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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

1738 **For Kidney Transplant Patients:**

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

1763 **For Liver Transplant Patients:**

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

Active Ingredient Search Results from "Rx" table for query on "mycophenolate."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
050722		Yes	MYCOPHENOLATE MOFETIL	Capsule; Oral	250MG	CELLCEPT	ROCHE PALO
050759		Yes	MYCOPHENOLATE MOFETIL	Suspension; Oral	200MG/ML	CELLCEPT	ROCHE PALO
050723		Yes	MYCOPHENOLATE MOFETIL	Tablet; Oral	500MG	CELLCEPT	ROCHE PALO
050758		Yes	MYCOPHENOLATE MOFETIL HYDROCHLORIDE	Injectable; Injection	500MG/VIAL	CELLCEPT	ROCHE PALO

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CellCept®
 (mycophenolate mofetil capsules)
 (mycophenolate mofetil tablets)

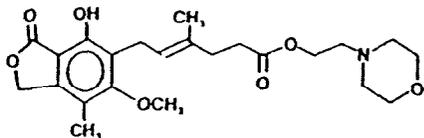
CellCept® Oral Suspension
 (mycophenolate mofetil for oral suspension)

CellCept® Intravenous
 (mycophenolate mofetil hydrochloride for injection)

WARNING: Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of renal, cardiac or hepatic transplant patients should use CellCept. 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: CellCept (mycophenolate mofetil) is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an immunosuppressive agent; inosine monophosphate dehydrogenase (IMPDH) inhibitor.

The chemical name for mycophenolate mofetil (MMF) is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuran-4-yl)-4-methyl-4-hexenoate. It has an empirical formula of $C_{23}H_{31}NO_7$, a molecular weight of 433.50, and the following structural formula:



Mycophenolate mofetil is a white to off-white crystalline powder. It is slightly soluble in water (43 $\mu\text{g/mL}$ at pH 7.4); the solubility increases in acidic medium (4.27 mg/mL at pH 3.6). It is freely soluble in acetone, soluble in methanol, and sparingly soluble in ethanol. The apparent partition coefficient in 1-octanol/water (pH 7.4) buffer solution is 238. The pKa values for mycophenolate mofetil are 5.6 for the morpholino group and 8.5 for the phenolic group.

Mycophenolate mofetil hydrochloride has a solubility of 65.8 mg/mL in 5% Dextrose Injection USP (D5W). The pH of the reconstituted solution is 2.4 to 4.1.

CellCept® (mycophenolate mofetil)

CellCept is available for oral administration as capsules containing 250 mg of mycophenolate mofetil, tablets containing 500 mg of mycophenolate mofetil, and as a powder for oral suspension, which when constituted contains 200 mg/mL mycophenolate mofetil.

Inactive ingredients in CellCept 250 mg capsules include croscarmellose sodium, magnesium stearate, povidone (K-90) and pregelatinized starch. The capsule shells contain black iron oxide, FD&C blue #2, gelatin, red iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide.

Inactive ingredients in CellCept 500 mg tablets include black iron oxide, croscarmellose sodium, FD&C blue #2 aluminum lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, povidone (K-90), red iron oxide, talc, and titanium dioxide; may also contain ammonium hydroxide, ethyl alcohol, methyl alcohol, n-butyl alcohol, propylene glycol, and shellac.

Inactive ingredients in CellCept Oral Suspension include aspartame, citric acid anhydrous, colloidal silicon dioxide, methylparaben, mixed fruit flavor, sodium citrate dihydrate, sorbitol, soybean lecithin, and xanthan gum.

CellCept Intravenous is the hydrochloride salt of mycophenolate mofetil. The chemical name for the hydrochloride salt of mycophenolate mofetil is 2-morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate hydrochloride. It has an empirical formula of $C_{23}H_{31}NO_7$ HCl and a molecular weight of 469.96.

CellCept Intravenous is available as a sterile white to off-white lyophilized powder in vials containing mycophenolate mofetil hydrochloride for administration by intravenous infusion only. Each vial of CellCept Intravenous contains the equivalent of 500 mg mycophenolate mofetil as the hydrochloride salt. The inactive ingredients are polysorbate 80, 25 mg, and citric acid, 5 mg. Sodium hydroxide may have been used in the manufacture of CellCept Intravenous to adjust the pH. Reconstitution and dilution with 5% Dextrose Injection USP yields a slightly yellow solution of mycophenolate mofetil, 6 mg/mL. (For detailed method of preparation, see DOSAGE AND ADMINISTRATION.)

CLINICAL PHARMACOLOGY:

Mechanism of Action: Mycophenolate mofetil has been demonstrated in experimental animal models to prolong the survival of allogeneic transplants (kidney, heart, liver, intestine, limb, small bowel, pancreatic islets, and bone marrow).

Mycophenolate mofetil has also been shown to reverse ongoing acute rejection in the canine renal and rat cardiac allograft models. Mycophenolate mofetil also inhibited proliferative arteriopathy in experimental models of aortic and cardiac allografts in rats, as well as in primate cardiac xenografts. Mycophenolate mofetil was used alone or in combination with other immunosuppressive agents in these studies. Mycophenolate mofetil has been demonstrated to inhibit immunologically mediated inflammatory responses in animal models and to inhibit tumor development and prolong survival in murine tumor transplant models.

CellCept® (mycophenolate mofetil)

Mycophenolate mofetil is rapidly absorbed following oral administration and hydrolyzed to form MPA, which is the active metabolite. MPA is a potent, selective, uncompetitive, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), and therefore inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on de novo synthesis of purines, whereas other cell types can utilize salvage pathways, MPA has potent cytostatic effects on lymphocytes. MPA inhibits proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific stimulation. Addition of guanosine or deoxyguanosine reverses the cytostatic effects of MPA on lymphocytes. MPA also suppresses antibody formation by B-lymphocytes. MPA prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in intercellular adhesion to endothelial cells and may inhibit recruitment of leukocytes into sites of inflammation and graft rejection. Mycophenolate mofetil did not inhibit early events in the activation of human peripheral blood mononuclear cells, such as the production of interleukin-1 (IL-1) and interleukin-2 (IL-2), but did block the coupling of these events to DNA synthesis and proliferation.

Pharmacokinetics: Following oral and intravenous administration, mycophenolate mofetil undergoes rapid and complete metabolism to MPA, the active metabolite. Oral absorption of the drug is rapid and essentially complete. MPA is metabolized to form the phenolic glucuronide of MPA (MPAG) which is not pharmacologically active. The parent drug, mycophenolate mofetil, can be measured systemically during the intravenous infusion; however, shortly (about 5 minutes) after the infusion is stopped or after oral administration, MMF concentration is below the limit of quantitation (0.4 µg/mL).

Absorption: In 12 healthy volunteers, the mean absolute bioavailability of oral mycophenolate mofetil relative to intravenous mycophenolate mofetil (based on MPA AUC) was 94%. The area under the plasma-concentration time curve (AUC) for MPA appears to increase in a dose-proportional fashion in renal transplant patients receiving multiple doses of mycophenolate mofetil up to a daily dose of 3 g (see table below on pharmacokinetic parameters).

Food (27 g fat, 650 calories) had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil when administered at doses of 1.5 g bid to renal transplant patients. However, MPA C_{max} was decreased by 40% in the presence of food (see DOSAGE AND ADMINISTRATION).

Distribution: The mean (\pm SD) apparent volume of distribution of MPA in 12 healthy volunteers is approximately 3.6 (\pm 1.5) and 4.0 (\pm 1.2) L/kg following intravenous and oral administration, respectively. MPA, at clinically relevant concentrations, is 97% bound to plasma albumin. MPAG is 82% bound to plasma albumin at MPAG concentration ranges that are normally seen in stable renal transplant patients; however, at higher MPAG concentrations (observed in patients with renal impairment or delayed renal graft function), the binding of MPA may be reduced as a result of competition between MPAG and MPA for protein binding. Mean blood to plasma ratio of radioactivity concentrations was approximately 0.6 indicating that MPA and MPAG do not extensively distribute into the cellular fractions of blood.

CellCept® (mycophenolate mofetil)

In vitro studies to evaluate the effect of other agents on the binding of MPA to human serum albumin (HSA) or plasma proteins showed that salicylate (at 25 mg/dL with HSA) and MPAG (at ≥ 460 $\mu\text{g/mL}$ with plasma proteins) increased the free fraction of MPA. At concentrations that exceeded what is encountered clinically, cyclosporine, digoxin, naproxen, prednisone, propranolol, tacrolimus, theophylline, tolbutamide, and warfarin did not increase the free fraction of MPA. MPA at concentrations as high as 100 $\mu\text{g/mL}$ had little effect on the binding of warfarin, digoxin or propranolol, but decreased the binding of theophylline from 53% to 45% and phenytoin from 90% to 87%.

Metabolism: Following oral and intravenous dosing, mycophenolate mofetil undergoes complete metabolism to MPA, the active metabolite. Metabolism to MPA occurs presystemically after oral dosing. MPA is metabolized principally by glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG) which is not pharmacologically active. In vivo, MPAG is converted to MPA via enterohepatic recirculation. The following metabolites of the 2-hydroxyethyl-morpholino moiety are also recovered in the urine following oral administration of mycophenolate mofetil to healthy subjects: N-(2-carboxymethyl)-morpholine, N-(2-hydroxyethyl)-morpholine, and the N-oxide of N-(2-hydroxyethyl)-morpholine.

Secondary peaks in the plasma MPA concentration-time profile are usually observed 6 to 12 hours postdose. The coadministration of cholestyramine (4 g tid) resulted in approximately a 40% decrease in the MPA AUC (largely as a consequence of lower concentrations in the terminal portion of the profile). These observations suggest that enterohepatic recirculation contributes to MPA plasma concentrations.

Increased plasma concentrations of mycophenolate mofetil metabolites (MPA 50% increase and MPAG about a 3-fold to 6-fold increase) are observed in patients with renal insufficiency (see CLINICAL PHARMACOLOGY: *Special Populations*).

Excretion: Negligible amount of drug is excreted as MPA (<1% of dose) in the urine. Orally administered radiolabeled mycophenolate mofetil resulted in complete recovery of the administered dose, with 93% of the administered dose recovered in the urine and 6% recovered in feces. Most (about 87%) of the administered dose is excreted in the urine as MPAG. At clinically encountered concentrations, MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 $\mu\text{g/mL}$), small amounts of MPAG are removed. Bile acid sequestrants, such as cholestyramine, reduce MPA AUC by interfering with enterohepatic circulation of the drug (see OVERDOSAGE).

Mean (\pm SD) apparent half-life and plasma clearance of MPA are 17.9 (\pm 6.5) hours and 193 (\pm 48) mL/min following oral administration and 16.6 (\pm 5.8) hours and 177 (\pm 31) mL/min following intravenous administration, respectively.

Pharmacokinetics in Healthy Volunteers, Renal, Cardiac, and Hepatic Transplant Patients: Shown below are the mean (\pm SD) pharmacokinetic parameters for MPA following the administration of mycophenolate mofetil given as single doses to healthy volunteers and multiple doses to renal, cardiac, and hepatic transplant patients. In the early posttransplant period (<40

CellCept® (mycophenolate mofetil)

days posttransplant), renal, cardiac, and hepatic transplant patients had mean MPA AUCs approximately 20% to 41% lower and mean C_{max} approximately 32% to 44% lower compared to the late transplant period (3 to 6 months posttransplant).

Mean MPA AUC values following administration of 1 g bid intravenous mycophenolate mofetil over 2 hours to renal transplant patients for 5 days were about 24% higher than those observed after oral administration of a similar dose in the immediate posttransplant phase. In hepatic transplant patients, administration of 1 g bid intravenous CellCept followed by 1.5 g bid oral CellCept resulted in mean MPA AUC values similar to those found in renal transplant patients administered 1 g CellCept bid.

Pharmacokinetic Parameters for MPA [mean (\pm SD)] Following Administration of Mycophenolate Mofetil to Healthy Volunteers (Single Dose), Renal, Cardiac, and Hepatic Transplant Patients (Multiple Doses)

	Dose/Route	T_{max} (h)	C_{max} (μ g/mL)	Total AUC (μ g·h/mL)
Healthy Volunteers (single dose)	1 g/oral	0.80 (\pm 0.36) (n=129)	24.5 (\pm 9.5) (n=129)	63.9 (\pm 16.2) (n=117)
Renal Transplant Patients (bid dosing) Time After Transplantation	Dose/Route	T_{max} (h)	C_{max} (μg/mL)	Interdosing Interval AUC(0-12h) (μg·h/mL)
5 days	1 g/iv	1.58 (\pm 0.46) (n=31)	12.0 (\pm 3.82) (n=31)	40.8 (\pm 11.4) (n=31)
6 days	1 g/oral	1.33 (\pm 1.05) (n=31)	10.7 (\pm 4.83) (n=31)	32.9 (\pm 15.0) (n=31)
Early (<40 days)	1 g/oral	1.31 (\pm 0.76) (n=25)	8.16 (\pm 4.50) (n=25)	27.3 (\pm 10.9) (n=25)
Early (<40 days)	1.5 g/oral	1.21 (\pm 0.81) (n=27)	13.5 (\pm 8.18) (n=27)	38.4 (\pm 15.4) (n=27)
Late (>3 months)	1.5 g/oral	0.90 (\pm 0.24) (n=23)	24.1 (\pm 12.1) (n=23)	65.3 (\pm 35.4) (n=23)
Cardiac Transplant Patients (bid dosing) Time After Transplantation	Dose/Route	T_{max} (h)	C_{max} (μg/mL)	Interdosing Interval AUC(0-12h) (μg·h/mL)

CellCept® (mycophenolate mofetil)

Early (Day before discharge)	1.5 g/oral	1.8 (±1.3) (n=11)	11.5 (±6.8) (n=11)	43.3 (±20.8) (n=9)
Late (>6 months)	1.5 g/oral	1.1 (±0.7) (n=52)	20.0 (±9.4) (n=52)	54.1* (±20.4) (n=49)
Hepatic Transplant Patients (bid dosing) Time After Transplantation	Dose/Route	T_{max} (h)	C_{max} (µg/mL)	Interdosing Interval AUC(0-12h) (µg·h/mL)
4 to 9 days	1 g/iv	1.50 (±0.517) (n=22)	17.0 (±12.7) (n=22)	34.0 (±17.4) (n=22)
Early (5 to 8 days)	1.5 g/oral	1.15 (±0.432) (n=20)	13.1 (±6.76) (n=20)	29.2 (±11.9) (n=20)
Late (>6 months)	1.5 g/oral	1.54 (±0.51) (n=6)	19.3 (±11.7) (n=6)	49.3 (±14.8) (n=6)

* AUC(0-12h) values quoted are extrapolated from data from samples collected over 4 hours.

Two 500 mg tablets have been shown to be bioequivalent to four 250 mg capsules. Five mL of the 200 mg/mL constituted oral suspension have been shown to be bioequivalent to four 250 mg capsules.

Special Populations: Shown below are the mean (±SD) pharmacokinetic parameters for MPA following the administration of oral mycophenolate mofetil given as single doses to non-transplant subjects with renal or hepatic impairment.

CellCept® (mycophenolate mofetil)

Pharmacokinetic Parameters for MPA [mean (\pm SD)] Following Single Doses of Mycophenolate Mofetil Capsules in Chronic Renal and Hepatic Impairment

Renal Impairment (no. of patients)	Dose	T _{max} (h)	C _{max} (μ g/mL)	AUC(0-96h) (μ g•h/mL)
Healthy Volunteers GFR >80 mL/min/1.73 m ² (n=6)	1 g	0.75 (\pm 0.27)	25.3 (\pm 7.99)	45.0 (\pm 22.6)
Mild Renal Impairment GFR 50 to 80 mL/min/1.73 m ² (n=6)	1 g	0.75 (\pm 0.27)	26.0 (\pm 3.82)	59.9 (\pm 12.9)
Moderate Renal Impairment GFR 25 to 49 mL/min/1.73 m ² (n=6)	1 g	0.75 (\pm 0.27)	19.0 (\pm 13.2)	52.9 (\pm 25.5)
Severe Renal Impairment GFR <25 mL/min/1.73 m ² (n=7)	1 g	1.00 (\pm 0.41)	16.3 (\pm 10.8)	78.6 (\pm 46.4)
Hepatic Impairment (no. of patients)	Dose	T _{max} (h)	C _{max} (μ g/mL)	AUC(0-48h) (μ g•h/mL)
Healthy Volunteers (n=6)	1 g	0.63 (\pm 0.14)	24.3 (\pm 5.73)	29.0 (\pm 5.78)
Alcoholic Cirrhosis (n=18)	1 g	0.85 (\pm 0.58)	22.4 (\pm 10.1)	29.8 (\pm 10.7)

Renal Insufficiency: In a single-dose study, MMF was administered as capsule or intravenous infusion over 40 minutes. Plasma MPA AUC observed after oral dosing to volunteers with severe chronic renal impairment [glomerular filtration rate (GFR) <25 mL/min/1.73 m²] was about 75% higher relative to that observed in healthy volunteers (GFR >80 mL/min/1.73 m²). In addition, the single-dose plasma MPAG AUC was 3-fold to 6-fold higher in volunteers with severe renal impairment than in volunteers with mild renal impairment or healthy volunteers, consistent with the known renal elimination of MPAG. No data are available on the safety of long-term exposure to this level of MPAG.

Plasma MPA AUC observed after single-dose (1 g) intravenous dosing to volunteers (n=4) with severe chronic renal impairment (GFR <25 mL/min/1.73 m²) was 62.4 μ g•h/mL (\pm 19.3). Multiple dosing of mycophenolate mofetil in patients with severe chronic renal impairment has not been studied (see PRECAUTIONS: *General* and DOSAGE AND ADMINISTRATION).

In patients with delayed renal graft function posttransplant, mean MPA AUC(0-12h) was comparable to that seen in posttransplant patients without delayed renal graft function. There is a potential for a transient increase in the free fraction and concentration of plasma MPA in patients with delayed renal graft function. However, dose adjustment does not appear to be necessary in patients with delayed renal graft function. Mean plasma MPAG AUC(0-12h) was 2-fold to 3-fold higher than in posttransplant patients without delayed renal graft function (see PRECAUTIONS: *General* and DOSAGE AND ADMINISTRATION).

CellCept® (mycophenolate mofetil)

In 8 patients with primary graft non-function following renal transplantation, plasma concentrations of MPAG accumulated about 6-fold to 8-fold after multiple dosing for 28 days. Accumulation of MPA was about 1-fold to 2-fold.

The pharmacokinetics of mycophenolate mofetil are not altered by hemodialysis. Hemodialysis usually does not remove MPA or MPAG. At high concentrations of MPAG (>100 µg/mL), hemodialysis removes only small amounts of MPAG.

Hepatic Insufficiency: In a single-dose (1 g oral) study of 18 volunteers with alcoholic cirrhosis and 6 healthy volunteers, hepatic MPA glucuronidation processes appeared to be relatively unaffected by hepatic parenchymal disease when pharmacokinetic parameters of healthy volunteers and alcoholic cirrhosis patients within this study were compared. However, it should be noted that for unexplained reasons, the healthy volunteers in this study had about a 50% lower AUC as compared to healthy volunteers in other studies, thus making comparisons between volunteers with alcoholic cirrhosis and healthy volunteers difficult. Effects of hepatic disease on this process probably depend on the particular disease. Hepatic disease with other etiologies, such as primary biliary cirrhosis, may show a different effect. In a single-dose (1 g intravenous) study of 6 volunteers with severe hepatic impairment (aminopyrine breath test less than 0.2% of dose) due to alcoholic cirrhosis, MMF was rapidly converted to MPA. MPA AUC was 44.1 µg·h/mL (±15.5).

Pediatrics: The pharmacokinetic parameters of MPA and MPAG have been evaluated in 55 pediatric patients (ranging from 1 year to 18 years of age) receiving CellCept oral suspension at a dose of 600 mg/m² bid (up to a maximum of 1 g bid) after allogeneic renal transplantation. The pharmacokinetic data for MPA is provided in the following table:

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Mean (±SD) Computed Pharmacokinetic Parameters for MPA by Age and Time After Allogeneic Renal Transplantation

Age Group (n)	Time	T _{max} (h)	Dose Adjusted ^a C _{max} (µg/mL)	Dose Adjusted ^a AUC ₀₋₁₂ (µg·h/mL)
1 to <2 yr (6) ^d	Early (Day 7)	3.03 (4.70)	10.3 (5.80)	22.5 (6.66)
1 to <6 yr (17)		1.63 (2.85)	13.2 (7.16)	27.4 (9.54)
6 to <12 yr (16)		0.940 (0.546)	13.1 (6.30)	33.2 (12.1)
12 to 18 yr (21)		1.16 (0.830)	11.7 (10.7)	26.3 (9.14) ^b
1 to <2 yr (4) ^d	Late (Month 3)	0.725 (0.276)	23.8 (13.4)	47.4 (14.7)
1 to <6 yr (15)		0.989 (0.511)	22.7 (10.1)	49.7 (18.2)
6 to <12 yr (14)		1.21 (0.532)	27.8 (14.3)	61.9 (19.6)
12 to 18 yr (17)		0.978 (0.484)	17.9 (9.57)	53.6 (20.3) ^c
1 to <2 yr (4) ^d	Late (Month 9)	0.604 (0.208)	25.6 (4.25)	55.8 (11.6)
1 to <6 yr (12)		0.869 (0.479)	30.4 (9.16)	61.0 (10.7)
6 to <12 yr (11)		1.12 (0.462)	29.2 (12.6)	66.8 (21.2)
12 to 18 yr (14)		1.09 (0.518)	18.1 (7.29)	56.7 (14.0)

^a adjusted to a dose of 600 mg/m²^b n=20^c n=16^d a subset of 1 to <6 yr

The CellCept oral suspension dose of 600 mg/m² bid (up to a maximum of 1 g bid) achieved mean MPA AUC values in pediatric patients similar to those seen in adult renal transplant patients receiving CellCept capsules at a dose of 1 g bid in the early posttransplant period. There was wide variability in the data. As observed in adults, early posttransplant MPA AUC values were approximately 45% to 53% lower than those observed in the later posttransplant period (>3 months). MPA AUC values were similar in the early and late posttransplant period across the 1 year to 18 year age range.

Gender: Data obtained from several studies were pooled to look at any gender-related differences in the pharmacokinetics of MPA (data were adjusted to 1 g oral dose). Mean (±SD) MPA AUC(0-12h) for males (n=79) was 32.0 (±14.5) and for females (n=41) was 36.5 (±18.8) µg·h/mL while mean (±SD) MPA C_{max} was 9.96 (±6.19) in the males and 10.6 (±5.64) µg/mL in the females. These differences are not of clinical significance.

Geriatrics: Pharmacokinetics in the elderly have not been studied.

CLINICAL STUDIES: The safety and efficacy of CellCept in combination with corticosteroids and cyclosporine for the prevention of organ rejection were assessed in randomized, double-

CellCept® (mycophenolate mofetil)

blind, multicenter trials in renal (3 trials), in cardiac (1 trial), and in hepatic (1 trial) adult transplant patients.

Renal Transplant: The three renal studies compared two dose levels of oral CellCept (1 g bid and 1.5 g bid) with azathioprine (2 studies) or placebo (1 study) when administered in combination with cyclosporine (Sandimmune®*) and corticosteroids to prevent acute rejection episodes. One study also included antithymocyte globulin (ATGAM®†) induction therapy. These studies are described by geographic location of the investigational sites. One study was conducted in the USA at 14 sites, one study was conducted in Europe at 20 sites, and one study was conducted in Europe, Canada, and Australia at a total of 21 sites.

The primary efficacy endpoint was the proportion of patients in each treatment group who experienced treatment failure within the first 6 months after transplantation (defined as biopsy-proven acute rejection on treatment or the occurrence of death, graft loss or early termination from the study for any reason without prior biopsy-proven rejection). CellCept, when administered with antithymocyte globulin (ATGAM®) induction (one study) and with cyclosporine and corticosteroids (all three studies), was compared to the following three therapeutic regimens: (1) antithymocyte globulin (ATGAM®) induction/azathioprine/cyclosporine/corticosteroids, (2) azathioprine/cyclosporine/corticosteroids, and (3) cyclosporine/corticosteroids.

CellCept, in combination with corticosteroids and cyclosporine reduced (statistically significant at 0.05 level) the incidence of treatment failure within the first 6 months following transplantation. The following tables summarize the results of these studies. These tables show (1) the proportion of patients experiencing treatment failure, (2) the proportion of patients who experienced biopsy-proven acute rejection on treatment, and (3) early termination, for any reason other than graft loss or death, without a prior biopsy-proven acute rejection episode. Patients who prematurely discontinued treatment were followed for the occurrence of death or graft loss, and the cumulative incidence of graft loss and patient death are summarized separately. Patients who prematurely discontinued treatment were not followed for the occurrence of acute rejection after termination. More patients receiving CellCept discontinued without prior biopsy-proven rejection, death or graft loss than discontinued in the control groups, with the highest rate in the CellCept 3 g/day group. Therefore, the acute rejection rates may be underestimates, particularly in the CellCept 3 g/day group.

* Sandimmune is a registered trademark of Novartis Pharmaceuticals Corporation.

† ATGAM is a registered trademark of Pharmacia and Upjohn Company.

CellCept® (mycophenolate mofetil)

**Renal Transplant Studies
Incidence of Treatment Failure
(Biopsy-proven Rejection or Early Termination for Any Reason)**

USA Study† (N=499 patients)	CellCept 2 g/day (n=167 patients)	CellCept 3 g/day (n=166 patients)	Azathioprine 1 to 2 mg/kg/day (n=166 patients)
All treatment failures	31.1%	31.3%	47.6%
Early termination without prior acute rejection*	9.6%	12.7%	6.0%
Biopsy-proven rejection episode on treatment	19.8%	17.5%	38.0%
Europe/Canada/ Australia Study‡ (N=503 patients)	CellCept 2 g/day (n=173 patients)	CellCept 3 g/day (n=164 patients)	Azathioprine 100 to 150 mg/day (n=166 patients)
All treatment failures	38.2%	34.8%	50.0%
Early termination without prior acute rejection*	13.9%	15.2%	10.2%
Biopsy-proven rejection episode on treatment	19.7%	15.9%	35.5%
Europe Study§ (N=491 patients)	CellCept 2 g/day (n=165 patients)	CellCept 3 g/day (n=160 patients)	Placebo (n=166 patients)
All treatment failures	30.3%	38.8%	56.0%
Early termination without prior acute rejection*	11.5%	22.5%	7.2%
Biopsy-proven rejection episode on treatment	17.0%	13.8%	46.4%

*Does not include death and graft loss as reason for early termination.

†Antithymocyte globulin induction/MMF or azathioprine/cyclosporine/corticosteroids.

‡MMF or azathioprine/cyclosporine/corticosteroids.

§MMF or placebo/cyclosporine/corticosteroids.

The cumulative incidence of 12-month graft loss or patient death is presented below. No advantage of CellCept with respect to graft loss or patient death was established. Numerically, patients receiving CellCept 2 g/day and 3 g/day experienced a better outcome than controls in all three studies; patients receiving CellCept 2 g/day experienced a better outcome than CellCept 3 g/day in two of the three studies. Patients in all treatment groups who terminated treatment early were found to have a poor outcome with respect to graft loss or patient death at 1 year.

CellCept® (mycophenolate mofetil)

Renal Transplant Studies
Cumulative Incidence of Combined Graft Loss or Patient Death at 12 Months

Study	CellCept 2 g/day	CellCept 3 g/day	Control (Azathioprine or Placebo)
USA	8.5%	11.5%	12.2%
Europe/Canada/Australia	11.7%	11.0%	13.6%
Europe	8.5%	10.0%	11.5%

Pediatrics: One open-label, safety and pharmacokinetic study of CellCept oral suspension 600 mg/m² bid (up to 1 g bid) in combination with cyclosporine and corticosteroids was performed at centers in the US (9), Europe (5) and Australia (1) in 100 pediatric patients (3 months to 18 years of age) for the prevention of renal allograft rejection. CellCept was well tolerated in pediatric patients (see ADVERSE REACTIONS), and the pharmacokinetics profile was similar to that seen in adult patients dosed with 1 g bid CellCept capsules (see CLINICAL

PHARMACOLOGY: *Pharmacokinetics*). The rate of biopsy-proven rejection was similar across the age groups (3 months to <6 years, 6 years to <12 years, 12 years to 18 years). The overall biopsy-proven rejection rate at 6 months was comparable to adults. The combined incidence of graft loss (5%) and patient death (2%) at 12 months posttransplant was similar to that observed in adult renal transplant patients.

Cardiac Transplant: A double-blind, randomized, comparative, parallel-group, multicenter study in primary cardiac transplant recipients was performed at 20 centers in the United States, 1 in Canada, 5 in Europe and 2 in Australia. The total number of patients enrolled was 650; 72 never received study drug and 578 received study drug. Patients received CellCept 1.5 g bid (n=289) or azathioprine 1.5 to 3 mg/kg/day (n=289), in combination with cyclosporine (Sandimmune® or Neoral®*) and corticosteroids as maintenance immunosuppressive therapy. The two primary efficacy endpoints were: (1) the proportion of patients who, after transplantation, had at least one endomyocardial biopsy-proven rejection with hemodynamic compromise, or were retransplanted or died, within the first 6 months, and (2) the proportion of patients who died or were retransplanted during the first 12 months following transplantation. Patients who prematurely discontinued treatment were followed for the occurrence of allograft rejection for up to 6 months and for the occurrence of death for 1 year.

(1) *Rejection:* No difference was established between CellCept and azathioprine (AZA) with respect to biopsy-proven rejection with hemodynamic compromise.

(2) *Survival:* CellCept was shown to be at least as effective as AZA in preventing death or retransplantation at 1 year (see table below).

* Neoral is a registered trademark of Novartis Pharmaceuticals Corporation.

CellCept® (mycophenolate mofetil)**Rejection at 6 Months/
Death or Retransplantation at 1 Year**

	All Patients		Treated Patients	
	AZA N = 323	CellCept N = 327	AZA N = 289	CellCept N = 289
Biopsy-proven rejection with hemodynamic compromise at 6 months*	121 (38%)	120 (37%)	100 (35%)	92 (32%)
Death or retransplantation at 1 year	49 (15.2%)	42 (12.8%)	33 (11.4%)	18 (6.2%)

* Hemodynamic compromise occurred if any of the following criteria were met: pulmonary capillary wedge pressure ≥ 20 mm or a 25% increase; cardiac index < 2.0 L/min/m² or a 25% decrease; ejection fraction $\leq 30\%$; pulmonary artery oxygen saturation $\leq 60\%$ or a 25% decrease; presence of new S₃ gallop; fractional shortening was $\leq 20\%$ or a 25% decrease; inotropic support required to manage the clinical condition.

Hepatic Transplant: A double-blind, randomized, comparative, parallel-group, multicenter study in primary hepatic transplant recipients was performed at 16 centers in the United States, 2 in Canada, 4 in Europe and 1 in Australia. The total number of patients enrolled was 565. Per protocol, patients received CellCept 1 g bid intravenously for up to 14 days followed by CellCept 1.5 g bid orally or azathioprine 1 to 2 mg/kg/day intravenously followed by azathioprine 1 to 2 mg/kg/day orally, in combination with cyclosporine (Neoral®) and corticosteroids as maintenance immunosuppressive therapy. The actual median oral dose of azathioprine on study was 1.5 mg/kg/day (range of 0.3 to 3.8 mg/kg/day) initially and 1.26 mg/kg/day (range of 0.3 to 3.8 mg/kg/day) at 12 months. The two primary endpoints were: (1) the proportion of patients who experienced, in the first 6 months posttransplantation, one or more episodes of biopsy-proven and treated rejection or death or retransplantation, and (2) the proportion of patients who experienced graft loss (death or retransplantation) during the first 12 months posttransplantation. Patients who prematurely discontinued treatment were followed for the occurrence of allograft rejection and for the occurrence of graft loss (death or retransplantation) for 1 year.

Results: In combination with corticosteroids and cyclosporine, CellCept obtained a lower rate of acute rejection at 6 months and a similar rate of death or retransplantation at 1 year compared to azathioprine.