TACROLIMUS- tacrolimus capsule
Sandoz Inc

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use tacrolimus capsules safely and effectively. See full prescribing information for tacrolimus capsules.

TACROLIMUS Capsules , USP for oral use
Initial U.S. Approval: 1994

WARNING: MALIGNANCIES AND SERIOUS INFECTIONS

See full prescribing information for complete boxed warning

- **Increased risk of development of lymphoma and other malignancies, particularly of the skin, due to immunosuppression (5.2)**
- **Increased susceptibility to bacterial, viral, fungal, and protozoal infections, including opportunistic infections (5.3, 5.4, 5.5)**
- **Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe tacrolimus capsules (5.1)**

RECENT MAJOR CHANGES

Warnings and Precautions, Use with CYP3A4 Inhibitors and Inducers (5.13) 08/2013
Warnings and Precautions, QT Prolongation (5.14) 08/2013
Warnings and Precautions, Gastrointestinal Perforation (5.18) 08/2013

INDICATIONS AND USAGE

Tacrolimus capsules are a calcineurin-inhibitor immunosuppressant indicated for

- Prophylaxis of organ rejection in patients receiving allogeneic liver, kidney or heart transplants (1.1, 1.2, 1.3)
- Use concomitantly with adrenal corticosteroids; in kidney and heart transplant, use in conjunction with azathioprine or mycophenolate mofetil (MMF) (1.1, 1.2, 1.3)
- Limitations of Use (1.4):
  - Do not use simultaneously with cyclosporine
  - Intravenous use reserved for patients who can not tolerate capsules orally
  - Use with sirolimus is not recommended in liver and heart transplant; use with sirolimus in kidney transplant has not been established

DOSAGE AND ADMINISTRATION

Summary of Initial Oral Dosage Recommendation and Observed Whole Blood Trough Concentrations (2.1, 2.2).

Patient Population	**Recommended Initial Oral Dosage (two divided doses every 12 hours)**	**Observed Whole Blood Trough Concentrations**
Adult Kidney transplant In combination with azathioprine In combination with MMF/IL-2 receptor antagonist	 0.2 mg/kg/day 0.1 mg/kg/day	 month 1 to 3: 7 to 20 ng/mL month 4 to 12: 5 to 15 ng/mL month 1 to 12: 4 to 11 ng/mL
Adult Liver transplant Pediatric Liver transplant	0.10 to 0.15 mg/kg/day 0.15 to 0.20 mg/kg/day	month 1 to 12: 5 to 20 ng/mL month 1 to 12: 5 to 20 ng/mL
Adult Heart transplant	0.075 mg/kg/day	month 1 to 3: 10 to 20 ng/mL month ≥4: 5 to 15 ng/mL

- Careful and frequent monitoring of tacrolimus trough concentrations is recommended; Black patients may require higher doses in order to achieve comparable trough concentrations (2.1)
- Hepatic/Renal impaired patients should receive doses at the lowest value of the recommended initial oral dosing

range (2.3, 2.4)
- Administer capsules consistently with or without food; do not drink grapefruit juice (2.5, 7.2)

DOSAGE FORMS AND STRENGTHS

- Capsules: 0.5 mg, 1 mg and 5 mg (3)

CONTRAINDICATIONS

- Hypersensitivity to tacrolimus (4)

WARNINGS AND PRECAUTIONS

- Lymphoma and Other Malignancies: Risk of lymphomas, including post transplant lymphoproliferative disorder (PTLD); appears related to intensity and duration of use. Avoid prolonged exposure to UV light and sunlight (5.2)
- Serious infections: Increased risk of bacterial, viral, fungal and protozoal infections, including opportunistic infections: combination immunosuppression should be used with caution (5.3)
- Polyoma Virus Infections: Serious, sometimes fatal outcomes, including polyoma virus-associated nephropathy (PVAN), mostly due to BK virus, and JC virus-associated progressive multifocal leukoencephalopathy (PML); consider reducing immunosuppression (5.4)
- Cytomegalovirus (CMV) Infections: Increased risk of CMV viremia and disease; consider reducing immunosuppression (5.5)
- New Onset Diabetes After Transplant: Monitor blood glucose (5.6)
- Nephrotoxicity: Acute and/or chronic; reduce the dose; use caution with other nephrotoxic drugs (5.7)
- Neurotoxicity: Risk of Posterior Reversible Encephalopathy Syndrome, monitor for neurologic abnormalities; reduce or discontinue tacrolimus and other immunosuppressants (5.8)
- Hyperkalemia: Monitor serum potassium levels. Careful consideration should be given prior to use of other agents also associated with hyperkalemia (5.9)
- Hypertension: May require antihypertensive therapy. Monitor relevant drug-drug interactions (5.10)
- Anaphylactic Reactions with IV formulation: Observe patients receiving tacrolimus injection for signs and symptoms of anaphylaxic (5.11)
- Use with Sirolimus: Not recommended in liver and heart transplant due to increased risk of serious adverse reactions (5.12)
- Myocardial Hypertrophy: Consider dosage reduction or discontinuation (5.15)
- Immunizations: Use of live vaccines should be avoided (5.16)
- Pure Red Cell Aplasia: Discontinuation should be considered (5.17)

ADVERSE REACTIONS

- Kidney Transplant: The most common adverse reactions (≥ 30%) were infection, tremor, hypertension, abnormal renal function, constipation, diarrhea, headache, abdominal pain, insomnia, nausea, hypomagnesemia, urinary tract infection, hypophosphatemia, peripheral edema, asthenia, pain, hyperlipidemia, hyperkalemia, and anemia (6.1)
- Liver Transplant: The most common adverse reactions (≥ 40%) were tremor, headache, diarrhea, hypertension, nausea, abnormal renal function, abdominal pain, insomnia, paresthesia, anemia, pain, fever, asthenia, hyperkalemia, hypomagnesemia, and hyperglycemia (6.1)
- Heart Transplant: The most common adverse reactions (≥ 15%) were abnormal renal function, hypertension, diabetes mellitus, CMV infection, tremor, hyperglycemia, leukopenia, infection, anemia, bronchitis, pericardial effusion, urinary tract infection and hyperlipemia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Mycophenolic Acid Products: Can increase MPA exposure after crossover from cyclosporine to tacrolimus; monitor for MPA-related adverse reactions and adjust MMF or MPA-dose as needed (7.1)
- Nelfinavir and Grapefruit Juice: Increased tacrolimus concentrations via CYP3A inhibition; avoid concomitant use (7.2, 7.3)
- CYP3A Inhibitors: Increased tacrolimus concentrations; monitor concentrations and adjust tacrolimus dose as needed with concomitant use (5.13, 7.3, 7.4, 7.5, 7.6)
- CYP3A4 Inducers: Decreased tacrolimus concentrations; monitor concentrations and adjust tacrolimus dose as needed with concomitant use (5.13, 7.7, 7.8, 7.9)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data may cause fetal harm. Use only if the potential benefit justifies the risk (8.1)
- Nursing Mothers: Discontinue nursing taking into consideration importance of drug to mother (8.3)
- Hepatic/Renal impaired patients: Administer at the lower end of the recommended starting dose. Monitor renal function in patients with impaired renal function (2.3, 2.4, 8.6,8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 9/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

BOXED WARNINGS: MALIGNANCIES AND SERIOUS INFECTIONS

- **Increased risk of development of lymphoma and other malignancies, particularly of the skin, due to immunosuppression [see WARNINGS AND PRECAUTIONS (5.2)].**
- **Increased susceptibility to bacterial, viral, fungal, and protozoal infections, including opportunistic infections [see WARNINGS AND PRECAUTIONS (5.3, 5.4, 5.5)].**
- **Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe tacrolimus capsules. 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 [see WARNINGS AND PRECAUTIONS (5.1)].**

1 INDICATIONS AND USAGE

1.1 Prophylaxis of Organ Rejection in Kidney Transplant

Tacrolimus capsules, USP are indicated for the prophylaxis of organ rejection in patients receiving allogeneic kidney transplants. It is recommended that tacrolimus capsules, USP be used concomitantly with azathioprine or mycophenolate mofetil (MMF) and adrenal corticosteroids [see **CLINICAL STUDIES (14.1)**]. Therapeutic drug monitoring is recommended for all patients receiving tacrolimus capsules, USP [see **DOSAGE AND ADMINISTRATION (2.6)**].

1.2 Prophylaxis of Organ Rejection in Liver Transplant

Tacrolimus capsules, USP are indicated for the prophylaxis of organ rejection in patients receiving allogeneic liver transplants. It is recommended that tacrolimus capsules, USP be used concomitantly with adrenal corticosteroids [see **CLINICAL STUDIES (14.2)**]. Therapeutic drug monitoring is recommended for all patients receiving tacrolimus capsules, USP [see **DOSAGE AND ADMINISTRATION (2.6)**].

1.3 Prophylaxis of Organ Rejection in Heart Transplant

Tacrolimus capsules, USP are indicated for the prophylaxis of organ rejection in patients receiving allogeneic heart transplants. It is recommended that tacrolimus capsules, USP be used concomitantly with azathioprine or mycophenolate mofetil (MMF) and adrenal corticosteroids [see **CLINICAL STUDIES (14.3)**]. Therapeutic drug monitoring is recommended for all patients receiving tacrolimus capsules, USP [see **DOSAGE AND ADMINISTRATION (2.6)**].

1.4 Limitations of Use

Tacrolimus capsules, USP should not be used simultaneously with cyclosporine [see **DOSAGE AND ADMINISTRATION (2.5)**].

Tacrolimus injection should be reserved for patients unable to take tacrolimus capsules, USP orally [see **DOSAGE AND ADMINISTRATION (2.1)** and **WARNINGS AND PRECAUTIONS (5.11)**].

Use with sirolimus is not recommended in liver and heart transplant. The safety and efficacy of tacrolimus capsules, USP with sirolimus has not been established in kidney transplant [see **WARNINGS AND PRECAUTIONS (5.12)**].

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Adult Kidney, Liver or Heart Transplant Patients

The initial oral dosage recommendations for adult patients with kidney, liver or heart transplants along with recommendations for whole blood trough concentrations are shown in **Table 1**. The initial dose of tacrolimus capsules, USP should be administered no sooner than 6 hours after transplantation in the liver and heart transplant patients. In kidney transplant patients, the initial dose of tacrolimus capsules, USP may be administered within 24 hours of transplantation, but should be delayed until renal function has recovered. For blood concentration monitoring details see **DOSAGE AND ADMINISTRATION (2.6)**.

Table 1. Summary of Initial Oral Dosage Recommendations and Observed Whole Blood Trough Concentrations in Adults

Patient Population	**Recommended Tacrolimus Capsules Initial Oral Dosage** Note: daily doses should be administered as two divided doses, every 12 hours	**Observed Tacrolimus Whole Blood Trough Concentrations**
Adult kidney transplant patients In combination with azathioprine	0.2 mg/kg/day	month 1 to 3: 7 to 20 ng/mL month 4 to 12: 5 to 15 ng/mL
In combination with MMF/IL-2 receptor antagonist*	0.1 mg/kg/day	month 1 to 12: 4 to 11 ng/mL
Adult liver transplant patients	0.10 to 0.15 mg/kg/day	month 1 to 12: 5 to 20 ng/mL
Adult heart transplant patients	0.075 mg/kg/day	month 1 to 3: 10 to 20 ng/mL month ≥4: 5 to 15 ng/mL

* In a second smaller trial, the initial dose of tacrolimus was 0.15 to 0.2 mg/kg/day and observed tacrolimus concentrations were 6 to 16 ng/mL during months 1 to 3 and 5 to 12 ng/mL during months 4 to 12 [see **CLINICAL STUDIES (14.1)**].

Dosing should be titrated based on clinical assessments of rejection and tolerability. Lower tacrolimus capsules, USP dosages than the recommended initial dosage may be sufficient as maintenance therapy. Adjunct therapy with adrenal corticosteroids is recommended early post-transplant.

The data in kidney transplant patients indicate that the Black patients required a higher dose to attain comparable trough concentrations compared to Caucasian patients (**Table 2**).

Table 2. Comparative Dose and Trough Concentrations Based on Race

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	0.23	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

Initial Dose – Injection

Tacrolimus injection should be used only as a continuous IV infusion and when the patient cannot

tolerate oral administration of tacrolimus capsules, USP. Tacrolimus injection should be discontinued as soon as the patient can tolerate oral administration of tacrolimus capsules, USP, usually within 2 to 3 days. In a patient receiving an IV infusion, the first dose of oral therapy should be given 8 to 12 hours after discontinuing the IV infusion.

The observed trough concentrations described above pertain to oral administration of tacrolimus capsules, USP only; while monitoring tacrolimus capsules concentrations in patients receiving tacrolimus injection as a continuous IV infusion may have some utility, the observed concentrations will not represent comparable exposures to those estimated by the trough concentrations observed in patients on oral therapy.

The recommended starting dose of tacrolimus injection is 0.03 to 0.05 mg/kg/day in kidney and liver transplant and 0.01 mg/kg/day in heart transplant given as a continuous IV infusion. Adult patients should receive doses at the lower end of the dosing range. Concomitant adrenal corticosteroid therapy is recommended early post-transplantation.

Anaphylactic reactions have occurred with injectables containing castor oil derivatives, such as tacrolimus injection [see **WARNINGS AND PRECAUTIONS (5.11)**].

2.2 Dosage in Pediatric Liver Transplant Patients

The initial oral dosage recommendations for pediatric patients with liver transplants along with recommendations for whole blood trough concentrations are shown in **Table 3**. For blood concentration monitoring details see **DOSAGE AND ADMINISTRATION (2.6)**. If necessary, pediatric patients may start on an IV dose of 0.03 to 0.05 mg/kg/day.

Table 3. Summary of Initial Oral Dosage Recommendations and Observed Whole Blood Trough Concentrations in Children

Patient Population	**Recommended Tacrolimus Capsules Initial Oral Dosage** Note: daily doses should be administered as two divided doses, every 12 hours	**Observed Tacrolimus Whole Blood Trough Concentrations**
Pediatric liver transplant patients	0.15 to 0.20 mg/kg/day	Month 1 to 12: 5 to 20 ng/mL

Pediatric liver transplantation patients without pre-existing renal or hepatic dysfunction have required and tolerated higher doses than adults to achieve similar blood concentrations.

Experience in pediatric kidney and heart transplantation patients is limited.

2.3 Dosage Adjustment in Patients with Renal Impairment

Due to its potential for nephrotoxicity, consideration should be given to dosing tacrolimus capsules, USP at the lower end of the therapeutic dosing range in patients who have received a liver or heart transplant and have pre-existing renal impairment. Further reductions in dose below the targeted range may be required.

In kidney transplant patients with post-operative oliguria, the initial dose of tacrolimus capsules, USP should be administered no sooner than 6 hours and within 24 hours of transplantation, but may be delayed until renal function shows evidence of recovery.

2.4 Dosage Adjustments in Patients with Hepatic Impairment

Due to the reduced clearance and prolonged half-life, patients with severe hepatic impairment (Child Pugh ≥ 10) may require lower doses of tacrolimus capsules, USP. Close monitoring of blood concentrations is warranted.

The use of tacrolimus capsules, USP in liver transplant recipients experiencing post-transplant hepatic impairment may be associated with increased risk of developing renal insufficiency related to high whole-blood concentrations of tacrolimus. These patients should be monitored closely and dosage adjustments should be considered. Some evidence suggests that lower doses should be used in these patients [see **DOSAGE AND ADMINISTRATION (2.1), USE IN SPECIFIC POPULATIONS (8.7)** and **CLINICAL PHARMACOLOGY (12.3)**].

2.5 Administration Instructions

It is recommended that patients initiate oral therapy with tacrolimus capsules, USP if possible.

Initial dosage and observed tacrolimus whole blood trough concentrations for adults are shown in **Table 1** and for pediatrics in **Table 3** [see **DOSAGE AND ADMINISTRATION (2.1, 2.2)**]; for blood concentration monitoring details in kidney transplant patients [see **DOSAGE AND ADMINISTRATION (2.1)**].

It is important to take tacrolimus capsules, USP consistently every day either with or without food because the presence and composition of food decreases the bioavailability of tacrolimus capsules, USP [see **CLINICAL PHARMACOLOGY (12.3)**].

Patients should not eat grapefruit or drink grapefruit juice in combination with tacrolimus capsules, USP [see **DRUG INTERACTIONS (7.2)**]

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

In patients unable to take oral tacrolimus capsules, USP, therapy may be initiated with tacrolimus injection as a continuous IV infusion. If IV therapy is necessary, conversion from IV to oral tacrolimus is recommended as soon as oral therapy can be tolerated. This usually occurs within 2 to 3 days. In patients receiving an IV infusion, the first dose of oral therapy should be given 8 to 12 hours after discontinuing the IV infusion.

2.6 Therapeutic Drug Monitoring

Monitoring of tacrolimus blood concentrations in conjunction with other laboratory and clinical parameters is considered an essential aid to patient management for the evaluation of rejection, toxicity, dose adjustments and compliance. Observed whole blood trough concentrations can be found in **Table 1**. Factors influencing frequency of monitoring include but are not limited to hepatic or renal dysfunction, the addition or discontinuation of potentially interacting drugs and the post-transplant time. Blood concentration monitoring is not a replacement for renal and liver function monitoring and tissue biopsies. Data from clinical trials show that tacrolimus whole blood concentrations were most variable during the first week post-transplantation.

The relative risks of toxicity and efficacy failure are related to tacrolimus whole blood trough concentrations. Therefore, monitoring of whole blood trough concentrations is recommended to assist in the clinical evaluation of toxicity and efficacy failure.

Methods commonly used for the assay of tacrolimus include high performance liquid chromatography with tandem mass spectrometric detection (HPLC/MS/MS) and immunoassays. Immunoassays may react with metabolites as well as parent compound. Therefore assay results obtained with immunoassays may have a positive bias relative to results of HPLC/MS. The bias may depend upon the specific assay and laboratory. Comparison of the concentrations in published literature to patient concentrations using the current assays must be made with detailed knowledge of the assay methods and biological matrices employed. Whole blood is the matrix of choice and specimens should be collected into tubes containing ethylene diamine tetraacetic acid (EDTA) anti-coagulant. Heparin anti-coagulation is not recommended because of the tendency to form clots on storage. Samples which are not analyzed immediately should

be stored at room temperature or in a refrigerator and assayed within 7 days; see assay instructions for specifics. If samples are to be kept longer they should be deep frozen at -20° C. One study showed drug recovery >90% for samples stored at -20° C for 6 months, with reduced recovery observed after 6 months.

3 DOSAGE FORMS AND STRENGTHS

Tacrolimus capsules, USP are available in 0.5 mg, 1 mg, and 5 mg strengths.

Tacrolimus capsules, USP containing white to off white powder equivalent to 0.5 mg of anhydrous tacrolimus, are hard gelatin capsules with white opaque body and ivory cap. The body is imprinted '643' and cap is imprinted '' in black ink.

Tacrolimus capsules, USP containing white to off white powder equivalent to 1 mg of anhydrous tacrolimus, are hard gelatin capsules with white opaque body and brown cap. The body is imprinted '644' and cap is imprinted '' in black ink.

Tacrolimus capsules, USP containing white to off white powder equivalent to 5 mg of anhydrous tacrolimus, are hard gelatin capsules with white opaque body and orange cap. The body is imprinted '645' and cap is imprinted '' in black ink.

4 CONTRAINDICATIONS

Tacrolimus capsules are contraindicated in patients with a hypersensitivity to tacrolimus. Hypersensitivity symptoms reported include dyspnea, rash, pruritus, and acute respiratory distress syndrome [see **ADVERSE REACTIONS (6)**].

5 WARNINGS AND PRECAUTIONS

5.1 Management of Immunosuppression

Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should use tacrolimus. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physicians responsible for maintenance therapy should have complete information requisite for the follow up of the patient [see **BOXED WARNING**].

5.2 Lymphoma and Other Malignancies

Patients receiving immunosuppressants, including tacrolimus, are at increased risk of developing lymphomas and other malignancies, particularly of the skin [see **BOXED WARNING**]. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Post transplant lymphoproliferative disorder (PTLD) has been reported in immunosuppressed organ transplant recipients. The majority of PTLD events appear related to Epstein Barr Virus (EBV) infection. The risk of PTLD appears greatest in those individuals who are EBV seronegative, a population which includes many young children.

5.3 Serious Infections

Patients receiving immunosuppressants, including tacrolimus, are at increased risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections [see **BOXED**

WARNING and **WARNINGS AND PRECAUTIONS (5.4, 5.5)**].

These infections may lead to serious, including fatal, outcomes. Because of the danger of oversuppression of the immune system which can increase susceptibility to infection, combination immunosuppressant therapy should be used with caution.

5.4 Polyoma Virus Infections

Patients receiving immunosuppressants, including tacrolimus, are at increased risk for opportunistic infections, including polyoma virus infections. Polyoma virus infections in transplant patients may have serious, and sometimes fatal, outcomes. These include polyoma virus-associated nephropathy (PVAN), mostly due to BK virus infection, and JC virus-associated progressive multifocal leukoencephalopathy (PML) which have been observed in patients receiving tacrolimus [see **ADVERSE REACTIONS (6.2)**].

PVAN is associated with serious outcomes, including deteriorating renal function and kidney graft loss [see **ADVERSE REACTIONS (6.2)**]. Patient monitoring may help detect patients at risk for PVAN.

Cases of PML have been reported in patients treated with tacrolimus. PML, which is sometimes fatal, commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies and ataxia. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

Reductions in immunosuppression should be considered for patients who develop evidence of PVAN or PML. Physicians should also consider the risk that reduced immunosuppression represents to the functioning allograft.

5.5 Cytomegalovirus (CMV) Infections

Patients receiving immunosuppressants, including tacrolimus, are at increased risk of developing CMV viremia and CMV disease. The risk of CMV disease is highest among transplant recipients seronegative for CMV at time of transplant who receive a graft from a CMV seropositive donor. Therapeutic approaches to limiting CMV disease exist and should be routinely provided. Patient monitoring may help detect patients at risk for CMV disease. Consideration should be given to reducing the amount of immunosuppression in patients who develop CMV viremia and/or CMV disease.

5.6 New Onset Diabetes After Transplant

Tacrolimus was shown to cause new onset diabetes mellitus in clinical trials of kidney, liver and heart transplantation. New onset diabetes after transplantation may be reversible in some patients. Black and Hispanic kidney transplant patients are at an increased risk. Blood glucose concentrations should be monitored closely in patients using tacrolimus [see **ADVERSE REACTIONS (6.1)**].

5.7 Nephrotoxicity

Tacrolimus, like other calcineurin-inhibitors, can cause acute or chronic nephrotoxicity, particularly when used in high doses. Acute nephrotoxicity is most often related to vasoconstriction of the afferent renal arteriole, is characterized by increasing serum creatinine, hyperkalemia, and/or a decrease in urine output, and is typically reversible. Chronic calcineurin-inhibitor nephrotoxicity is associated with increased serum creatinine, decreased kidney graft life, and characteristic histologic changes observed on renal biopsy; the changes associated with chronic calcineurin-inhibitor nephrotoxicity are typically progressive. Patients with impaired renal function should be monitored closely as the dosage of tacrolimus 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.

Based on reported adverse reactions terms related to decreased renal function, nephrotoxicity was reported in approximately 52% of kidney transplantation patients and in 40% and 36% of liver transplantation patients receiving tacrolimus in the U.S. and European randomized trials, respectively, and in 59% of heart transplantation patients in a European randomized trial [see **ADVERSE REACTIONS (6.1)**].

Due to the potential for additive or synergistic impairment of renal function, care should be taken when administering tacrolimus with drugs that may be associated with renal dysfunction. These include, but are not limited to, aminoglycosides, ganciclovir, amphotericin B, cisplatin, nucleotide reverse transcriptase inhibitors (e.g., tenofovir) and protease inhibitors (e.g., ritonavir, indinavir). Similarly, care should be exercised when administering with CYP3A4 inhibitors such as antifungal drugs (e.g., ketoconazole), calcium channel blockers (e.g., diltiazem, verapamil), and macrolide antibiotics (e.g., clarithromycin, erythromycin, troleandomycin) which will result in increased tacrolimus whole blood concentrations due to inhibition of tacrolimus metabolism [see **DRUG INTERACTIONS (7.3, 7.4, 7.5, 7.6)**].

5.8 Neurotoxicity

Tacrolimus may cause a spectrum of neurotoxicities, particularly when used in high doses. The most severe neurotoxicities include posterior reversible encephalopathy syndrome (PRES), delirium, and coma. Patients treated with tacrolimus have been reported to develop PRES. Symptoms indicating PRES include headache, altered mental status, seizures, visual disturbances and hypertension. Diagnosis may be confirmed by radiological procedure. If PRES is suspected or diagnosed, blood pressure control should be maintained and immediate reduction of immunosuppression is advised. This syndrome is characterized by reversal of symptoms upon reduction or discontinuation of immunosuppression.

Coma and delirium, in the absence of PRES, have also been associated with high plasma concentrations of tacrolimus. Seizures have occurred in adult and pediatric patients receiving tacrolimus [see **ADVERSE REACTIONS (6.1)**].

Less severe neurotoxicities, include tremors, parathesias, headache, and other changes in motor function, mental status, and sensory function [see **ADVERSE REACTIONS (6.1)**]. Tremor and headache have been associated with high whole-blood concentrations of tacrolimus and may respond to dosage adjustment.

5.9 Hyperkalemia

Hyperkalemia has been reported with tacrolimus use. Serum potassium levels should be monitored. Careful consideration should be given prior to use of other agents also associated with hyperkalemia (e.g., potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers) during tacrolimus therapy [see **ADVERSE REACTIONS (6.1)**].

5.10 Hypertension

Hypertension is a common adverse effect of tacrolimus therapy and may require antihypertensive therapy [see **ADVERSE REACTIONS (6.1)**]. The control of blood pressure can be accomplished with any of the common antihypertensive agents, though careful consideration should be given prior to use of antihypertensive agents associated with hyperkalemia (e.g., potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers) [see **WARNINGS AND PRECAUTIONS (5.9)**]. Calcium-channel blocking agents may increase tacrolimus blood concentrations and therefore require dosage reduction of tacrolimus [see **DRUG INTERACTIONS (7.5)**].

5.11 Anaphylactic Reactions with Tacrolimus Injection

Anaphylactic reactions have occurred with injectables containing castor oil derivatives, including tacrolimus, in a small percentage of patients (0.6%). The exact cause of these reactions is not known. Tacrolimus injection should be reserved for patients who are unable to take tacrolimus capsules [see

INDICATIONS AND USAGE (1.4)].

Patients receiving tacrolimus 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.

5.12 Use with Sirolimus

The safety and efficacy of tacrolimus with sirolimus has not been established in kidney transplant patients.

Use of sirolimus with tacrolimus in studies of *de novo* liver transplant patients was associated with an excess mortality, graft loss, and hepatic artery thrombosis (HAT) and is not recommended [see **INDICATIONS AND USAGE (1.4)**].

Use of sirolimus (2 mg per day) with tacrolimus in heart transplant patients in a U.S. trial was associated with increased risk of renal function impairment, wound healing complications, and insulin-dependent post–transplant diabetes mellitus, and is not recommended [see **CLINICAL STUDIES (14.3)**].

5.13 Use with CYP3A4 Inhibitors and Inducers

When co-oadministering tacrolimus with strong CYP3A4-inhibitors (e.g., telaprevir, boceprevir, ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin) and strong inducers (e.g., rifampin, rifabutin) adjustments in the dosing regimen of tacrolimus and subsequent frequent monitoring of tacrolimus whole blood trough concentrations and tacrolimus-associated adverse reactions [see **DRUG INTERACTIONS (7)**].

5.14 QT Prolongation

Tacrolimus may prolong the QT/QTc interval and may cause Torsade de Pointes. Avoid tacrolimus in patients with congenital long QT syndrome. In patients with congestive heart failure, bradyarrhythmias, those taking certain antiarrhythmic medications or other medicinal products that lead to QT prolongation and those with electrolyte disturbances such as hypokalemia, hypocalcemia, or hypomagnesemia, consider obtaining electgrocardiograms and monitoring electrolytes (magnesium potassium calcium) periodically during treatment.

When coadministering tacrolimus with other substrates and/or inhibitors of CYP3A4 that also have the potential to prolong the QT interval, a reduction in tacrolimus dose, frequent monitoring of tacrolimus whole blood concentrations, and monitoring for QT prolongation is recommended. Use of tacrolimus with amiodarone has been reported to result in increased tacrolimus whole blood concentrations with or without concurrent QT prolongation.

5.15 Myocardial Hypertrophy

Myocardial hypertrophy has been reported in infants, children, and adults, particularly those with high tacrolimus trough concentrations, and is generally manifested by echocardiographically demonstrated concentric increases in left ventricular posterior wall and interventricular septum thickness. This condition appears reversible in most cases following dose reduction or discontinuance of therapy. In patients who develop renal failure or clinical manifestations of ventricular dysfunction while receiving tacrolimus therapy, echocardiographic evaluation should be considered. If myocardial hypertrophy is diagnosed, dosage reduction or discontinuation of tacrolimus should be considered [see **ADVERSE REACTIONS (6.2)**].

5.16 Immunizations

The use of live vaccines should be avoided during treatment with tacrolimus; examples include (not limited to) the following: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

5.17 Pure Red Cell Aplasia

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. A mechanism for tacrolimus-induced PRCA has not been elucidated. All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease, or concomitant medications associated with PRCA. If PRCA is diagnosed, discontinuation of tacrolimus should be considered [see **ADVERSE REACTIONS (6.2)**].

5.18 Gastrointestinal Perforation

Gastrointestinal perforation has been reported in patients treated with tacrolimus; all reported cases were considered to be a complication of transplant surgery or accompanied by infection, diverticulum, or malignant neoplasm. As gastrointestinal perforation may be serious or life-threatening, appropriate medical/surgical management should be instituted promptly [see **ADVERSE REACTIONS (6.1)**].

6 ADVERSE REACTIONS

The following serious and otherwise important adverse drug reactions are discussed in greater detail in other sections of labeling:

- Lymphoma and Other Malignancies [see **BOXED WARNING, WARNINGS AND PRECAUTIONS (5.2**)]
- Serious Infections [see **BOXED WARNING, WARNINGS AND PRECAUTIONS (5.3)**]
- Polyoma Virus Infections [see **BOXED WARNING, WARNINGS AND PRECAUTIONS (5.4)**]
- CMV Infections [see **BOXED WARNING, WARNINGS AND PRECAUTIONS (5.5)**]
- New Onset Diabetes After Transplant [see **WARNINGS AND PRECAUTIONS (5.6)**]
- Nephrotoxicity [see **WARNINGS AND PRECAUTIONS (5.7)**]
- Neurotoxicity [see **WARNINGS AND PRECAUTIONS (5.8)**]
- Hyperkalemia [see **WARNINGS AND PRECAUTIONS (5.9)**]
- Hypertension [see **WARNINGS AND PRECAUTIONS (5.10)**]
- Anaphylaxis with Tacrolimus Injection [see **WARNINGS AND PRECAUTIONS (5.11)**]
- Myocardial Hypertrophy [see **WARNINGS AND PRECAUTIONS (5.15)**]
- Pure Red Cell Aplasia [see **WARNINGS AND PRECAUTIONS (5.17)**]
- Gastrointestinal Perforation [see **WARNINGS AND PRECAUTIONS (5.18)**]

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In addition, the clinical trials were not designed to establish comparative differences across study arms with regards to the adverse reactions discussed below.

Kidney Transplant

The incidence of adverse reactions was determined in three randomized kidney transplant trials. One of the trials used azathioprine (AZA) and corticosteroids and two of the trials used mycophenolate mofetil (MMF) and corticosteroids concomitantly for maintenance immunosuppression.

Tacrolimus-based immunosuppression in conjunction with azathioprine and corticosteroids following kidney transplantation was assessed in trial where 205 patients received tacrolimus based immunosuppression and 207 patients received cyclosporine based immunosuppression. The trial population had a mean age of 43 years (mean±sd was 43±13 years on tacrolimus and 44±12 years on

cyclosporine arm), the distribution was 61% male, and the composition was White (58%), Black (25%), Hispanic (12%) and Other (5%). The 12 month post-transplant information from this trial is presented below.

The most common adverse reactions (≥ 30%) observed in tacrolimus-treated kidney transplant patients are: infection, tremor, hypertension, abnormal renal function, constipation, diarrhea, headache, abdominal pain, insomnia, nausea, hypomagnesemia, urinary tract infection, hypophosphatemia, peripheral edema, asthenia, pain, hyperlipidemia, hyperkalemia and anemia.

Adverse reactions that occurred in ≥ 15% of kidney transplant patients treated with tacrolimus in conjunction with azathioprine are presented below:

Table 4. Kidney Transplantation: Adverse Reactions Occurring in ≥ 15% of Patients Treated with Tacrolimus in Conjunction with Azathioprine (AZA)

	Tacrolimus /AZA (N=205)	**Cyclosporine/AZA (N=207)**
Nervous System		
Tremor	54%	34%
Headache	44%	38%
Insomnia	32%	30%
Paresthesia	23%	16%
Dizziness	19%	16%
Gastrointestinal		
Diarrhea	44%	41%
Nausea	38%	36%
Constipation	35%	43%
Vomiting	29%	23%
Dyspepsia	28%	20%
Cardiovascular		
Hypertension	50%	52%
Chest Pain	19%	13%
Urogenital		
Creatinine Increased	45%	42%
Urinary Tract Infection	34%	35%
Metabolic and Nutritional		
Hypophosphatemia	49%	53%
Hypomagnesemia	34%	17%
Hyperlipemia	31%	38%
Hyperkalemia	24%	9%
Diabetes Mellitus	31%	32%
Hypokalemia	22%	25%
Hyperglycemia	22%	16%
Edema	18%	19%
Hemic and Lymphatic		
Anemia	30%	24%
Leukopenia	15%	17%
Miscellaneous		
Infection	45%	49%
Peripheral Edema	36%	48%

Asthenia	34%	30%
Abdominal Pain	33%	31%
Pain	32%	30%
Fever	29%	29%
Back Pain	24%	20%
Respiratory System		
Dyspnea	22%	18%
Cough Increased	18%	15%
Musculoskeletal		
Arthralgia	25%	24%
Skin		
Rash	17%	12%
Pruritus	15%	7%

Two trials were conducted for tacrolimus -based immunosuppression in conjunction with MMF and corticosteroids. In the non-US trial (Study 1), the incidence of adverse reactions was based on 1,195 kidney transplant patients that received tacrolimus (Group C, n=403), or one of two cyclosporine (CsA) regimens (Group A, n=384 and Group B, n=408) in combination with MMF and corticosteroids; all patients, except those in one of the two cyclosporine groups, also received induction with daclizumab. The trial population had a mean age of 46 years (range 17 to 76), the distribution was 65% male, and the composition was 93% Caucasian. The 12 month post-transplant information from this trial is presented below.

Adverse reactions that occurred in ≥ 10% of kidney transplant patients treated with tacrolimus in conjunction with MMF in Study 1 [Note: This trial was conducted entirely outside of the United States. Such trials often report a lower incidence of adverse reactions in comparison to U.S. trials] are presented below:

Table 5. Kidney Transplantation: Adverse Reactions Occurring in ≥ 10% of Patients Treated with Tacrolimus in Conjunction with MMF (Study 1)

	Tacrolimus (Group C)	**Cyclosporine (Group A)**	**Cyclosporine (Group B)**
	(N=403)	**(N=384)**	**(N=408)**
Diarrhea	25%	16%	13%
Urinary Tract Infection	24%	28%	24%
Anemia	17%	19%	17%
Hypertension	13%	14%	12%
Leukopenia	13%	10%	10%
Edema Peripheral	11%	12%	13%
Hyperlipidemia	10%	15%	13%
Key: Group A = CsA/MMF/CS, B = CsA/MMF/CS/Daclizumab, C= Tac/MMF/CS/Daclizumab CsA= Cyclosporine, CS = Corticosteroids, Tac = Tacrolimus, MMF = mycophenolate mofetil			

In the U.S. trial (Study 2) with tacrolimus-based immunosuppression in conjunction with MMF and corticosteroids, 424 kidney transplant patients received tacrolimus (n=212) or cyclosporine (n=212) in combination with MMF 1 gram twice daily, basiliximab induction, and corticosteroids. The trial population had a mean age of 48 years (range 17 to 77), the distribution was 63% male, and the composition was White (74%), Black (20%), Asian (3%) and other (3%). The 12 month post-transplant information from this trial is presented below.

Adverse reactions that occurred in ≥15% of kidney transplant patients treated with tacrolimus in conjunction with MMF in Study 2 are presented below:

Table 6. Kidney Transplantation: Adverse Reactions Occurring in ≥ 15% of Patients Treated with Tacrolimus in Conjunction with MMF (Study 2)

	Tacrolimus /MMF	**Cyclosporine/MMF**
	(N=212)	**(N=212)**
Gastrointestinal Disorders		
Diarrhea	44%	26%
Nausea	39%	47%
Constipation	36%	41%
Vomiting	26%	25%
Dyspepsia	18%	15%
Injury, Poisoning, and Procedural Complications		
Post-Procedural Pain	29%	27%
Incision Site Complication	28%	23%
Graft Dysfunction	24%	18%
Metabolism and Nutrition Disorders		
Hypomagnesemia	28%	22%
Hypophosphatemia	28%	21%
Hyperkalemia	26%	19%
Hyperglycemia	21%	15%
Hyperlipidemia	18%	25%
Hypokalemia	16%	18%
Nervous System Disorders		
Tremor	34%	20%
Headache	24%	25%
Blood and Lymphatic System Disorders		
Anemia	30%	28%
Leukopenia	16%	12%
Miscellaneous		
Edema Peripheral	35%	46%
Hypertension	32%	35%
Insomnia	30%	21%
Urinary Tract Infection	26%	22%
Blood Creatinine Increased	23%	23%

Less frequently observed adverse reactions in both liver transplantation and kidney transplantation patients are described under the subsection *Less Frequently Reported Adverse Reactions.*

Liver Transplantation

There were two randomized comparative liver transplant trials. In the U.S. trial, 263 adult and pediatric patients received tacrolimus and steroids and 266 patients received cyclosporine-based immunosuppressive regimen (CsA/AZA). The trial population had a mean age of 44 years (range 0.4 to 70), the distribution was 52% male, and the composition was White (78%), Black (5%), Asian (2%), Hispanic (13%) and Other (2%). In the European trial, 270 patients received tacrolimus and steroids and 275 patients received CsA/AZA. The trial population had a mean age of 46 years (range 15 to 68), the distribution was 59% male, and the composition was White (95.4%), Black (1%), Asian (2%) and Other

(2%).

The proportion of patients reporting more than one adverse event was > 99% in both the tacrolimus group and the CsA/AZA group. Precautions must be taken when comparing the incidence of adverse reactions in the U.S. trial to that in the European trial. The 12-month post-transplant information from the U.S. trial and from the European trial is presented below. The two trials also included different patient populations and patients were treated with immunosuppressive regimens of differing intensities. Adverse reactions reported in ≥15% in tacrolimus patients (combined trial results) are presented below for the two controlled trials in liver transplantation.

The most common adverse reactions (≥ 40%) observed in tacrolimus-treated liver transplant patients are: tremor, headache, diarrhea, hypertension, nausea, abnormal renal function, abdominal pain, insomnia, paresthesia, anemia, pain, fever, asthenia, hyperkalemia, hypomagnesemia, and hyperglycemia. These all occur with oral administration of tacrolimus and some may respond to a reduction in dosing (e.g., tremor, headache, paresthesia, hypertension). Diarrhea was sometimes associated with other gastrointestinal complaints such as nausea and vomiting.

Table 7. Liver Transplantation: Adverse Reactions Occurring in ≥ 15% of Patients Treated with Tacrolimus

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

Hypokalemia	29%	34%	13%	16%
Hemic and Lymphatic				
Anemia	47%	38%	5%	1%
Leukocytosis	32%	26%	8%	8%
Thrombocytopenia	24%	20%	14%	19%
Miscellaneous				
Pain	63%	57%	24%	22%
Abdominal Pain	59%	54%	29%	22%
Asthenia	52%	48%	11%	7%
Fever	48%	56%	19%	22%
Back Pain	30%	29%	17%	17%
Ascites	27%	22%	7%	8%
Peripheral Edema	26%	26%	12%	14%
Respiratory System				
Pleural Effusion	30%	32%	36%	35%
Dyspnea	29%	23%	5%	4%
Atelectasis	28%	30%	5%	4%
Skin and Appendages				
Pruritus	36%	20%	15%	7%
Rash	24%	19%	10%	4%

Less frequently observed adverse reactions in both liver transplantation and kidney transplantation patients are described under the subsection *Less Frequently Reported Adverse Reactions*.

Heart Transplantation

The incidence of adverse reactions was determined based on two trials in primary orthotopic heart transplantation. In a trial conducted in Europe, 314 patients received a regimen of antibody induction, corticosteroids and azathioprine (AZA) in combination with tacrolimus (n=157) or cyclosporine (n=157) for 18 months. The trial population had a mean age of 51 years (range 18 to 65), the distribution was 82% male, and the composition was White (96%), Black (3%) and other (1%).

The most common adverse reactions (≥ 15%) observed in tacrolimus-treated heart transplant patients are: abnormal renal function, hypertension, diabetes mellitus, CMV infection, tremor, hyperglycemia, leukopenia, infection, anemia, bronchitis, pericardial effusion, urinary tract infection and hyperlipemia.

Adverse reactions in heart transplant patients in the European trial are presented below:

Table 8. Heart Transplantation: Adverse Reactions Occurring in ≥ 15% of Patients Treated with Tacrolimus in Conjunction with Azathioprine (AZA)

	Tacrolimus/AZA	**Cyclosporine/AZA**
	(n=157)	**(n=157)**
Cardiovascular System		
Hypertension	62%	69%
Pericardial Effusion	15%	14%
Body as a Whole		
CMV Infection	32%	30%
Infection	24%	21%

Metabolism and Nutrition Disorders		
Diabetes Mellitus	26%	16%
Hyperglycemia	23%	17%
Hyperlipemia	18%	27%
Hemic and Lymphatic System		
Anemia	50%	36%
Leukopenia	48%	39%
Urogenital System		
Kidney Function Abnormal	56%	57%
Urinary Tract Infection	16%	12%
Respiratory System		
Bronchitis	17%	18%
Nervous System		
Tremor	15%	6%

In the European trial, the cyclosporine trough concentrations were above the pre-defined target range (i.e. 100 to 200 ng/mL) at Day 122 and beyond in 32to 68% of the patients in the cyclosporine treatment arm, whereas the tacrolimus trough concentrations were within the pre-defined target range (i.e., 5 to 15 ng/mL) in74 to 86% of the patients in the tacrolimus treatment arm.

In the U.S. trial, the incidence of adverse reactions was based on 331 heart transplant patients that received corticosteroids and tacrolimus in combination with sirolimus (n=109), tacrolimus in combination with MMF (n=107) or cyclosporine modified in combination with MMF (n=115) for 1 year. The trial population had a mean age of 53 years (range 18 to 75), the distribution was 78% male, and the composition was White (83%), Black (13%) and other (4%).

Only selected targeted treatment-emergent adverse reactions were collected in the U.S. heart transplantation trial. Those reactions that were reported at a rate of 15% or greater in patients treated with tacrolimus and MMF include the following: any target adverse reactions (99%), hypertension (89%), hyperglycemia requiring antihyperglycemic therapy (70%), hypertriglyceridemia (65%), anemia (hemoglobin < 10 g/dL) (65%), fasting blood glucose > 140 mg/dL (on two separate occasions) (61%), hypercholesterolemia (57%), hyperlipidemia (34%), WBCs <3000 cells/mcL (34%), serious bacterial infections (30%), magnesium <1.2 mEq/L (24%), platelet count <75,000 cells/mcL (19%), and other opportunistic infections (15%).

Other targeted treatment-emergent adverse reactions in tacrolimus-treated patients occurred at a rate of less than 15%, and include the following: Cushingoid features, impaired wound healing, hyperkalemia, *Candida* infection, and CMV infection/syndrome.

New Onset Diabetes After Transplant

Kidney Transplant

New Onset Diabetes After Transplant (NODAT) is defined as a composite of fasting plasma glucose ≥126 mg/dL,
HbA_{1C} ≥ 6%, insulin use ≥ 30 days or oral hypoglycemic use. In a trial in kidney transplant patients (Study 2), NODAT was observed in 75% in the tacrolimus-treated and 61% in the Neoral-treated patients without pre-transplant history of diabetes mellitus (**Table 9**) [see **CLINICAL STUDIES (14.1)**].

Table 9. Incidence of New Onset Diabetes After Transplant at 1 Year in Kidney Transplant Recipients in a Phase 3 Trial (Study 2)

Parameter	**Treatment Group**	
	Tacrolimus/MMF	**Neoral/MMF**

	(n = 212)	(n = 212)
NODAT	112/150 (75%)	93/152 (61%)
Fasting Plasma Glucose ≥ 126 mg/dL	96/150 (64%)	80/152 (53%)
HbA_{1C} ≥ 6%	59/150 (39%)	28/152 (18%)
Insulin Use ≥ 30 days	9/150 (6%)	4/152 (3%)
Oral Hypoglycemic Use	15/150 (10%)	5/152 (3%)

In early trials of tacrolimus, Post-Transplant Diabetes Mellitus (PTDM) was evaluated with a more limited criteria of "use of insulin for 30 or more consecutive days with < 5 day gap" in patients without a prior history of insulin-dependent diabetes mellitus or non-insulin dependent diabetes mellitus. Data are presented in **Tables 10** to **13**. PTDM was reported in 20% of tacrolimus/Azathioprine (AZA)-treated kidney transplant patients without pre-transplant history of diabetes mellitus in a Phase 3 trial (**Table 10**). 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 2 years post-transplant. Black and Hispanic kidney transplant patients were at an increased risk of development of PTDM (**Table 11**).

Table 10. Incidence of Post-Transplant Diabetes Mellitus and Insulin Use at 2 Years in Kidney Transplant Recipients in a Phase 3 Trial using Azathioprine (AZA)

Status of PTDM*	**Tacrolimus/AZA**	**CsA/AZA**
Patients without pre-transplant history of diabetes mellitus	151	151
New onset PTDM[a], 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[a] post 1 year	1	0
Patients with PTDM[a] at 2 years	16/151 (11%)	5/151 (3%)

* 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.

Table 11. Development of Post-Transplant Diabetes Mellitus by Race or Ethnicity and by Treatment Group During First Year Post Kidney Transplantation in a Phase 3 Trial

Patient Race	**Patients Who Developed PTDM***	
	Tacrolimus	**Cyclosporine**
Black	15/41 (37%)	3 (8%)
Hispanic	5/17 (29%)	1 (6%)
Caucasian	10/82 (12%)	1 (1%)
Other	0/11 (0%)	1 (10%)
Total	30/151 (20%)	6 (4%)

* 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.

Liver Transplant

Insulin-dependent PTDM was reported in 18% and 11% of tacrolimus-treated liver transplant patients and was reversible in 45% and 31% of these patients at 1 year post-transplant, in the U.S. and European randomized trials, respectively (**Table 12**). Hyperglycemia was associated with the use of tacrolimus in 47% and 33% of liver transplant recipients in the U.S. and European randomized trials, respectively, and may require treatment [see **ADVERSE REACTIONS (6.1)**].

Table 12. Incidence of Post-Transplant Diabetes Mellitus and Insulin Use at 1 Year in Liver Transplant Recipients

Status of PTDM*	US Trial		European Trial	
	Tacrolimus	Cyclosporine	Tacrolimus	Cyclosporine
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%)

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

† Patients without pre-transplant history of diabetes mellitus.

Heart Transplant

Insulin-dependent PTDM was reported in 13% and 22% of tacrolimus-treated heart transplant patients receiving mycophenolate mofetil (MMF) or azathioprine (AZA) and was reversible in 30% and 17% of these patients at one year post-transplant, in the U.S. and European randomized trials, respectively (**Table 13**). Hyperglycemia defined as two fasting plasma glucose levels ≥126 mg/dL was reported with the use of tacrolimus plus MMF or AZA in 32% and 35% of heart transplant recipients in the U.S. and European randomized trials, respectively, and may require treatment [see **ADVERSE REACTIONS (6.1)**].

Table 13. Incidence of Post-Transplant Diabetes Mellitus and Insulin Use at 1 Year in Heart Transplant Recipients

Status of PTDM*	US Trial		European Trial	
	Tacrolimus/MMF	Cyclosporine/MMF	Tacrolimus/AZA	Cyclosporine/AZA
Patients at risk†	75	83	132	138
New Onset PTDM*	10 (13%)	6 (7%)	29 (22%)	5 (4%)
Patients still on insulin at 1 year‡	7 (9%)	1 (1%)	24 (18%)	4 (3%)

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

† Patients without pre-transplant history of diabetes mellitus.

‡ 7 to 12 months for the U.S. trial.

Less Frequently Reported Adverse Reactions (>3% and <15%)

The following adverse reactions were reported in either liver, kidney, and/or heart transplant recipients who were treated with tacrolimus in clinical trials.

Nervous System [see **WARNINGS AND PRECAUTIONS (5.8)**]

Abnormal dreams, agitation, amnesia, anxiety, confusion, convulsion, crying, depression, elevated mood, emotional lability, encephalopathy, haemorrhagic stroke, hallucinations, hypertonia, incoordination, monoparesis, myoclonus, nerve compression, nervousness, neuralgia, neuropathy, paralysis flaccid, psychomotor skills impaired, psychosis, quadriparesis, somnolence, thinking

abnormal, vertigo, writing impaired

Special Senses

Abnormal vision, amblyopia, ear pain, otitis media, tinnitus

Gastrointestinal

Cholangitis, cholestatic jaundice, duodenitis, dysphagia, esophagitis, flatulence, gastritis, gastroesophagitis, gastrointestinal hemorrhage, GGT increase, GI disorder, GI perforation, hepatitis, hepatitis granulomatous, ileus, increased appetite, jaundice, liver damage, oesophagitis ulcerative, oral moniliasis, pancreatic pseudocyst, rectal disorder, stomatitis

Cardiovascular

Abnormal ECG, angina pectoris, arrhythmia, atrial fibrillation, atrial flutter, bradycardia, cardiac fibrillation, cardiopulmonary failure, cardiovascular disorder, congestive heart failure, deep thrombophlebitis, echocardiogram abnormal, electrocardiogram QRS complex abnormal, electrocardiogram ST segment abnormal, heart failure, heart rate decreased, hemorrhage, hypotension, peripheral vascular disorder, phlebitis, postural hypotension, syncope, tachycardia, thrombosis, vasodilatation

Urogenital

Acute kidney failure [see **WARNINGS AND PRECAUTIONS (5.7)**], albuminuria, BK nephropathy, bladder spasm, cystitis, dysuria, hematuria, hydronephrosis, kidney failure, kidney tubular necrosis, nocturia, pyuria, toxic nephropathy, urge incontinence, urinary frequency, urinary incontinence, urinary retention, vaginitis

Metabolic/Nutritional

Acidosis, alkaline phosphatase increased, alkalosis, ALT (SGPT) increased, AST (SGOT) increased, bicarbonate decreased, bilirubinemia, dehydration, GGT increased, gout, healing abnormal, hypercalcemia, hypercholesterolemia, hyperphosphatemia, hyperuricemia, hypervolemia, hypocalcemia, hypoglycemia, hyponatremia, hypoproteinemia, lactic dehydrogenase increase, weight gain

Endocrine

Cushing’s syndrome

Hemic/Lymphatic

Coagulation disorder, ecchymosis, haematocrit increased, haemoglobin abnormal, hypochromic anemia, leukocytosis, polycythemia, prothrombin decreased, serum iron decreased

Miscellaneous

Abdomen enlarged, abscess, accidental injury, allergic reaction, cellulitis, chills, fall, feeling abnormal, flu syndrome, generalized edema, hernia, mobility decreased, peritonitis, photosensitivity reaction, sepsis, temperature intolerance, ulcer

Musculoskeletal

Arthralgia, cramps, generalized spasm, joint disorder, leg cramps, myalgia, myasthenia, osteoporosis

Respiratory

Asthma, emphysema, hiccups, lung disorder, lung function decreased, pharyngitis, pneumonia, pneumothorax, pulmonary edema, respiratory disorder, rhinitis, sinusitis, voice alteration

Skin

Acne, alopecia, exfoliative dermatitis, fungal dermatitis, herpes simplex, herpes zoster, hirsutism, neoplasm skin benign, skin discoloration, skin disorder, skin ulcer, sweating

6.2 Postmarketing Adverse Reactions

The following adverse reactions have been reported from worldwide marketing experience with tacrolimus. Because these reactions are reported voluntarily from a population of uncertain size it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of the reporting, or (3) strength of causal connection to the drug.

Other reactions include:

Cardiovascular

Atrial fibrillation, atrial flutter, cardiac arrhythmia, cardiac arrest, electrocardiogram T wave abnormal, flushing, myocardial infarction, myocardial ischaemia, pericardial effusion, QT prolongation, Torsade de Pointes, venous thrombosis deep limb, ventricular extrasystoles, ventricular fibrillation, myocardial hypertrophy [see **WARNINGS AND PRECAUTIONS (5.14)**].

Gastrointestinal

Bile duct stenosis, colitis, enterocolitis, gastroenteritis, gastroesophageal reflux disease, hepatic cytolysis, hepatic necrosis, hepatotoxicity, impaired gastric emptying, liver fatty, mouth ulceration, pancreatitis haemorrhagic, pancreatitis necrotizing, stomach ulcer, venoocclusive liver disease

Hemic/Lymphatic

Agranulocytosis, disseminated intravascular coagulation, hemolytic anemia, neutropenia, pancytopenia, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pure red cell aplasia [see **WARNINGS AND PRECAUTIONS (5.17)**]

Infections

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal; -polyoma virus-associated nephropathy, (PVAN) including graft loss [see **WARNINGS AND PRECAUTIONS (5.4)**]

Metabolic/Nutritional

Glycosuria, increased amylase including pancreatitis, weight decreased

Miscellaneous

Feeling hot and cold, feeling jittery, hot flushes, multi-organ failure, primary graft dysfunction

Nervous System

Carpal tunnel syndrome, cerebral infarction, hemiparesis, leukoencephalopathy, mental disorder, mutism, posterior reversible encephalopathy syndrome (PRES) [see **WARNINGS AND PRECAUTIONS (5.8)**], progressive multifocal leukoencephalopathy (PML) [see **WARNINGS AND PRECAUTIONS (5.4)**], quadriplegia, speech disorder, syncope

Respiratory

Acute respiratory distress syndrome, interstitial lung disease, lung infiltration, respiratory distress, respiratory failure

Skin

Stevens-Johnson syndrome, toxic epidermal necrolysis

Special Senses

Blindness, blindness cortical, hearing loss including deafness, photophobia

Urogenital

Acute renal failure, cystitis haemorrhagic, hemolytic-uremic syndrome, micturition disorder

7 DRUG INTERACTIONS

Since tacrolimus is metabolized mainly by CYP3A enzymes, drugs or substances known to inhibit these enzymes may increase tacrolimus whole blood concentrations. Drugs known to induce CYP3A enzymes may decrease tacrolimus whole blood concentrations [see **WARNINGS AND PRECAUTIONS (5.13)** and **CLINICAL PHARMACOLOGY (12.3)**]. Dose adjustments may be needed along with frequent monitoring of tacrolimus whole blood trough concentrations when tacrolimus is administered with CYP3A inhibitors or inducers. In addition, patients should be monitored for adverse reactions including changes in renal function and QT prolongation [see **WARNINGS AND PRECAUTIONS (5.7)** and **(5.14)**].

7.1 Mycophenolic Acid Products

With a given dose of mycophenolic acid (MPA) products, exposure to MPA is higher with tacrolimus co-administration than with cyclosporine co-administration because cyclosporine interrupts the enterohepatic recirculation of MPA while tacrolimus does not. Clinicians should be aware that there is also a potential for increased MPA exposure after crossover from cyclosporine to tacrolimus in patients concomitantly receiving MPA-containing products.

7.2 Grapefruit Juice

Grapefruit juice inhibits CYP3A-enzymes resulting in increased tacrolimus whole blood trough concentrations, and patients should avoid eating grapefruit or drinking grapefruit juice with tacrolimus [see **DOSAGE AND ADMINISTRATION (2.5)**].

7.3 Protease Inhibitors

Most protease inhibitors inhibit CYP3A enzymes and may increase tacrolimus whole blood concentrations. It is recommended to avoid concomitant use of tacrolimus with nelfinavir unless the benefits outweigh the risks [see **CLINICAL PHARMACOLOGY (12.3)**]. Whole blood concentrations of tacrolimus are markedly increased when coadministered with telaprevir or with boceprevir [see **CLINICAL PHARMACOLOGY (12.3)**]. Monitoring of tacrolimus whole blood concentrations and tacrolimus-associated adverse reactions, and appropriate adjustments in the dosing regimen of tacrolimus are recommended when tacrolimus and protease inhibitors (e.g., ritonavir, telaprevir, boceprevir) are used concomitantly.

7.4 Antifungal Agents

Frequent monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when concomitant use of the following antifungal drugs with tacrolimus is initiated or discontinued [see **CLINICAL PHARMACOLOGY (12.3)**].

Azoles: Voriconazole, posaconazole, itraconazole, ketoconazole, fluconazole and clotrimazole inhibit CYP3A metabolism of tacrolimus and increase tacrolimus whole blood concentrations. When initiating therapy with voriconazole or posaconazole in patients already receiving tacrolimus, it is recommended that the tacrolimus dose be initially reduced to one-third of the original dose and the subsequent tacrolimus doses be adjusted based on the tacrolimus whole blood concentrations.

Caspofungin is an inducer of CYP3A and decreases whole blood concentrations of tacrolimus.

7.5 Calcium Channel Blockers

Verapamil, diltiazem, nifedipine, and nicardipine inhibit CYP3A metabolism of tacrolimus and may increase tacrolimus whole blood concentrations. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these calcium channel blocking drugs and tacrolimus are used concomitantly.

7.6 Antibacterials

Erythromycin, clarithromycin, troleandomycin and chloramphenicol inhibit CYP3A metabolism of tacrolimus and may increase tacrolimus whole blood concentrations. Monitoring of blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these drugs and tacrolimus are used concomitantly.

7.7 Antimycobacterials

Rifampin [see **CLINICAL PHARMACOLOGY (12.3)**] and rifabutin are inducers of CYP3A enzymes and may decrease tacrolimus whole blood concentrations. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these antimycobacterial drugs and tacrolimus are used concomitantly.

7.8 Anticonvulsants

Phenytoin, carbamazepine and phenobarbital induce CYP3A enzymes and may decrease tacrolimus whole blood concentrations. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these drugs and tacrolimus are used concomitantly.

Concomitant administration of phenytoin with tacrolimus may also increase phenytoin plasma concentrations. Thus, frequent monitoring phenytoin plasma concentrations and adjusting the phenytoin dose as needed are recommended when tacrolimus and phenytoin are administered concomitantly.

7.9 St. John's Wort (*Hypericum perforatum*)

St. John's Wort induces CYP3A enzymes and may decrease tacrolimus whole blood concentrations. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when St. John's Wort and tacrolimus are co-administered.

7.10 Gastric Acid Suppressors/Neutralizers

Lansoprazole and omeprazole, as CYP2C19 and CYP3A4 substrates, may potentially inhibit the CYP3A4 metabolism of tacrolimus and thereby substantially increase tacrolimus whole blood concentrations, especially in transplant patients who are intermediate or poor CYP2C19 metabolizers, as compared to those patients who are efficient CYP2C19 metabolizers.

Cimetidine may also inhibit the CYP3A4 metabolism of tacrolimus and thereby substantially increase tacrolimus whole blood concentrations.

Coadministration with magnesium and aluminum hydroxide antacids increase tacrolimus whole blood concentrations [see **CLINICAL PHARMACOLOGY (12.3)**]. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these drugs and tacrolimus are used concomitantly.

7.11 Others

Bromocriptine, nefazodone, metoclopramide, danazol, ethinyl estradiol, amiodarone and methylprednisolone may inhibit CYP3A metabolism of tacrolimus and increase tacrolimus whole blood concentrations. Monitoring of blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these drugs and tacrolimus are co-administered.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C - There are no adequate and well-controlled studies in pregnant women. Tacrolimus is transferred across the placenta. The use of tacrolimus during pregnancy in humans has been associated with neonatal hyperkalemia and renal dysfunction. Tacrolimus given orally to pregnant

rabbits at 0.5 to 4.3 times the clinical dose and pregnant rats at 0.8 to 6.9 times the clinical dose was associated with an increased incidence of fetal death *in utero*, fetal malformations (cardiovascular, skeletal, omphalocele, and gallbladder agenesis) and maternal toxicity. Tacrolimus should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In pregnant rabbits, tacrolimus at oral doses of 0.32 and 1 mg/kg, 0.5 to 4.3 times the clinical dose range (0.075 to 0.2 mg/kg) based on body surface area, was associated with maternal toxicity as well as an increased incidence of abortions. At the 1 mg/kg dose, fetal rabbits showed an increased incidence of malformations (ventricular hypoplasia, interventricular septal defect, bulbous aortic arch, stenosis of ductus arteriosis, interrupted ossification of vertebral arch, vertebral and rib malformations, omphalocele, and gallbladder agenesis) and developmental variations. In pregnant rats, tacrolimus at oral doses of 3.2 mg/kg, 2.6 to 6.9 times the clinical dose range was associated with maternal toxicity, an increase in late resorptions, decreased numbers of live births, and decreased pup weight and viability. Tacrolimus, given orally to pregnant rats after organogenesis and during lactation at 1 and 3.2 mg/kg, 0.8 to 6.9 times the recommended clinical dose range was associated with reduced pup weights and pup viability (3.2 mg/kg only); among the high dose pups that died early, an increased incidence of kidney hydronephrosis was observed.

8.3 Nursing Mothers

Tacrolimus is excreted in human milk. As the effect of chronic exposure to tacrolimus in healthy infants is not established, patients maintained on tacrolimus should discontinue nursing taking into consideration importance of drug to the mother.

8.4 Pediatric Use

The safety and efficacy of tacrolimus in pediatric kidney and heart transplant patients have not been established. Successful liver transplants have been performed in pediatric patients (ages up to 16 years) using tacrolimus. Two randomized active-controlled trials of tacrolimus in primary liver transplantation included 56 pediatric patients. Thirty-one patients were randomized to tacrolimus-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 tacrolimus to maintain blood trough concentrations of tacrolimus similar to adult patients [see **DOSAGE AND ADMINISTRATION (2.2)**].

8.5 Geriatric Use

Clinical trials of tacrolimus did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Use in Renal Impairment

The pharmacokinetics of tacrolimus in patients with renal impairment was similar to that in healthy volunteers with normal renal function. However, consideration should be given to dosing tacrolimus at the lower end of the therapeutic dosing range in patients who have received a liver or heart transplant and have pre-existing renal impairment. Further reductions in dose below the targeted range may be required [see **DOSAGE AND ADMINISTRATION (2.3)** and **CLINICAL PHARMACOLOGY (12.3)**].

8.7 Use in Hepatic Impairment

The mean clearance of tacrolimus was substantially lower in patients with severe hepatic impairment (mean Child-Pugh score: >10) compared to healthy volunteers with normal hepatic function. Close

monitoring of tacrolimus trough concentrations is warranted in patients with hepatic impairment [see **CLINICAL PHARMACOLOGY (12.3)**].

The use of tacrolimus in liver transplant recipients experiencing post-transplant hepatic impairment may be associated with increased risk of developing renal insufficiency related to high whole-blood trough concentrations of tacrolimus. These patients should be monitored closely and dosage adjustments should be considered. Some evidence suggests that lower doses should be used in these patients [see **DOSAGE AND ADMINISTRATION (2.3)** and **CLINICAL PHARMACOLOGY (12.3)**].

10 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. Acute overdosage was sometimes followed by adverse reactions consistent with those listed in **ADVERSE REACTIONS (6)** (including tremors, abnormal renal function, hypertension, and peripheral edema); in one case of acute overdosage, 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.

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

11 DESCRIPTION

Tacrolimus capsules, USP are available for oral administration containing the equivalent of 0.5 mg, 1 mg or 5 mg of anhydrous tacrolimus. In addition, each capsule contains the following inactive ingredients: croscarmellose sodium, hypromellose, lactose monohydrate, and magnesium stearate.

The tacrolimus capsule shell for 0.5 mg strength consists of gelatin, titanium dioxide and yellow iron oxide.

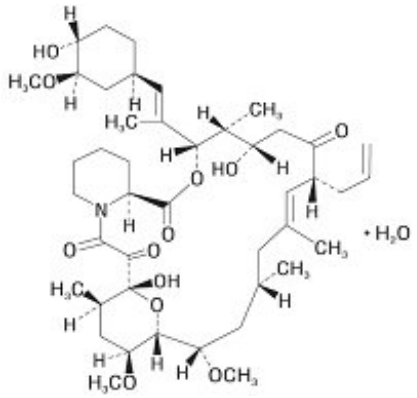
The tacrolimus capsule shell for 1 mg strength consists of black iron oxide, gelatin, red iron oxide, titanium dioxide, and yellow iron oxide.

The tacrolimus capsule shell for 5 mg strength consists of red iron oxide, gelatin, and titanium dioxide.

Tacrolimus capsules, USP 0.5 mg, 1 mg and 5 mg are printed with edible black ink. The black ink is comprised of ammonia, black iron oxide, butyl alcohol, potassium hydroxide, propylene glycol, and shellac.

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

The chemical structure of tacrolimus is:



Tacrolimus has a molecular formula of $C_{44}H_{69}NO_{12}$•H_2O and a formula weight of 822.03. Tacrolimus appears as white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform.

USP Dissolution test 2 and Organic Impurities procedure 2 used.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

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

12.3 Pharmacokinetics

Tacrolimus activity is primarily due to the parent drug. The pharmacokinetic parameters (mean±S.D.) of tacrolimus have been determined following intravenous (IV) and/or oral (PO) administration in healthy volunteers, and in kidney transplant, liver transplant, and heart transplant patients (**Table 14**).

Table 14. Pharmacokinetics Parameters (mean±S.D.) of Tacrolimus in Healthy Volunteers and Patients

Population	**N**	**Route (Dose)**	Parameters					
			C_{max} (ng/mL)	**T_{max} (hr)**	**AUC (ng•hr/mL)**	**$t_{1/2}$ (hr)**	**CI (L/hr/kg)**	**V (L/kg)**
Healthy Volunteers	8	IV (0.025 mg/kg/4hr)	a	a	598b ± 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	243c ± 73	34.8 ± 11.4	0.041d ± 0.008	1.94d ± 0.53
		IV (0.02 mg/kg/12	a	a	294e ± 262	18.8 ± 16.7	0.083 ± 0.050	1.41 ± 0.66

Kidney Transplant Patients	26	hr)						
		PO (0.2 mg/kg/day)	19.2 ± 10.3	3	203e ± 42	f	f	f
		PO (0.3 mg/kg/day)	24.2 ± 15.8	1.5	288e ± 93	f	f	f
Liver Transplant Patients	17	IV (0.05 mg/kg/12 hr)	a	a	3300e ± 2130	11.7 ± 3.9	0.053 ± 0.017	0.85 ± 0.30
		PO (0.3 mg/kg/day)	68.5 ± 30	2.3 ± 1.5	519e ± 179	f	f	f
Heart Transplant Patients	11	IV (0.01 mg/kg/day as a continuous infusion)	a	a	954[g] ± 334	23.6 ± 9.22	0.051 ± 0.015	f
	11	PO (0.075 mg/kg/day)[h]	14.7 ± 7.79	2.1 [0.5-6]i	82.7j ± 63.2	a	f	f
	14	PO (0.15 mg/kg/day)[h]	24.5 ± 13.7	1.5 [0.4-4]i	142j ± 116	a	f	f

[a]not applicable
[b]AUC_{0-120}
[c]AUC_{0-72}
[d]Corrected for individual bioavailability
[e]AUC_{0-inf}

[f]not available
[g]AUC_{0-t}
[h]Determined after the first dose
[i]Median [range]

[j]AUC_{0-12}

Due to intersubject variability in tacrolimus pharmacokinetics, individualization of dosing regimen is necessary for optimal therapy [see **DOSAGE AND ADMINISTRATION (2.6)**]. Pharmacokinetic data indicate that whole blood concentrations rather than plasma concentrations serve as the more appropriate sampling compartment to describe tacrolimus pharmacokinetics.

Absorption

Absorption of tacrolimus from the gastrointestinal tract after oral administration is incomplete and variable. The absolute bioavailability of tacrolimus was 17±10% in adult kidney transplant patients (N=26), 22±6% in adult liver transplant patients (N=17), 23±9% in adult heart transplant patients (N=11) and 18±5% in healthy volunteers (N=16).

A single dose trial conducted in 32 healthy volunteers established the bioequivalence of the 1 mg and 5 mg capsules. Another single dose trial in 32 healthy volunteers established the bioequivalence of the 0.5 mg and 1 mg capsules. Tacrolimus maximum blood concentrations (C_{max}) and area under the curve

(AUC) appeared to increase in a dose-proportional fashion in 18 fasted healthy volunteers receiving a single oral dose of 3, 7, and 10 mg.

In 18 kidney transplant patients, tacrolimus trough concentrations from 3 to 30 ng/mL measured at 10 to 12 hours post-dose (C_{min}) correlated well with the AUC (correlation coefficient 0.93). In 24 liver transplant patients over a concentration range of 10 to 60 ng/mL, the correlation coefficient was 0.94. In 25 heart transplant patients over a concentration range of 2 to 24 ng/mL, the correlation coefficient was 0.89 after an oral dose of 0.075 or 0.15 mg/kg/day at steady-state.

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.

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.

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

In 11 liver transplant patients, tacrolimus 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.

Tacrolimus capsules should be taken consistently every day either with or without food because the presence and composition of food decreases the bioavailability of tacrolimus [see **DOSAGE AND ADMINISTRATION (2.5)**].

Distribution

The plasma protein binding of tacrolimus is approximately 99% and is independent of concentration over a range of 5 to 50 ng/mL. Tacrolimus is bound mainly to albumin and alpha-1-acid glycoprotein, and has a high level of association with erythrocytes. The distribution of tacrolimus between whole blood and plasma depends on several factors, such as hematocrit, temperature at the time of plasma separation, drug concentration, and plasma protein concentration. In a U.S. trial, the ratio of whole blood concentration to plasma concentration averaged 35 (range 12 to 67).

Metabolism

Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P-450 system (CYP3A). A metabolic pathway leading to the formation of 8 possible metabolites has been proposed. Demethylation and hydroxylation were identified as the primary mechanisms of biotransformation *in vitro*. The major metabolite identified in incubations with human liver microsomes is 13-demethyl tacrolimus. In *in vitro* studies, a 31-demethyl metabolite has been reported to have the same activity as tacrolimus.

Excretion

The mean clearance following IV administration of tacrolimus is 0.040, 0.083, and 0.053, and 0.051 L/hr/kg in healthy volunteers, adult kidney transplant patients, adult liver transplant patients, and adult heart transplant patients, respectively. In man, less than 1% of the dose administered is excreted unchanged in urine.

In a mass balance study of IV administered radiolabeled tacrolimus to 6 healthy volunteers, the mean recovery of radiolabel was 77.8±12.7%. Fecal elimination accounted for 92.4±1% and the elimination half-life based on radioactivity was 48.1±15.9 hours whereas it was 43.5±11.6 hours based on tacrolimus concentrations. The mean clearance of radiolabel was 0.029±0.015 L/hr/kg and clearance of tacrolimus was 0.029±0.009 L/hr/kg. When administered PO, the mean recovery of the radiolabel was

94.9±30.7%. Fecal elimination accounted for 92.6±30.7%, urinary elimination accounted for 2.3±1.1% and the elimination half-life based on radioactivity was 31.9±10.5 hours whereas it was 48.4±12.3 hours based on tacrolimus concentrations. The mean clearance of radiolabel was 0.226±0.116 L/hr/kg and clearance of tacrolimus 0.172±0.088 L/hr/kg.

Specific Populations

Pediatric

Pharmacokinetics of tacrolimus have been studied in liver transplantation patients, 0.7 to 13.2 years of age. Following oral administration to 9 patients, mean AUC and C_{max} were 337±167 ng·hr/mL and 48.4±27.9 ng/mL, respectively. The absolute bioavailability was 31±24%.

Whole blood trough concentrations from 31 patients less than 12 years old showed that pediatric patients needed higher doses than adults to achieve similar tacrolimus trough concentrations [see **DOSAGE AND ADMINISTRATION (2.2)**].

Pharmacokinetics of tacrolimus have also been studied in kidney transplantation patients, 8.2±2.4 years of age. Following oral administration, mean AUC and C_{max} were 181±65 (range 81 to 300) ng·hr/mL and 30±11 (range 14 to 49) ng/mL, respectively. The absolute bioavailability was 19±14 (range 5.2 to 56) %.

Renal and Hepatic Impairment
The mean pharmacokinetic parameters for tacrolimus following single administrations to patients with renal and hepatic impairment are given in **Table 15**.

Table 15. Pharmacokinetic In Renal and Hepatic Impaired Patients

Population (No. of Patients)	**Dose**	**AUC_{0-t} (ng·hr/mL)**	**$t_{1/2}$ (hr)**	**V (L/kg)**	**CI 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 to 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 to 138	3.7±4.7*	0.034 ±0.019†
Severe Hepatic Impairment (n=6, IV)	0.02 mg/kg/4hr IV (n=2) 0.01 mg/kg/8hr IV (n=4)	762±204 (t=120 hr) 289±117 (t=144 hr)	198±158 Range: 81 to 436	3.9±1	0.017 ±0.013
(n=5, PO)*	8 mg PO (n=1) 5 mg PO (n=4) 4 mg PO (n=1)	658 (t=120 hr) 533±156 (t=144 hr)	119±35 Range: 85 to 178	3.1±3.4†	0.016 ±0.011†

* 1 patient did not receive the PO dose.

† Corrected for bioavailability.

Renal Impairment: Tacrolimus pharmacokinetics following a single IV administration were determined in 12 patients (7 not on dialysis and 5 on dialysis, serum creatinine of 3.9±1.6 and 12±2.4 mg/dL,

respectively) prior to their kidney transplant. The pharmacokinetic parameters obtained were similar for both groups. The mean clearance of tacrolimus in patients with renal dysfunction was similar to that in normal volunteers (**Table 15**) [see **DOSAGE AND ADMINISTRATION (2.3)** and **USE IN SPECIFIC POPULATIONS (8.6)**].

Hepatic Impairment: Tacrolimus pharmacokinetics have been determined in six patients with mild hepatic dysfunction (mean Pugh score: 6.2) following oral administrations. The mean clearance of tacrolimus in patients with mild hepatic dysfunction was not substantially different from that in normal volunteers (see previous table). Tacrolimus pharmacokinetics were studied in 6 patients with severe hepatic dysfunction (mean Pugh score: >10). The mean clearance was substantially lower in patients with severe hepatic dysfunction, irrespective of the route of administration [see **DOSAGE AND ADMINISTRATION (2.4)** and **USE IN SPECIFIC POPULATIONS (8.7)]**.

Race

The pharmacokinetics of tacrolimus have been studied following single IV and oral administration of tacrolimus to 10 African-American, 12 Latino-American, and 12 Caucasian healthy volunteers. There were no significant pharmacokinetic differences among the three ethnic groups following a 4-hour IV infusion of 0.015 mg/kg. However, after single oral administration of 5 mg, mean (±SD) tacrolimus C_{max} in African-Americans (23.6±12.1 ng/mL) was significantly lower than in Caucasians (40.2±12.6 ng/mL) and the Latino-Americans (36.2±15.8 ng/mL) ($p<0.01$). Mean $AUC_{0\text{-}inf}$ tended to be lower in African-Americans (203±115 ng·hr/mL) than Caucasians (344±186 ng·hr/mL) and Latino-Americans (274±150 ng·hr/mL). The mean (±SD) absolute oral bioavailability (F) in African-Americans (12±4.5%) and Latino-Americans (14±7.4%) was significantly lower than in Caucasians (19±5.8%, $p=0.011$). There was no significant difference in mean terminal $T_{1/2}$ among the three ethnic groups (range from approximately 25 to 30 hours). A retrospective comparison of African-American and Caucasian kidney transplant patients indicated that African-American patients required higher tacrolimus doses to attain similar trough concentrations [see **DOSAGE AND ADMINISTRATION (2.1)**].

Gender

A formal trial to evaluate the effect of gender on tacrolimus pharmacokinetics has not been conducted, however, there was no difference in dosing by gender in the kidney transplant trial. A retrospective comparison of pharmacokinetics in healthy volunteers, and in kidney, liver and heart transplant patients indicated no gender-based differences.

Drug Interactions

Frequent monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when concomitant use of the following drugs with tacrolimus is initiated or discontinued [see **DRUG INTERACTIONS (7)**].

Telaprevir: In a single dose study in 9 healthy volunteers, coadministration of tacrolimus (0.5 mg single dose) with telaprevir (750 mg three times daily for 13 days) increased the tacrolimus dose normalized C_{max} by 9.3-fold and AUC by 70-fold compared to tacrolimus alone *[see***DRUG INTERACTIONS (7.3)***]*.

Boceprevir: In a single dose study in 12 subjects, coadministration of tacrolimus (0.5 mg single dose) with boceprevir (800 mg three times daily for 11 days) increased tacrolimus C_{max} by 9.9-fold and AUC by 17-fold compared to tacrolimus alone *[see***DRUG INTERACTIONS (7.3)***]*.

Nelfinavir: Based on a clinical study of 5 liver transplant recipients, co-administration of tacrolimus with nelfinavir increased blood concentrations of tacrolimus significantly and, as a result, a reduction in the tacrolimus dose by an average of 16-fold was needed to maintain mean trough tacrolimus blood concentrations of 9.7 ng/mL. It is recommended to avoid concomitant use of tacrolimus and nelfinavir unless the benefits outweigh the risks [see **DRUG INTERACTIONS (7.3)**].

Rifampin: In a study of 6 normal volunteers, a significant decrease in tacrolimus oral bioavailability

(14±6% vs. 7±3%) was observed with concomitant rifampin administration (600 mg). In addition, there was a significant increase in tacrolimus clearance (0.036±0.008 L/hr/kg vs. 0.053±0.010 L/hr/kg) with concomitant rifampin administration [see **DRUG INTERACTIONS** (**7.7**)].

Magnesium-aluminum-hydroxide: In a single-dose crossover study in healthy volunteers, co-administration of tacrolimus and magnesium-aluminum-hydroxide resulted in a 21% increase in the mean tacrolimus AUC and a 10% decrease in the mean tacrolimus C_{max} relative to tacrolimus administration alone [see **DRUG INTERACTIONS (7.10)**].

Ketoconazole: In a study of 6 normal volunteers, a significant increase in tacrolimus oral bioavailability (14±5% vs. 30±8%) was observed with concomitant ketoconazole administration (200 mg). The apparent oral clearance of tacrolimus during ketoconazole administration was significantly decreased compared to tacrolimus alone (0.430±0.129 L/hr/kg vs. 0.148±0.043 L/hr/kg). Overall, IV clearance of tacrolimus was not significantly changed by ketoconazole co-administration, although it was highly variable between patients [see **DRUG INTERACTIONS (7.4)**].

Voriconazole (see complete prescribing information for Voriconazole): Repeat oral dose administration of voriconazole (400 mg every 12 hours for one day, then 200 mg every 12 hours for 6 days) increased tacrolimus (0.1 mg/kg single dose) C_{max} and AUCτ in healthy subjects by an average of 2-fold (90% CI: 1.9, 2.5) and 3-fold (90% CI: 2.7, 3.8), respectively [see **DRUG INTERACTIONS (7.4)**].

Posaconazole (see complete prescribing information for Noxafil®): Repeat oral administration of posaconazole (400 mg twice daily for 7 days) increased tacrolimus (0.05 mg/kg single dose) C_{max} and AUC in healthy subjects by an average of 2-fold (90% CI: 2.01, 2.42) and 4.5-fold (90% CI 4.03, 5.19), respectively [see **DRUG INTERACTIONS (7.4)**].

Caspofungin (see complete prescribing information for CANCIDAS®): Caspofungin reduced the blood AUC_{0-12} of tacrolimus by approximately 20%, peak blood concentration (C_{max}) by 16%, and 12-hour blood concentration (C12hr) by 26% in healthy adult subjects when tacrolimus (2 doses of 0.1 mg/kg 12 hours apart) was administered on the 10th day of CANCIDAS® 70 mg daily, as compared to results from a control period in which tacrolimus was administered alone [see **DRUG INTERACTIONS (7.4)**].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were conducted in male and female rats and mice. In the 80-week mouse oral study and in the 104-week rat oral study, no relationship of tumor incidence to tacrolimus dosage was found. The highest dose used in the mouse was 3 mg/kg/day (0.9 to 2.2 times the AUC at clinical doses of 0.075 to 0.2 mg/kg/day) and in the rat was 5 mg/kg/day (0.265 to 0.65 times the AUC at clinical doses of 0.075 to 0.2 mg/kg/day [see **BOXED WARNING** and **WARNINGS AND PRECAUTIONS (5.2)**].

A 104-week dermal carcinogenicity study was performed in mice with tacrolimus ointment (0.03% - 3%), equivalent to tacrolimus doses of 1.1 to 118 mg/kg/day or 3.3 to 354 mg/m^2/day. In the study, the incidence of skin tumors was minimal and the topical application of tacrolimus was not associated with skin tumor formation under ambient room lighting. However, a statistically significant elevation in the incidence of pleomorphic lymphoma in high dose male (25/50) and female animals (27/50) and in the incidence of undifferentiated lymphoma in high dose female animals (13/50) was noted in the mouse dermal carcinogenicity study. Lymphomas were noted in the mouse dermal carcinogenicity study at a daily dose of 3.5 mg/kg (0.1% tacrolimus ointment). No drug-related tumors were noted in the mouse dermal carcinogenicity study at a daily dose of 1.1 mg/kg (0.03% tacrolimus ointment). The relevance of topical administration of tacrolimus in the setting of systemic tacrolimus use is unknown.

The implications of these carcinogenicity studies to the human condition are limited; doses of tacrolimus were administered that likely induced immunosuppression in these animals impairing their immune system's ability to inhibit unrelated carcinogenesis.

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.

Tacrolimus given orally at 1 mg/kg (0.8 to 2.2 times the clinical dose range of 0.075 to 0.2 mg/kg/day based on body surface area) to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryolethality and 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 (2.6 to 6.9 times the clinical dose range based on body surface area), 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.

14 CLINICAL STUDIES

14.1 Kidney Transplantation

Tacrolimus/azathioprine (AZA)

Tacrolimus-based immunosuppression in conjunction with azathioprine and corticosteroids following kidney transplantation was assessed in a randomized, multicenter, non-blinded, prospective trial. There were 412 kidney transplant patients enrolled at 19 clinical sites in the United States. Study therapy was initiated when renal function was stable as indicated by a serum creatinine ≤ 4 mg/dL (median of 4 days after transplantation, range 1 to 14 days). Patients less than 6 years of age were excluded.

There were 205 patients randomized to tacrolimus-based immunosuppression and 207 patients were randomized to cyclosporine-based immunosuppression. All patients received prophylactic induction therapy consisting of an antilymphocyte antibody preparation, corticosteroids and azathioprine. Overall 1 year patient and graft survival was 96.1% and 89.6%, respectively.

Data from this trial of tacrolimus in conjunction with azathioprine indicate that during the first three months of that trial, 80% of the patients maintained trough concentrations between 7 to 20 ng/mL, and then between 5 to 15 ng/mL, through 1 year.

Tacrolimus/mycophenolate mofetil (MMF)

Tacrolimus-based immunosuppression in conjunction with MMF, corticosteroids, and induction has been studied. In a randomized, open-label, multi-center trial (Study 1), 1,589 kidney transplant patients received tacrolimus (Group C, n=401), sirolimus (Group D, n=399), or one of two cyclosporine (CsA) regimens (Group A, n=390 and Group B, n=399) in combination with MMF and corticosteroids; all patients, except those in one of the two cyclosporine groups, also received induction with daclizumab. The trial was conducted outside the United States; the trial population was 93% Caucasian. In this trial, mortality at 12 months in patients receiving tacrolimus/MMF was similar (3%) compared to patients receiving cyclosporine/MMF (3% and 2%) or sirolimus/MMF (3%). Patients in the tacrolimus group exhibited higher estimated creatinine clearance rates (eCL_{cr}) using the Cockcroft-Gault formula (**Table 16**) and experienced fewer efficacy failures, defined as biopsy proven acute rejection (BPAR), graft loss, death, and/or lost to follow-up (**Table 17**) in comparison to each of the other three groups. Patients randomized to tacrolimus/MMF were more likely to develop diarrhea and diabetes after the transplantation and experienced similar rates of infections compared to patients randomized to either cyclosporine/MMF regimen [see **ADVERSE REACTIONS (6.1)**].

Table 16. Estimated Creatinine Clearance at 12 Months (Study 1)

Group	**eCL_{cr} [mL/min] at Month 12***				
	N	**MEAN**	**SD**	**MEDIAN**	Treatment

					Difference with Group C (99.2% CI†)
(A) CsA/MMF/CS	390	56.5	25.8	56.9	-8.6 (-13.7, -3.7)
(B) CsA/MMF/CS/Daclizumab	399	58.9	25.6	60.9	-6.2 (-11.2, -1.2)
(C) Tac/MMF/CS/Daclizumab	401	65.1	27.4	66.2	-
(D) Siro/MMF/CS/Daclizumab	399	56.2	27.4	57.3	-8.9 (-14.1, -3.9)
Total	1589	59.2	26.8	60.5	
Key: CsA=Cyclosporine, CS=Corticosteroids, Tac=Tacrolimus, Siro=Sirolimus					

* All death graft loss (n=41, 27, 23 and 42 in Groups A, B, C and D) and patients whose last recorded creatinine values were prior to month 3 visit (n=10, 9, 7 and 9 in Groups A, B, C and D, respectively) were inputed with Glomerular Filtration Rate (GFR) of 10 mL/min; a subject's last observed creatinine value from month 3 on was used for the remainder of subjects with missing creatinine at month 12 (n=11, 12, 15 and 19 for Groups A, B, C and D, respectively). Weight was also imputed in the calculation of estimated GFR, if missing.

† Adjusted for multiple (6) pairwise comparisons using Bonferroni corrections.

Table 17. Incidence of BPAR, Graft Loss, Death or Loss to Follow-up at 12 Months (Study 1)

	Group A N=390	**Group B N=399**	**Group C N=401**	**Group D N=399**
Overall Failure	141 (36.2%)	126 (31.6%)	82 (20.4%)	185 (46.4%)
Components of efficacy failure				
BPAR	113 (29%)	106 (26.6%)	60 (15%)	152 (38.1%)
Graft loss excluding death	28 (7.2%)	20 (5%)	12 (3%)	30 (7.5%)
Mortality	13 (3.3%)	7 (1.8%)	11 (2.7%)	12 (3%)
Lost to follow-up	5 (1.3%)	7 (1.8%)	5 (1.3%)	6 (1.5%)
Treatment Difference of efficacy failure compared to Group C (99.2% CI*)	15.8% (7.1%, 24.3%)	11.2% (2.7%, 19.5%)	-	26% (17.2%, 34.7%)
Key: Group A=CsA/MMF/CS, B=CsA/MMF/CS/Daclizumab, C=Tac/MMF/CS/Daclizumab, and D=Siro/MMF/CS/Daclizumab				

* Adjusted for multiple (6) pairwise comparisons using Bonferroni corrections.

The protocol-specified target tacrolimus trough concentrations ($C_{trough,Tac}$) were 3 to 7 ng/mL; however, the observed median $C_{troughs,Tac}$ approximated 7 ng/mL throughout the 12 month trial (**Table 18**). Approximately 80% of patients maintained tacrolimus whole blood concentrations between 4 to 11 ng/mL through 1 year post-transplant.

Table 18. Tacrolimus Whole Blood Trough Concentrations (Study 1)

Time	**Median (P10-P90*) tacrolimus whole blood trough concentrations (ng/mL)**
Day 30 (N=366)	6.9 (4.4 to 11.3)
Day 90 (N=351)	6.8 (4.1 to 10.7)
Day 180 (N=355)	6.5 (4 to 9.6)
Day 365 (N=346)	6.5 (3.8 to 10)

* 10 to the 90th Percentile: range of $C_{trough,Tac}$ that excludes lowest 10% and highest 10% of $C_{trough, Tac}$.

The protocol-specified target cyclosporine trough concentrations ($C_{trough,CsA}$) for Group B were 50 to 100 ng/mL; however, the observed median $C_{troughs,CsA}$ approximated 100 ng/mL throughout the 12 month trial. The protocol-specified target $C_{troughs,CsA}$ for Group A were 150 to 300 ng/mL for the first 3 months and 100 to 200 ng/mL from month 4 to month 12; the observed median $C_{troughs, CsA}$ approximated 225 ng/mL for the first 3 months and 140 ng/mL from month 4 to month 12.

While patients in all groups started MMF at 1gram twice daily, the MMF dose was reduced to less than 2 g per day in 63% of patients in the tacrolimus treatment arm by month 12 (**Table 19**); approximately 50% of these MMF dose reductions were due to adverse reactions. By comparison, the MMF dose was reduced to less than 2 g per day in 49% and 45% of patients in the two cyclosporine arms (Group A and Group B, respectively), by month 12 and approximately 40% of MMF dose reductions were due to adverse reactions.

Table 19. MMF Dose Over Time in Tacrolimus/MMF (Group C) (Study 1)

Time period (Days)	**Time-averaged MMF dose (grams per day)***		
	Less than 2	2	Greater than 2
0 to 30 (N=364)	37%	60%	2%
0 to 90 (N=373)	47%	51%	2%
0 to 180 (N=377)	56%	42%	2%
0 to 365 (N=380)	63%	36%	1%
Key: Time-averaged MMF dose = (total MMF dose)/(duration of treatment)			

* Percentage of patients for each time-averaged MMF dose range during various treatment periods. Administration of 2 g per day of time-averaged MMF dose means that MMF dose was not reduced in those patients during the treatment periods.

In a second randomized, open-label, multi-center trial (Study 2), 424 kidney transplant patients received tacrolimus (N=212) or cyclosporine (N=212) in combination with MMF 1 gram twice daily, basiliximab induction, and corticosteroids. In this trial, the rate for the combined endpoint of BPAR, graft failure, death, and/or lost to follow-up at 12 months in the tacrolimus/MMF group was similar to the rate in the cyclosporine/MMF group. There was, however, an imbalance in mortality at 12 months in those patients receiving tacrolimus/MMF (4%) compared to those receiving cyclosporine/MMF (2%), including cases attributed to overimmunosuppression (**Table 20**).

Table 20. Incidence of BPAR, Graft Loss, Death or Loss to Follow-up at 12 Months (Study 2)

	Tacrolimus/MMF	**Cyclosporine/MMF**
	(N=212)	**(N=212)**
Overall Failure	32 (15.1%)	36 (17%)
Components of efficacy failure		
BPAR	16 (7.5%)	29 (13.7%)
Graft loss excluding death	6 (2.8%)	4 (1.9%)
Mortality	9 (4.2%)	5 (2.4%)
Lost to follow-up	4 (1.9%)	1 (0.5%)
Treatment Difference of efficacy failure compared to tacrolimus/MMF group (95% CI*)		1.9% (-5.2%, 9%)

* 95% confidence interval calculated using Fisher's Exact Test.

The protocol-specified target tacrolimus whole blood trough concentrations ($C_{trough,Tac}$) in Study 2 were 7 to 16 ng/mL for the first three months and 5 to 15 ng/mL thereafter. The observed median $C_{troughs,Tac}$ approximated 10 ng/mL during the first three months and 8 ng/mL from month 4 to month 12 (**Table 21**). Approximately 80% of patients maintained tacrolimus whole trough blood concentrations between 6 to 16 ng/mL during months 1 through 3 and, then, between 5 to 12 ng/mL from month 4 through 1 year.

Table 21. Tacrolimus Whole Blood Trough Concentrations (Study 2)

Time	**Median (P10-P90*) tacrolimus whole blood trough concentrations (ng/mL)**
Day 30 (N=174)	10.5 (6.3 to 16.8)
Day 60 (N=179)	9.2 (5.9 to 15.3)
Day 120 (N=176)	8.3 (4.6 to 13.3)
Day 180 (N=171)	7.8 (5.5 to 13.2)
Day 365 (N=178)	7.1 (4.2 to 12.4)

* 10 to 90th Percentile: range of $C_{trough, Tac}$ that excludes lowest 10% and highest 10% of $C_{trough, Tac}$.

The protocol-specified target cyclosporine whole blood concentrations ($C_{trough,CsA}$) were 125 to 400 ng/mL for the first three months, and 100 to 300 ng/mL thereafter. The observed median $C_{troughs, CsA}$ approximated 280 ng/mL during the first three months and 190 ng/mL from month 4 to month 12.

Patients in both groups started MMF at 1gram twice daily. The MMF dose was reduced to less than 2 grams per day by month 12 in 62% of patients in the tacrolimus/MMF group (**Table 22**) and in 47% of patients in the cyclosporine/MMF group. Approximately 63% and 55% of these MMF dose reductions were because of adverse reactions in the tacrolimus/MMF group and the cyclosporine/MMF group, respectively [see **ADVERSE REACTIONS (6.1)**].

Table 22. MMF Dose Over Time in the Tacrolimus /MMF Group (Study 2)

Time period (Days)	**Time-averaged MMF dose (grams per day)***		
	Less than 2	2	Greater than 2
0 to 30 (N=212)	25%	69%	6%
0 to 90 (N=212)	41%	53%	6%
0 to 180 (N=212)	52%	41%	7%
0 to 365 (N=212)	62%	34%	4%
Key: Time-averaged MMF dose=(total MMF dose)/(duration of treatment)			

* Percentage of patients for each time-averaged MMF dose range during various treatment periods. Two grams per day of time-averaged MMF dose means that MMF dose was not reduced in those patients during the treatment periods.

14.2 Liver Transplantation

The safety and efficacy of tacrolimus-based immunosuppression following orthotopic liver transplantation were assessed in two prospective, randomized, non-blinded multicenter trials. The active control groups were treated with a cyclosporine-based immunosuppressive regimen (CsA/AZA). Both trials used concomitant adrenal corticosteroids as part of the immunosuppressive regimens. These trials compared patient and graft survival rates at 12 months following transplantation.

In one trial, 529 patients were enrolled at 12 clinical sites in the United States; prior to surgery, 263 were randomized to the tacrolimus-based immunosuppressive regimen and 266 to the CsA/AZA. In 10 of the 12 sites, the same CsA/AZA protocol was used, while 2 sites used different control protocols. This trial excluded patients with renal dysfunction, fulminant hepatic failure with Stage IV

encephalopathy, and cancers; pediatric patients (≤ 12 years old) were allowed.

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

One-year patient survival and graft survival in the tacrolimus-based treatment groups were similar to those in the CsA/AZA treatment groups in both trials. The overall 1-year patient survival (CsA/AZA and tacrolimus-based treatment groups combined) was 88% in the U.S. trial and 78% in the European trial. The overall 1-year graft survival (CsA/AZA and tacrolimus-based treatment groups combined) was 81% in the U.S. trial and 73% in the European trial. In both trials, the median time to convert from IV to oral tacrolimus dosing was 2 days.

Although there is a lack of direct correlation between tacrolimus concentrations and drug efficacy, data from clinical trials of liver transplant patients have shown an increasing incidence of adverse reactions with increasing trough blood concentrations. Most patients are stable when trough whole blood concentrations are maintained between 5 to 20 ng/mL. Long-term post-transplant patients often are maintained at the low end of this target range.

Data from the U.S. clinical trial show that the median trough blood concentrations, measured at intervals from the second week to one year post-transplantation ranged from 9.8 ng/mL to 19.4 ng/mL.

14.3 Heart Transplant

Two open-label, randomized, comparative trials evaluated the safety and efficacy of tacrolimus-based and cyclosporine-based immunosuppression in primary orthotopic heart transplantation. In a trial conducted in Europe, 314 patients received a regimen of antibody induction, corticosteroids and azathioprine in combination with tacrolimus or cyclosporine modified for 18 months. In a 3-arm trial conducted in the US, 331 patients received corticosteroids and tacrolimus plus sirolimus, tacrolimus plus mycophenolate mofetil (MMF) or cyclosporine modified plus MMF for 1 year.

In the European trial, patient/graft survival at 18 months post-transplant was similar between treatment arms, 92% in the tacrolimus group and 90% in the cyclosporine group. In the U.S. trial, patient and graft survival at 12 months was similar with 93% survival in the tacrolimus plus MMF group and 86% survival in the cyclosporine modified plus MMF group. In the European trial, the cyclosporine trough concentrations were above the pre-defined target range (i.e., 100 to 200 ng/mL) at Day 122 and beyond in 32 to 68% of the patients in the cyclosporine treatment arm, whereas the tacrolimus trough concentrations were within the pre-defined target range (i.e., 5 to 15 ng/mL) in 74 to 86% of the patients in the tacrolimus treatment arm. Data from this European trial indicate that from 1 week to 3 months post-transplant, approximately 80% of patients maintained trough concentrations between 8 to 20 ng/mL and, from 3 months through 18 months post-transplant, approximately 80% of patients maintained trough concentrations between 6 to18 ng/mL.

The U.S. trial contained a third arm of a combination regimen of sirolimus, 2 mg per day, and full-dose tacrolimus; however, this regimen was associated with increased risk of wound healing complications, renal function impairment, and insulin-dependent post-transplant diabetes mellitus, and is not recommended [see **WARNINGS AND PRECAUTIONS (5.12)**].

16 HOW SUPPLIED/STORAGE AND HANDLING

Tacrolimus capsules, USP containing white to off white powder equivalent to 0.5 mg of anhydrous tacrolimus, are hard gelatin capsules with white opaque body and ivory cap. The body is imprinted '643' and cap is imprinted '  ' in black ink.

They are supplied as follows:

NDC 0781-2102-01, bottle of 100 capsules with child-resistant closure

Tacrolimus capsules, USP containing white to off white powder equivalent to 1 mg of anhydrous tacrolimus, are hard gelatin capsules with white opaque body and brown cap. The body is imprinted '644' and cap is imprinted '' in black ink.

They are supplied as follows:

NDC 0781-2103-01, bottle of 100 capsules with child-resistant closure

Tacrolimus capsules, USP containing white to off white powder equivalent to 5 mg of anhydrous tacrolimus, are hard gelatin capsules with white opaque body and orange cap. The body is imprinted '645' and cap is imprinted '' in black ink.

They are supplied as follows:

NDC 0781-2104-01, bottle of 100 capsules with child-resistant closure

Tacrolimus capsules, USP should be stored at 20° to 25°C (68° to 77° F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

17.1 Administration

Advise patients to:

- Take tacrolimus capsules at the same 12-hour intervals every day to achieve consistent blood concentrations.
- Take tacrolimus capsules consistently either with or without food because the presence and composition of food decreases the bioavailability of tacrolimus capsules.
- Not to eat grapefruit or drink grapefruit juice in combination with tacrolimus capsules **[see DRUG INTERACTIONS (7.2)].**

17.2 Development of Lymphoma and Other Malignancies

Inform patients they are at increased risk of developing lymphomas and other malignancies, particularly of the skin, due to immunosuppression. Advise patients to limit exposure to sunlight and ultraviolet (UV) light by wearing protective clothing and use a sunscreen with a high protection factor [see **WARNINGS AND PRECAUTIONS (5.2)**].

17.3 Increased Risk of Infection

Inform patients they are at increased risk of developing a variety of infections, including opportunistic infections, due to immunosuppression and to contact their physician if they develop any symptoms of infection [see **WARNINGS AND PRECAUTIONS (5.3, 5.4, 5.5)**].

17.4 New Onset Diabetes After Transplant

Inform patients that tacrolimus capsules can cause diabetes mellitus and should be advised to contact their physician if they develop frequent urination, increased thirst or hunger [see **WARNINGS AND PRECAUTIONS (5.6)**].

17.5 Nephrotoxicity

Inform patients that tacrolimus capsules can have toxic effects on the kidney that should be monitored. Advise patients to attend all visits and complete all blood tests ordered by their medical team [see **WARNINGS AND PRECAUTIONS (5.7)**].

17.6 Neurotoxicity

Inform patients that they are at risk of developing adverse neurologic effects including seizure, altered mental status, and tremor. Advise patients to contact their physician should they develop vision changes, deliriums, or tremors [see **WARNINGS AND PRECAUTIONS (5.8)**].

17.7 Hyperkalemia

Inform patients that tacrolimus capsules can cause hyperkalemia. Monitoring of potassium levels may be necessary, especially with concomitant use of other drugs known to cause hyperkalemia [see **WARNINGS AND PRECAUTIONS (5.9)**].

17.8 Hypertension

Inform patients that tacrolimus capsules can cause high blood pressure which may require treatment with anti-hypertensive therapy [see **WARNINGS AND PRECAUTIONS (5.10)**].

17.9 Drug Interactions

Instruct patients to tell their health care providers when they start or stop taking all the medicines, including prescription medicines and non-prescription medicines, natural or herbal remedies, nutritional supplements and vitamins [see **DRUG INTERACTIONS (7)**].

17.10 Pregnant Women and Nursing Mothers

Instruct patients to tell their healthcare providers if they plan to become pregnant or breast-feed their infant [see **USE IN SPECIFIC POPULATIONS (8.1, 8.3)**]

17.11 Immunizations

Inform patients that tacrolimus capsules can interfere with the usual response to immunizations and that they should avoid live vaccines [see **WARNINGS AND PRECAUTIONS (5.16)**].

PATIENT INFORMATION

Tacrolimus Capsules, USP

Read this Patient Information before you start taking tacrolimus capsules and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about Tacrolimus Capsules?

Tacrolimus Capsules can cause serious side effects, including:

1. Increased risk of cancer. People who take tacrolimus capsules have an increased risk of getting some kinds of cancer, including skin and lymph gland cancer (lymphoma).

2.Increased risk of infection. Tacrolimus capsules are a medicine that affects your immune system. Tacrolimus capsules can lower the ability of your immune system to fight infections. Serious infections can happen in people receiving tacrolimus capsules that can cause death. **Call your doctor right away if you have symptoms of an infection such as:**

- fever
- sweats or chills
- cough or flu-like symptoms
- muscle aches
- warm, red, or painful areas on your skin

What are Tacrolimus Capsules?

Tacrolimus capsules are a prescription medicine used with other medicines to help prevent organ rejection in people who have had a kidney, liver, or heart transplant and tacrolimus capsules are not for use with medicines called cyclosporines (Gengraf®, Neoral®, and Sandimune®).

Tacrolimus capsules are not for use with a medicine called sirolimus (Rapamune®) in people who have had a liver or heart transplant.

It is not known if tacrolimus capsules are safe and effective when used with sirolimus in people who have had kidney transplants.

It is not known if tacrolimus capsules are safe and effective in children who have had a kidney or heart transplant.

Who should not take Tacrolimus Capsules?

Do not take Tacrolimus Capsules if you are allergic to tacrolimus or any of the ingredients in tacrolimus capsules. See the end of this leaflet for a complete list of ingredients in tacrolimus capsules.

What should I tell my doctor before taking Tacrolimus Capsules?

Before you take Tacrolimus Capsules, tell your doctor if you:

- plan to receive any live vaccines
- have or have had liver, kidney or heart problems
- are pregnant or plan to become pregnant. Tacrolimus capsules may harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- Are breastfeeding or plan to breastfeed. Tacrolimus capsules can pass into your breast milk. You and your doctor should decide if you will take tacrolimus capsules or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Especially tell your doctor if you take:

- cyclosporine (Gengraf®, Neoral®, and Sandimune®)
- sirolimus (Rapamune®)
- nelfinavir (Viracept®)
- telaprevir (Incivek™)
- boceprevir (Victrelis™)
- amiodarone (Cordarone™, Nexterone™, Pacerone™)

Ask your doctor or pharmacist if you are not sure if you take any of the medicines listed above.

Tacrolimus capsules may affect the way other medicines work, and other medicines may affect how tacrolimus capsules works.

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

How should I take Tacrolimus Capsules?

- Take tacrolimus capsules exactly as your doctor tells you to take it.
- Your doctor will tell you how many tacrolimus capsules to take and when to take them.
- Your doctor may change your tacrolimus capsules dose if needed. **Do not** stop taking or change

your dose of tacrolimus capsules without talking to your doctor.

- Take tacrolimus capsules with or without food.
- Take tacrolimus capsules the same way every day. For example, if you choose to take tacrolimus capsules with food, you should always take tacrolimus capsules with food.
- Take tacrolimus capsules at the same time each day, 12 hours apart. For example, if you take your first dose at 7:00 a.m. you should take your second dose at 7:00 p.m.
- Taking tacrolimus capsules at the same time each day helps to keep enough medicine in your body to give your transplanted organ the around-the-clock medicine it needs.
- **Do not** eat grapefruit or drink grapefruit juice while taking tacrolimus capsules.
- If you take too much tacrolimus capsules, call your doctor or go to the nearest hospital emergency room right away.

What should I avoid while taking Tacrolimus Capsules?

- While you take tacrolimus capsules you should not receive any live vaccines such as:

  - flu vaccine through your nose
  - measles
  - mumps
  - rubella
  - polio by mouth
  - BCG (TB vaccine)
  - yellow fever
  - chicken pox (varicella)
  - typhoid

- Avoid exposure to sunlight and UV light such as tanning machines. Wear protective clothing and use a sunscreen.

What are the possible side effects of Tacrolimus Capsules?

Tacrolimus Capsules may cause serious side effects, including:

- See “What is the most important information I should know about Tacrolimus Capsules?”
- **high blood sugar (diabetes).** Your doctor may do certain tests to check for diabetes while you take tacrolimus capsules. Call your doctor right away if you have:

  - frequent urination
  - increased thirst or hunger
  - blurred vision
  - confusion
  - drowsiness
  - loss of appetite
  - fruity smell on your breath
  - nausea, vomiting, or stomach pain

- **kidney problems**. Your doctor may do certain tests to check your kidney function while you take tacrolimus capsules.
- **nervous system problems**. Call your doctor right away if you get any of these symptoms while

taking tacrolimus capsules. These could be signs of a serious nervous system problem:

- confusion
- coma
- muscle tremors
- numbness and tingling
- headache
- seizures
- vision changes

- **high levels of potassium in your blood**. Your doctor may do certain tests to check your potassium level while you take tacrolimus capsules.
- **high blood pressure**. Your doctor will monitor your blood pressure while you take tacrolimus capsules.
- **heart problems (myocardial hypertrophy).** Tell your doctor right away if you get any of these symptoms of heart problems while taking tacrolimus capsules:

  - shortness of breath
  - chest pain
  - feel lightheaded
  - feel faint

The most common side effects of Tacrolimus Capsules in people receiving kidney transplant are:

- infection
- tremors (shaking of the body)
- high blood pressure
- kidney problems
- constipation
- diarrhea
- headache
- stomach pain
- trouble sleeping
- nausea
- low levels of phosphate in your blood
- swelling of the hands, ankles, or legs
- weakness
- pain
- high levels of fat in your blood
- high levels of potassium in your blood
- low red blood cell count (anemia)

The most common side effects of Tacrolimus Capsules in people receiving liver transplants are:

- shaking of the body tremors
- headache
- diarrhea
- high blood pressure

- nausea
- kidney problems
- stomach pain
- trouble sleeping
- numbness or tingling in your hands or feet
- anemia
- pain
- fever
- weakness
- high levels of potassium in the blood
- low levels of magnesium in the blood

The most common side effects of tacrolimus capsules for heart transplant patients are:

- kidney problems
- high blood pressure

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of tacrolimus capsules. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Tacrolimus Capsules?

- Store tacrolimus capsules at 20° to 25°C (68° to 77° F).
- Safely throw away medicine that is out of date or no longer needed.

Keep Tacrolimus Capsules and all medicines out of reach of children.

General information about the safe and effective use of Tacrolimus Capsules

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use tacrolimus capsules for a condition for which it was not prescribed. Do not give tacrolimus capsules to other people, even if they have the same symptoms that you have. It may harm them.

How do Tacrolimus Capsules protect my new organ?

The body's immune system protects the body against anything that it does not recognize as part of the body. For example, when the immune system detects a virus or bacteria it tries to get rid of it to prevent infection. When a person has a liver, kidney, or heart transplant, the immune system does not recognize the new organ as a part of the body and tries to get rid of it, too. This is called "rejection". Tacrolimus capsules protect your new organ by slowing down the body's immune system.

This Patient Information leaflet summarizes the most important information about tacrolimus capsules. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about tacrolimus capsules that is written for health professionals.

For more information contact Sandoz Inc. at 1-800-525-8747.

What are the ingredients in Tacrolimus Capsules?

Active ingredient: tacrolimus

Inactive ingredients: croscarmellose sodium, hypromellose, lactose monohydrate, and magnesium stearate.

The tacrolimus capsule shell for 0.5 mg strength consists of gelatin, titanium dioxide and yellow iron oxide.

The tacrolimus capsule shell for 1 mg strength consists of black iron oxide, gelatin, red iron oxide, titanium dioxide, and yellow iron oxide.

The tacrolimus capsule shell for 5 mg strength consists of red iron oxide, gelatin, and titanium dioxide.

Tacrolimus capsules 0.5 mg, 1 mg and 5 mg are printed with edible black ink. The black ink is comprised of ammonia, black iron oxide, butyl alcohol, potassium hydroxide, propylene glycol, and shellac.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured in India by Sandoz Private Limited for

Sandoz Inc; Princeton NJ 08540

Revised: September 2013

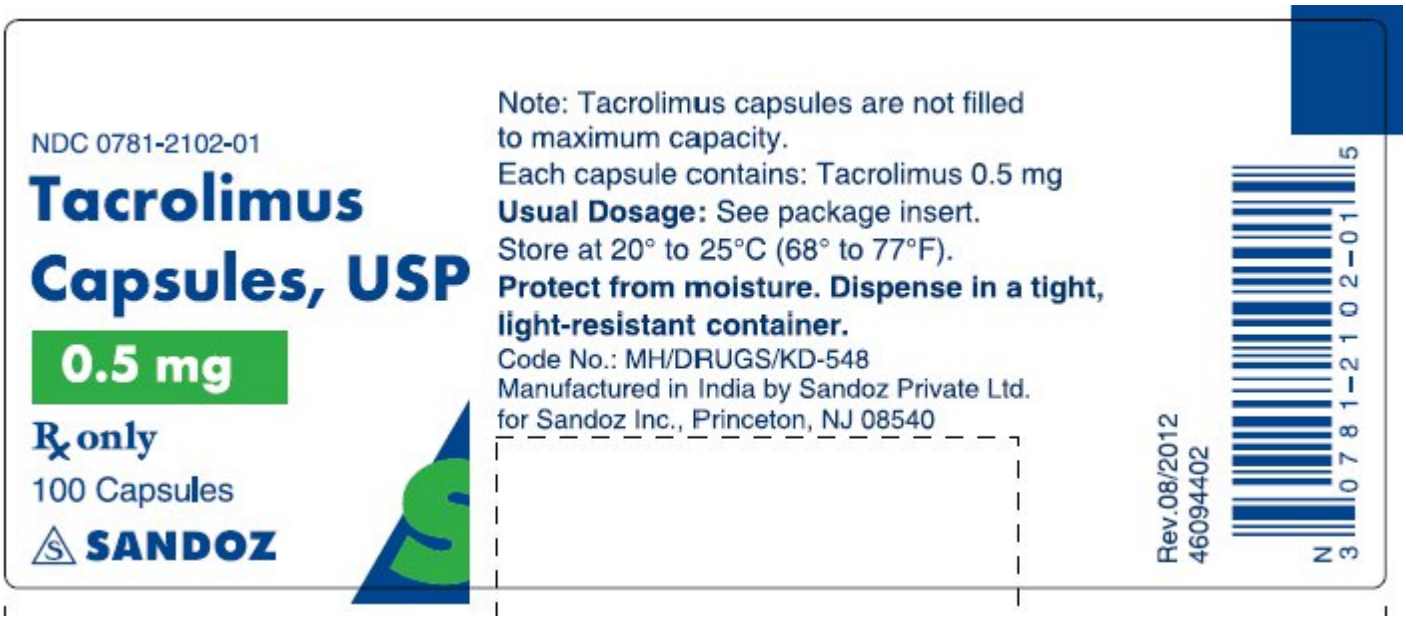
Principal Display Panel

NDC 0781-2102-01

Tacrolimus Capsules, USP

0.5 mg

100 Capsules



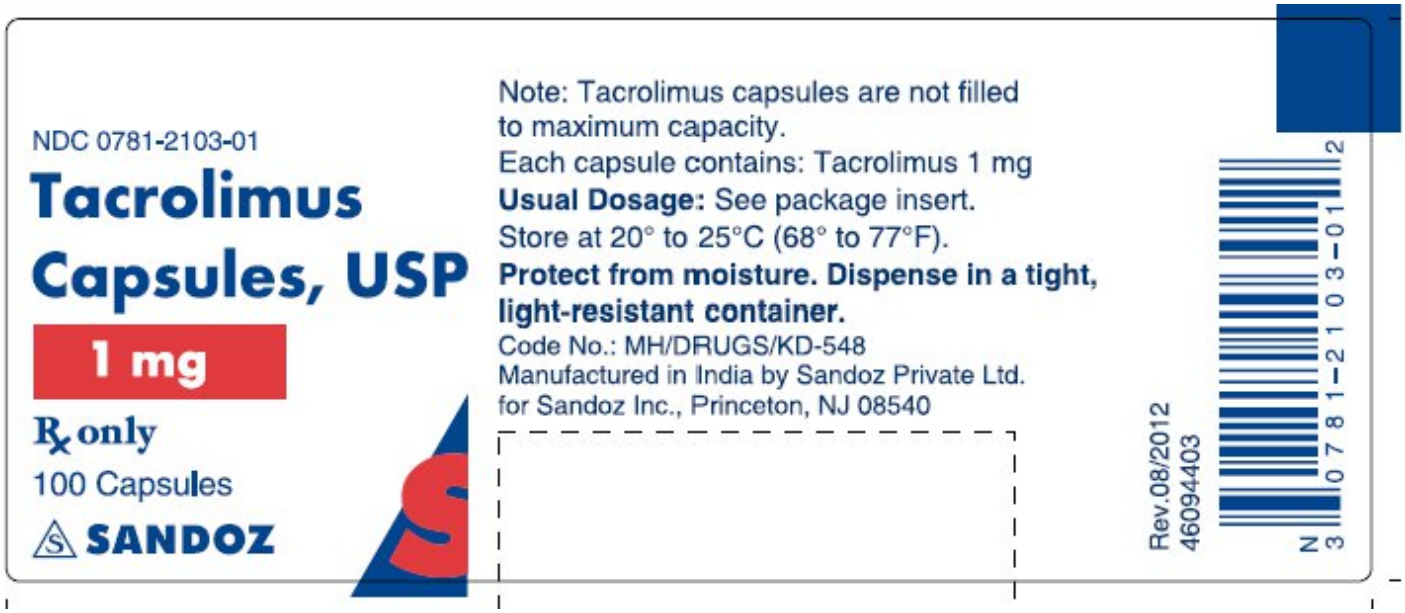
Principal Display Panel

NDC 0781-2103-01

Tacrolimus Capsules, USP

1 mg

100 Capsules



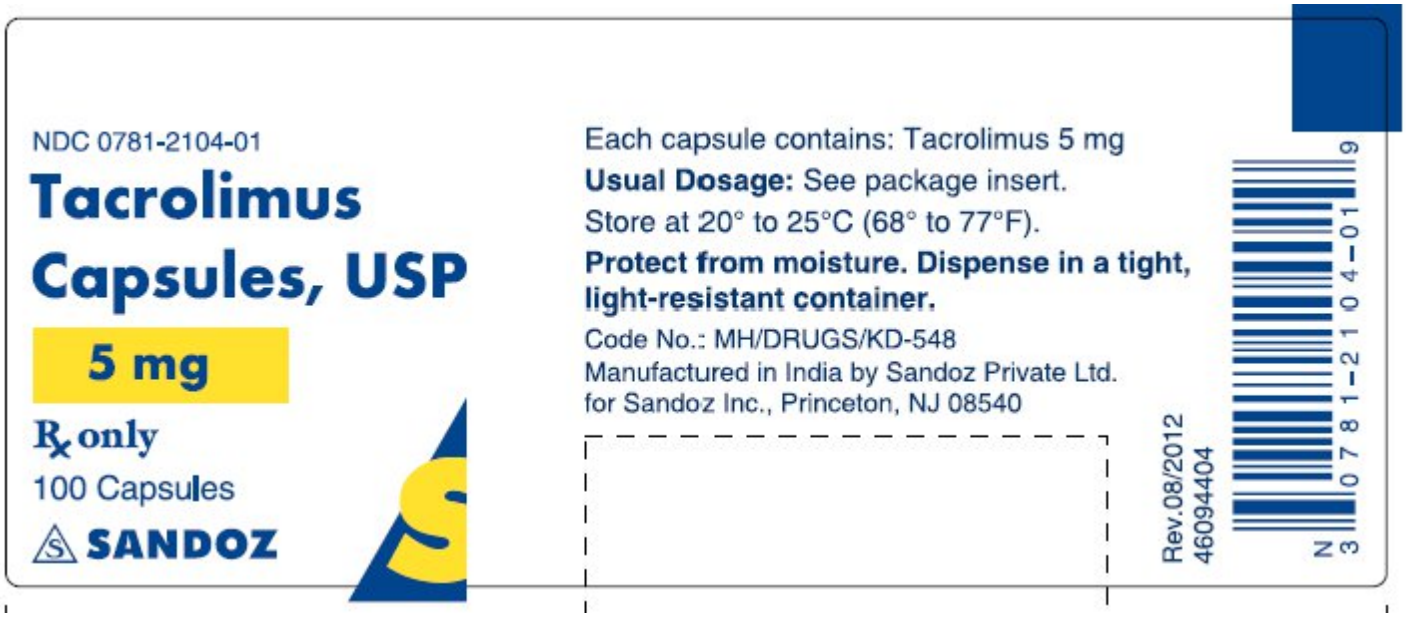
Principal Display Panel

NDC 781-2104-01

Tacrolimus Capsules, USP

5 mg

100 Capsules



TACROLIMUS

tacrolimus capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0781-2102
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TACROLIMUS (TACROLIMUS ANHYDROUS)	TACROLIMUS ANHYDROUS	0.5 mg

Inactive Ingredients

Ingredient Name	Strength
CROSCARMELLOSE SODIUM	
HYPROMELLOSE 2208 (100 MPA.S)	
LACTOSE MONOHYDRATE	
MAGNESIUM STEARATE	
GELATIN	
TITANIUM DIOXIDE	
FERRIC OXIDE YELLOW	
AMMONIA	
FERROSOFERRIC OXIDE	
POTASSIUM HYDROXIDE	
PROPYLENE GLYCOL	
SHELLAC	
BUTYL ALCOHOL	

Product Characteristics

Color	WHITE (white opaque body and ivory cap)	**Score**	no score
Shape	CAPSULE	**Size**	14mm
Flavor		**Imprint Code**	643;S
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0781-2102-01	100 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA065461	08/10/2009	

TACROLIMUS

tacrolimus capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0781-2103

Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TACROLIMUS (TACROLIMUS ANHYDROUS)	TACROLIMUS ANHYDROUS	1 mg

Inactive Ingredients

Ingredient Name	Strength
CROSCARMELLOSE SODIUM	
HYPROMELLOSE 2208 (100 MPA.S)	
LACTOSE MONOHYDRATE	
MAGNESIUM STEARATE	
FERROSOFERRIC OXIDE	
GELATIN	
FERRIC OXIDE RED	
TITANIUM DIOXIDE	
FERRIC OXIDE YELLOW	
AMMONIA	
POTASSIUM HYDROXIDE	
PROPYLENE GLYCOL	
SHELLAC	
BUTYL ALCOHOL	

Product Characteristics

Color	WHITE (white opaque body and brown cap)	**Score**	no score
Shape	CAPSULE	**Size**	14mm
Flavor		**Imprint Code**	644;S
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0781-2103-01	100 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA065461	08/10/2009	

TACROLIMUS

tacrolimus capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:0781-2104
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TACROLIMUS (TACROLIMUS ANHYDROUS)	TACROLIMUS ANHYDROUS	5 mg

Inactive Ingredients

Ingredient Name	Strength
CROSCARMELLOSE SODIUM	
HYPROMELLOSE 2208 (100 MPA.S)	
LACTOSE MONOHYDRATE	
MAGNESIUM STEARATE	
FERRIC OXIDE RED	
GELATIN	
TITANIUM DIOXIDE	
AMMONIA	
FERROSOFERRIC OXIDE	
POTASSIUM HYDROXIDE	
PROPYLENE GLYCOL	
SHELLAC	
BUTYL ALCOHOL	

Product Characteristics

Color	WHITE (white opaque body and orange cap)	**Score**	no score
Shape	CAPSULE	**Size**	14mm
Flavor		**Imprint Code**	645;S
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0781-2104-01	100 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA065461	08/10/2009	

Labeler - Sandoz Inc (110342024)