PRO- GRAFTED
FOR LONG-TERM SUCCESS

GARY
KIDNEY TRANSPLANT 1999
expecting first grandchild*

JANICE
LIVER TRANSPLANT 1997
planning daughter's wedding*

ANNA
KIDNEY TRANSPLANT 2002
starting ninth grade*

*Individual results may vary.

SUPERIOR REJECTION PREVENTION
Compared to cyclosporine, Prograf-treated patients experienced significantly lower rates of biopsy-confirmed acute rejection at 1 year following renal transplantation (P=0.001)[1]

STABLE RENAL FUNCTION
5-year study† demonstrated minimal change in serum creatinine throughout Prograf treatment (median serum creatinine mg/dL: 1.4 Prograf vs 1.7 cyclosporine; P=0.0014)[2]

FAVORABLE CARDIOVASCULAR PROFILE
Significantly fewer Prograf-treated patients required antihypertensive (P=0.047) and antihyperlipidemia (P<0.001) medications than cyclosporine-treated patients in the 5-year trial[2†]

OVER 10 YEARS OF SUCCESSFUL USE[3]

Prograf is indicated for the prophylaxis of organ rejection in patients receiving allogeneic liver or kidney transplants.**

WARNING: Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and qualified facilities should manage patients prescribed Prograf. Complete patient information is required for maintenance therapy.

Prograf is contraindicated in patients with a hypersensitivity to tacrolimus. Prograf injection is contraindicated in patients with a hypersensitivity to castor oil. Monitoring of patients for signs and symptoms of anaphylaxis during the initial infusion with Prograf is recommended.

In the original Phase III kidney transplant clinical study, where Prograf was used in combination with azathioprine and prednisone and dosed to initial target trough blood levels, insulin-dependent post-transplant diabetes mellitus (PTDM) was reported in 20% of Prograf-treated kidney patients. Insulin dependence was reversible in 15% of these patients at one year and 50% at two years post-transplant. Black and Hispanic kidney transplant patients were at an increased risk. In the original Phase III liver transplant clinical studies, insulin-dependent PTDM was reported in 18% and 11% of Prograf-treated liver transplant patients and was reversible in 45% and 31% of these patients at one year post-transplant, in the US and European randomized studies, respectively.

Prograf has been associated with nephrotoxicity, particularly when used in high doses. To avoid nephrotoxicity, Prograf should not be used simultaneously with cyclosporine. Discontinue Prograf or cyclosporine at least 24 hours prior to initiating the other. Further delay dosing if Prograf or cyclosporine concentrations are elevated.

Mild to severe hyperkalemia was reported in 31% of kidney transplant recipients and in 45% and 13% of liver transplant recipients treated with Prograf in the US and European randomized trials, respectively, and may require treatment. Serum potassium levels should be monitored and potassium-sparing diuretics should not be used during Prograf therapy.

Neurotoxicity, including tremor, headache, and other changes in motor function, mental status and sensory function were reported in approximately 55% of liver transplant recipients in the two randomized studies. Seizures have occurred in adult and pediatric patients receiving Prograf. Coma and delirium also have been associated with high plasma concentrations of tacrolimus.

The principal adverse reactions of Prograf are tremor, headache, hypertension, gastrointestinal disturbance, and renal dysfunction.

Please see brief summary of prescribing information on the adjacent page.

**It is recommended that Prograf be used concomitantly with adrenal corticosteroids. Because of the risk of anaphylaxis, Prograf injection should be reserved for patients unable to take Prograf capsules orally.

PROGRAF®
tacrolimus capsules and injection

THE EVIDENCE CONTINUES

†5-year results of the prospective Phase 3 trial. Patients continuing in the extension study were followed for 5 years from randomization or until death.

References: 1. Pirsch J, Miller J, Deierhoi MH, et al. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. *Transplantation.* 1997;63(7):977-983. 2. Vincenti F, Jensik SC, Filo RS, et al. A long-term comparison of tacrolimus (FK506) and cyclosporine in kidney transplantation: evidence for improved allograft survival at five years. *Transplantation.* 2002;73(5):775-782. 3. Data on File, Astellas Pharma US, Inc.

astellas

PROGRAF®

tacrolimus capsules

tacrolimus injection ***(for intravenous infusion only)***

Revised: April 2005

The following is a brief summary: see current package insert for complete information.

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.

INDICATIONS AND USAGE:

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

CONTRAINDICATIONS:

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

WARNINGS: (See boxed **WARNING**)

Insulin-dependent post-transplant diabetes mellitus (PTDM) was reported in 20% of Prograf-treated kidney transplant patients without pretransplant history of diabetes mellitus in the Phase III study. The median time to onset of PTDM was 68 days. Insulin dependence was reversible in 15% of these PTDM patients at one year and in 50% at two years post transplant. Black and Hispanic kidney transplant patients were at an increased risk of development of PTDM.

Insulin-dependent post-transplant diabetes mellitus was reported in 18% and 11% of Prograf-treated liver transplant patients and was reversible in 45% and 31% of these patients at one year post transplant, in the U.S. and European randomized studies, respectively. Hyperglycemia was associated with the use of Prograf in 47% and 33% of liver transplant recipients in the U.S. and European randomized studies, respectively, and may require treatment (see **ADVERSE REACTIONS**).

Prograf can cause neurotoxicity and nephrotoxicity, particularly when used in high doses. Nephrotoxicity was reported in approximately 52% of kidney transplantation patients and in 40% and 36% of liver transplantation patients receiving Prograf in the U.S. and European randomized trials, respectively (see **ADVERSE REACTIONS**). More overt nephrotoxicity is seen early after transplantation, characterized by increasing serum creatinine and a decrease in urine output. Patients with impaired renal function should be monitored closely as the dosage of Prograf may need to be reduced. In patients with persistent elevations of serum creatinine who are unresponsive to dosage adjustments, consideration should be given to changing to another immunosuppressive therapy. Care should be taken in using tacrolimus with other nephrotoxic drugs. **In particular, to avoid excess nephrotoxicity, Prograf should not be used simultaneously with cyclosporine. Prograf or cyclosporine should be discontinued at least 24 hours prior to initiating the other. In the presence of elevated Prograf or cyclosporine concentrations, dosing with the other drug usually should be further delayed.**

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

Neurotoxicity, including tremor, headache, and other changes in motor function, mental status, and sensory function were reported in approximately 55% of liver transplant recipients in the two randomized studies. Tremor occurred more often in Prograf-treated kidney transplant patients (54%) compared to cyclosporine-treated patients. The incidence of other neurological events in kidney transplant patients was similar in the two treatment groups (see **ADVERSE REACTIONS**). Tremor and headache have been associated with high whole-blood concentrations of tacrolimus and may respond to dosage adjustment. Seizures have occurred in adult and pediatric patients receiving Prograf (see **ADVERSE REACTIONS**). Coma and delirium also have been associated with high plasma concentrations of tacrolimus.

As in patients receiving other immunosuppressants, patients receiving Prograf are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. A lymphoproliferative disorder (LPD) related to Epstein-Barr Virus (EBV) infection has been reported in immunosuppressed organ transplant recipients. The risk of LPD appears greatest in young children who are at risk for primary EBV infection while immunosuppressed or who are switched to Prograf following long-term immunosuppression therapy. Because of the danger of oversuppression of the immune system which can increase susceptibility to infection, combination immunosuppressant therapy should be used with caution.

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

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

PRECAUTIONS:

General

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

Renally and Hepatically Impaired Patients

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

Myocardial Hypertrophy

Myocardial hypertrophy has been reported in association with the administration of Prograf, and is generally manifested by echocardiographically demonstrated concentric increases in left ventricular posterior wall and interventricular septum thickness. Hypertrophy has been observed in infants, children, and adults. This condition appears reversible in most cases following dose reduction or discontinuance of therapy. In a group of 20 patients with pre- and post-treatment echocardiograms who showed evidence of myocardial hypertrophy, mean tacrolimus whole blood concentrations during the period prior to diagnosis of myocardial hypertrophy ranged from 11 to 53 ng/mL in infants (N=10, age 0.4 to 2 years), 4 to 46 ng/mL in children (N=7, age 2 to 15 years), and 11 to 24 ng/mL in adults (N=3, age 37 to 53 years).

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

Information for Patients

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

Patients should be informed that Prograf can cause diabetes mellitus and should be advised of the need to see their physician if they develop frequent urination, increased thirst, or hunger. As with other immunosuppressive agents, owing to the potential risk of malignant skin changes, exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Laboratory Tests

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

Drug Interactions

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

Drugs That May Alter Tacrolimus Concentrations

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

Drugs that may increase tacrolimus blood concentrations: **Calcium Channel Blockers**: diltiazem, nicardipine, nifedipine, verapamil; **Antifungal Agents**: clotrimazole, fluconazole, itraconazole, ketoconazole, voriconazole; **Macrolide Antibiotics**: clarithromycin, erythromycin, troleandomycin; **Gastrointestinal Prokinetic Agents**: cisapride, metoclopramide; **Other Drugs**: bromocriptine, chloramphenicol, cimetidine, cyclosporine, danazol, ethinyl estradiol, methylprednisolone, omeprazole, protease inhibitors, nefazodone, magnesium-aluminum-hydroxide.

Drugs that may decrease tacrolimus blood concentrations: **Anticonvulsants**: carbamazepine, phenobarbital, phenytoin; **Antimicrobials**: rifabutin, caspofungin, rifampin; **Herbal Preparations**: St. John's Wort; **Other Drugs**: sirolimus.

This list of drugs is not all-inclusive.

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

Interaction studies with drugs used in HIV therapy have not been conducted. However, care should be exercised when drugs that are nephrotoxic (e.g., ganciclovir) or that are metabolized by CYP3A (e.g., nelfinavir, ritonavir) are administered concomitantly with tacrolimus. Tacrolimus may affect the pharmacokinetics of other drugs (e.g., phenytoin) and increase their concentration. Grapefruit juice affects CYP3A-mediated metabolism and should be avoided.

Other Drug Interactions

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

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 lymphomas and carcinomas of the skin. As with other immunosuppressive therapies, the risk of malignancies in Prograf recipients may be higher than in the normal, healthy population. Lymphoproliferative disorders associated with Epstein-Barr Virus infection have been seen. It has been reported that reduction or discontinuation of immunosuppression may cause the lesions to regress.

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

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

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

Pregnancy: Category C

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

No reduction in male or female fertility was evident.

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

Nursing Mothers

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

Pediatric Patients

Experience with Prograf in pediatric kidney transplant patients is limited. Successful liver transplants have been performed in pediatric patients (ages up to 16 years) using Prograf. Two randomized active-controlled trials of Prograf in primary liver transplantation included 56 pediatric patients. Thirty-one patients were randomized to Prograf-based and 25 to cyclosporine-based therapies. Additionally, a minimum of 122 pediatric patients were studied in an uncontrolled trial of tacrolimus in living related donor liver transplantation. Pediatric patients generally required higher doses of Prograf to maintain blood trough concentrations of tacrolimus similar to adult patients.

ADVERSE REACTIONS:

Liver Transplantation

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

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

Kidney Transplantation

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

Adverse events that occurred in ≥15% of Prograf-treated liver and kidney transplant patients: NERVOUS SYSTEM: headache, tremor, insomnia, paresthesia; GASTROINTESTINAL: diarrhea, nausea, constipation, vomiting; CARDIOVASCULAR: hypertension; UROGENITAL: creatinine increased, urinary tract infection; METABOLIC AND NUTRITIONAL: hyperkalemia, hypokalemia, hyperglycemia, hypomagnesemia; HEMIC AND LYMPHATIC: anemia; MISCELLANEOUS: abdominal pain, pain, fever, asthenia, back pain, peripheral edema; RESPIRATORY SYSTEM: dyspnea; SKIN AND APPENDAGES: pruritus, rash.

In addition, among liver transplantation patients: GASTROINTESTINAL: LFT abnormal; anorexia; UROGENITAL: kidney function abnormal, BUN increased, oliguria; HEMIC AND LYMPHATIC: leukocytosis, thrombocytopenia; MISCELLANEOUS: ascites; RESPIRATORY SYSTEM: pleural effusion, atelectasis.

In addition, among kidney transplantation patients: NERVOUS SYSTEM: dizziness; GASTROINTESTINAL: dyspepsia; CARDIOVASCULAR: chest pain; METABOLIC AND NUTRITIONAL: hypophosphatemia, hyperlipemia, diabetes mellitus, edema; HEMIC AND LYMPHATIC: leukopenia; MISCELLANEOUS: infection; RESPIRATORY SYSTEM: cough increased; MUSCULOSKELETAL: arthralgia.

Less Frequently Reported Adverse Reactions

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

NERVOUS SYSTEM: (see **WARNINGS**) abnormal dreams, agitation, amnesia, anxiety, confusion, convulsion, depression, dizziness, emotional lability, encephalopathy, hallucinations, hypertonia, incoordination, myoclonus, nervousness, neuropathy, psychosis, somnolence, abnormal thinking; SPECIAL SENSES: abnormal vision, amblyopia, ear pain, otitis media, tinnitus; GASTROINTESTINAL: anorexia, cholangitis, cholestatic jaundice, dyspepsia, dysphagia, esophagitis, flatulence, gastritis, gastrointestinal hemorrhage, GGT increase, GI perforation, hepatitis, ileus, increased appetite, jaundice, liver damage, liver function test abnormal, oral moniliasis, rectal disorder, stomatitis; CARDIOVASCULAR: angina pectoris, chest pain, deep thrombophlebitis, abnormal ECG, hemorrhage, hypotension, postural hypotension, peripheral vascular disorder, phlebitis, tachycardia, thrombosis, vasodilatation; UROGENITAL: (see **WARNINGS**) albuminuria, cystitis, dysuria, hematuria, hydronephrosis, kidney failure, kidney tubular necrosis, nocturia, pyuria, toxic nephropathy, oliguria, urinary frequency, urinary incontinence, vaginitis; METABOLIC/NUTRITIONAL: acidosis, alkaline phosphatase increased, alkalosis, ALT (SGPT) increased, AST (SGOT) increased, bicarbonate decreased, bilirubinemia, BUN increased, dehydration, GGT increased, healing abnormal, hypercalcemia, hypercholesterolemia, hyperlipemia, hyperphosphatemia, hyperuricemia, hypervolemia, hypocalcemia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, lactic dehydrogenase increase, weight gain; ENDOCRINE: (see **PRECAUTIONS**) Cushing's syndrome, diabetes mellitus; HEMIC/LYMPHATIC: coagulation disorder, ecchymosis, hypochromic anemia, leukocytosis, leukopenia, polycythemia, prothrombin decreased, serum iron decreased, thrombocytopenia; MISCELLANEOUS: abdomen enlarged, abscess, accidental injury, allergic reaction, cellulitis, chills, flu syndrome, generalized edema, hernia, peritonitis, photosensitivity reaction, sepsis; MUSCULOSKELETAL: arthralgia, cramps, generalized spasm, joint disorder, leg cramps, myalgia, myasthenia, osteoporosis; RESPIRATORY: asthma, bronchitis, cough increased, lung disorder, pneumothorax, pulmonary edema, pharyngitis, pneumonia, respiratory disorder, rhinitis, sinusitis, voice alteration; SKIN: acne, alopecia, exfoliative dermatitis, fungal dermatitis, herpes simplex, hirsutism, skin discoloration, skin disorder, skin ulcer, sweating.

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

Please see the current package insert for complete information regarding adverse effects.

Post Marketing

The following have been reported: increased amylase including pancreatitis, hearing loss including deafness, leukoencephalopathy, thrombocytopenic purpura, hemolytic-uremic syndrome, acute renal failure, Stevens-Johnson syndrome, stomach ulcer, glycosuria, cardiac arrhythmia, QT prolongation, torsades de pointes, and gastroenteritis.

Overdosage

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

Manufactured for: Astellas Pharma US, Inc. Deerfield, IL 60015-2548 Rx only

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

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