TACROLIMUS- tacrolimus extended-release capsules capsule, coated, extended release
Chengdu Suncadia Medicine Co., Ltd.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TACROLIMUS EXTENDED-RELEASE CAPSULES safely and effectively. See full prescribing information for TACROLIMUS EXTENDED-RELEASE CAPSULES.

TACROLIMUS extended-release capsules, for oral use
Initial U.S. Approval: 1994

WARNING: MALIGNANCIES AND SERIOUS INFECTIONS IN TRANSPLANT PATIENTS; and INCREASED MORTALITY IN FEMALE LIVER TRANSPLANT PATIENTS

See full prescribing information for complete boxed warning.

- **Increased risk for developing serious infections and malignancies with with tacrolimus extended-release capsules or other immunosuppressants that may lead to hospitalization or death. (5.1, 5.2)**
- **Increased mortality in female liver transplant patients with with tacrolimus extended-release capsules. Not approved for use in liver transplantation. (5.3)**

RECENT MAJOR CHANGES

Warnings and Precautions (5.6, 5.14) 11/2022
Warnings and Precautions, Cannabidiol Drug Interactions (5.15) 08/2023

INDICATIONS AND USAGE

Tacrolimus extended-release capsules is a calcineurin-inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in kidney transplant patients in combination with other immunosuppressants in adult patients who can swallow capsules intact. (1, 14.1, 14.2)

DOSAGE AND ADMINISTRATION

- Capsules must be taken whole. (2.1)
- Take consistently every morning at the same time on an empty stomach at least 1 hour before a meal or at least 2 hours after a meal. (2.1)
- Avoid eating grapefruit or drinking grapefruit juice or alcohol. (2.1)
- African-American patients and patients with severe hepatic impairment may require dosing adjustments. (2.3)
- Frequent monitoring of trough concentrations is recommended. (2.4)
- For complete dosing information, see Full Prescribing Information.

Recommended Tacrolimus Extended-Release Capsules Initial Dosage

Patient Population	Initial Oral Dosage	Whole Blood Trough Concentration Range
ADULT		
With basiliximab, MMF and steroids	0.15 mg/kg to 0.2 mg/kg once daily prior to reperfusion or within 48 hours of completion of transplant	• Month 1: 7 ng/mL to 15 ng/mL • Month 2 to Month 6: 5 ng/mL to 15 ng/mL • More than 6 Months: 5 ng/mL to 10 ng/mL
With MMF and steroids, without basiliximab induction	• First dose (pre-operative): 0.1 mg/kg, within 12 hours prior to reperfusion • Subsequent doses (post-operative): 0.2 mg/kg once daily at least 4 hours after pre-operative dose and within 12 hours after reperfusion	• Month 1: 10 ng/mL to 15 ng/mL • Month 2 to Month 6: 5 ng/mL to 15 ng/mL • More than 6 Months: 5 ng/mL to 10 ng/mL

MMF = Mycophenolate mofetil

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

Known hypersensitivity to tacrolimus. (4)

WARNINGS AND PRECAUTIONS

- Not Interchangeable with Other Tacrolimus Products-Medication Errors: Instruct patients or caregivers to recognize the appearance of tacrolimus extended-release capsules. (5.4)
- New onset diabetes after transplant: Monitor blood glucose. (5.5)
- Nephrotoxicity (acute and/or chronic): May occur due to tacrolimus extended-release capsules, drug interactions, concomitant nephrotoxic drugs. Monitor renal function; consider dosage reduction. (5.6)
- Neurotoxicity: Including risk of posterior reversible encephalopathy syndrome (PRES), monitor for neurologic abnormalities; reduce dosage or discontinue tacrolimus extended-release capsules. (5.7)
- Hyperkalemia: Risk may be increased with other agents associated with hyperkalemia; monitor serum potassium levels. (5.8)
- Hypertension: May require antihypertensive therapy; monitor relevant drug interactions. (5.9)
- QT prolongation: Consider obtaining electrocardiograms and monitoring electrolytes in patients at high risk. (5.11)
- Immunizations: Avoid live vaccines. (5.12)
- Pure red cell aplasia: Consider discontinuation of tacrolimus extended-release capsules. (5.13)
- Thrombotic Microangiopathy, Including Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura: May occur, especially in patients with infections and certain concomitant medications. (5.14)

ADVERSE REACTIONS

The most common adverse reactions (≥ 30%) are: diarrhea, constipation, nausea, peripheral edema, tremor and anemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact eVenus Pharmaceutical Laboratories, Inc. at 1-609-395-8625 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Risk of rejection with strong CYP3A inducers and risk of serious adverse reactions with strong CYP3A inhibitors: Adjust dose and monitor tacrolimus concentrations. (2.4, 5.10, 7.2)
- Therapeutic drug monitoring and dose reduction for tacrolimus extended-release capsules should be considered when tacrolimus extended-release capsules is co-administered with cannabidiol. (2.4, 5.15, 7.3)
- See Full Prescribing Information for clinically significant drug interactions. (7.1, 7.2, 7.3)

USE IN SPECIFIC POPULATIONS

Pregnancy: Can cause fetal harm. Advise pregnant women of the potential risk to the fetus. (8.1, 8.3)

Pediatric use information is approved for Astellas Pharma US, Inc.'s ASTAGRAF XL (tacrolimus extended-release capsules). However, due to Astellas Pharma US, Inc.'s marketing exclusivity rights, this drug product is not labeled with that information.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: MALIGNANCIES AND SERIOUS INFECTIONS IN TRANSPLANT PATIENTS; AND INCREASED MORTALITY IN FEMALE LIVER TRANSPLANT PATIENTS

- **Increased risk for developing serious infections and malignancies with tacrolimus extended-release capsulest or other immunosuppressants that may lead to hospitalization or death. *[see Warnings and Precautions(5.1, 5.2)]***
- **Increased mortality in female liver transplant patients with tacrolimus extended-release capsulest. Tacrolimus extended-release capsulest is not approved for use in liver transplantation. *[see Warnings and Precautions(5.3)]***

1 INDICATIONS AND USAGE

Tacrolimus extended-release capsules is indicated for the prophylaxis of organ rejection in kidney transplant patients in combination with other immunosuppressants in adult patients who can swallow capsules intact *[see Clinical Studies(14.1), (14.2)]* .

Pediatric use information is approved for Astellas Pharma US, Inc.'s ASTAGRAF XL (tacrolimus extended-release capsules). However, due to Astellas Pharma US, Inc.'s marketing exclusivity rights, this drug product is not labeled with that information.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- **Tacrolimus extended-release capsules should not be used without the supervision by a physician with experience in immunosuppressive therapy.**

- Tacrolimus extended-release capsules is not interchangeable or substitutable for tacrolimus extended-release tablets, tacrolimus immediate-release capsules or tacrolimus for oral suspension. Under or overexposure to tacrolimus may result in graft rejection or other serious adverse reactions. Changes between tacrolimus immediate-release and extended-release dosage forms must occur under physician supervision *[see Warnings and Precautions(5.4)].*
- Advise patients to swallow tacrolimus extended-release capsules whole with liquid; patients must not chew, divide, or crush the capsules.
- Tacrolimus extended-release capsules should be taken consistently every morning at the same time to ensure consistent and maximum possible drug exposure, on an empty stomach at least 1 hour before a meal, or at least 2 hours after a meal *[see Clinical Pharmacology(12.3)].*
- If a dose is missed, the dose may be taken up to 14 hours after the scheduled time (i.e., for a missed 8:00 AM dose, a dose may be taken by 10:00 PM). Beyond the 14-hour time frame, the patient should wait until the usual scheduled time the following morning to take the next regular daily dose. Instruct the patient not to double the next dose.
- Advise patients to avoid eating grapefruit or drinking grapefruit juice or alcoholic beverages while taking tacrolimus extended-release capsules *[see Drug Interactions(7.2)].*
- Therapeutic drug monitoring is recommended for all patients receiving tacrolimus extended-release capsules *[see Dosage and Administration(2.4)]* .

2.2 Dosage Recommendations for Kidney Transplant Patients

Table 1includes the recommended starting tacrolimus extended-release capsules dosages and whole blood trough concentration ranges; the observed trough concentrations are shown in another section of the Full Prescribing Information *[see Clinical Studies(14)]* . Titrate the tacrolimus extended-release capsules dosage based on clinical assessments of rejection and tolerability, and to achieve target trough concentration ranges *[see Dosage and Administration(2.4) and Warnings and Precautions(5.6, 5.7, 5.10, 5.11)]* .

Table 1: Recommended Starting Daily Dosage Regimen of Tacrolimus Extended-Release Capsules

Recommended Tacrolimus Extended-Release Capsules Initial Dosage*		
Patient Population	**Initial Oral Dosage**	**Whole Blood Trough Concentration Range**
ADULT		
With basiliximab, MMF and steroids	0.15 mg/kg to 0.2 mg/kg once daily prior to reperfusion or within 48 hours of completion of transplant	• Month 1: 7 ng/mL to 15 ng/mL • Month 2 to Month 6: 5 ng/mL to 15 ng/mL • More than 6 Months: 5 ng/mL to 10 ng/mL
With MMF and steroids, without	• First dose (pre-operative): 0.1 mg/kg, within 12 hours prior to reperfusion • Subsequent doses (post-	• Month 1: 10 ng/mL to 15 ng/mL • Month 2 to Month 6: 5 ng/mL to 15 ng/mL

steroids, without basiliximab induction	operative): 0.2 mg/kg once daily at least 4 hours after pre-operative dose and within 12 hours after reperfusion	• More than 6 Months: 5 ng/mL to 10 ng/mL

MMF = mycophenolate mofetil

Pediatric use information is approved for Astellas Pharma US, Inc.'s ASTAGRAF XL (tacrolimus extended-release capsules). However, due to Astellas Pharma US, Inc.'s marketing exclusivity rights, this drug product is not labeled with that information.

2.3 Dosage Modifications for African-American Patients, Patients with Hepatic Impairment, and Drug Interactions

African-American patients, compared to Caucasian patients, may need to be titrated to higher tacrolimus extended-release capsules dosages to attain comparable trough concentrations *[see Clinical Pharmacology(12.3) and Clinical Studies(14)]* .

Patients with severe hepatic impairment (Child-Pugh ≥ 10) may require a lower starting dosage of tacrolimus extended-release capsules, due to the reduced clearance and prolonged half-life *[see Clinical Pharmacology(12.3)].*

Dose adjustments of tacrolimus extended-release capsules may be necessary when administered concomitantly with CYP3A inducers or CYP3A inhibitors or cannabidiol *[see Warnings and Precautions(5.10, 5.15) and Drug Interactions(7.2, 7.3)].*

2.4 Therapeutic Drug Monitoring

Measure tacrolimus whole blood trough concentrations at least two times on separate days during the first week after initiation of dosing and after a change in dosage, after a change in co-administration of CYP3A4 inducers and/or inhibitors or cannabidiol *[see Drug Interactions (7.2, 7.3)]* , or after a change in renal or hepatic function. When interpreting measured concentrations, consider that the time to achieve tacrolimus steady state is approximately 7 days after initiating or changing the tacrolimus extended-release capsules dose.

Monitor tacrolimus whole blood trough concentrations using a validated assay [e.g., immunoassays or high performance liquid chromatography with tandem mass spectrometric detection (HPLC/MS/MS)]. The immunosuppressive activity of tacrolimus is mainly due to the parent drug rather than to its metabolites. Immunoassays may react with metabolites as well as the parent drug. Therefore, whole blood tacrolimus trough concentrations obtained with immunoassays may be numerically higher than concentrations obtained with an assay using HPLC/MS/MS. Comparison of the whole blood tacrolimus trough concentrations of patients to those described in the prescribing information and other published literature must be made with knowledge of the assay method(s) employed.

3 DOSAGE FORMS AND STRENGTHS

Tacrolimus extended-release capsules:

- 0.5 mg: opaque yellowish pink cap and opaque light orange body branded with dull red “SD-TC” on the capsule body and dull red “0.5 mg” on the capsule cap.

- 1 mg: opaque light yellow cap and opaque light orange body branded with dull red “SD-TC” on the capsule body and dull red “1 mg” on the capsule cap.
- 5 mg: opaque red-orange cap and opaque orange body branded with dull red “SD-TC” on the capsule body and dull red “5 mg” on the capsule cap.

4 CONTRAINDICATIONS

Tacrolimus extended-release capsules is contraindicated in patients with known hypersensitivity to tacrolimus *[see Adverse Reactions(6.2)]* .

5 WARNINGS AND PRECAUTIONS

5.1 Lymphoma and Other Malignancies

Immunosuppressants, including tacrolimus extended-release capsules, increase the risk of developing lymphomas and other malignancies, particularly of the skin .The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Examine patients for skin changes and advise to avoid or limit exposure to sunlight and UV light by wearing protective clothing and using a broad-spectrum sunscreen with a high protection factor.

Post-transplant lymphoproliferative disorder (PTLD), associated with Epstein-Barr Virus (EBV), has been reported in immunosuppressed organ transplant patients. The risk of PTLD appears greatest in patients who are EBV seronegative, a population which includes many young children. Monitor EBV serology during treatment.

5.2 Serious Infections

Immunosuppressants, including tacrolimus extended-release capsules, increase the risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes. Serious viral infections reported include:

- Polyomavirus-associated nephropathy (especially due to BK virus infection)
- JC virus-associated progressive multifocal leukoencephalopathy (PML)
- Cytomegalovirus (CMV) infections: CMV seronegative transplant patients who receive an organ from a CMV seropositive donor are at highest risk of CMV viremia and CMV disease.

Monitor for the development of infection and adjust the immunosuppressive regimen to balance the risk of rejection with the risk of infection *[see Adverse Reactions(6.1, 6.2)]* .

5.3 Increased Mortality in Female Liver Transplant Patients

In a clinical trial of 471 liver transplant patients randomized to tacrolimus extended-release capsules or tacrolimus immediate-release product, mortality at 12 months was 10% higher among the 76 female patients (18%) treated with tacrolimus extended-release capsules compared to the 64 female patients (8%) treated with tacrolimus immediate-release product. Tacrolimus extended-release capsules is not approved for the prophylaxis of organ rejection in patients who received a liver transplant.

5.4 Not Interchangeable with Other Tacrolimus Products - Medication Errors

Medication errors, including substitution and dispensing errors, between tacrolimus immediate-release products and tacrolimus extended-release capsules were reported outside the U.S. This led to serious adverse reactions, including graft rejection, or other adverse reactions due to under- or over-exposure to tacrolimus. Tacrolimus extended-release capsules is not interchangeable or substitutable for tacrolimus extended-release tablets, tacrolimus immediate-release capsules or tacrolimus for oral suspension. Changes between tacrolimus immediate-release and extended-release dosage forms must occur under physician supervision. Instruct patients and caregivers to recognize the appearance of tacrolimus extended-release capsules *[see Dosage Forms and Strengths(3)]* and to confirm with the healthcare provider if a different product is dispensed or if dosing instructions have changed.

5.5 New Onset Diabetes After Transplant

Tacrolimus extended-release capsules caused new onset diabetes after transplant (NODAT) in kidney transplant patients, which may be reversible in some patients. African-American and Hispanic kidney transplant patients are at an increased risk. Monitor blood glucose concentrations and treat appropriately *[see Adverse Reactions(6.1) and Use in Specific Populations(8.8)]* .

5.6 Nephrotoxicity due to Tacrolimus Extended-Release Capsules and Drug Interactions

Tacrolimus extended-release capsules, like other calcineurin-inhibitors, can cause acute or chronic nephrotoxicity in transplant patients due to its vasoconstrictive effect on renal vasculature, toxic tubulopathy and tubular-interstitial effects. Acute renal impairment associated with tacrolimus toxicity can result in high serum creatinine, hyperkalemia, decreased secretion of urea and hyperuricemia, and is usually reversible. In patients with elevated serum creatinine and tacrolimus whole blood trough concentrations greater than the recommended range, consider dosage reduction or temporary interruption of tacrolimus administration.

The risk for nephrotoxicity may increase when tacrolimus extended-release capsules is concomitantly administered with CYP3A inhibitors (by increasing tacrolimus whole blood concentrations) or drugs associated with nephrotoxicity (e.g., aminoglycosides, ganciclovir, amphotericin B, cisplatin, nucleotide reverse transcriptase inhibitors, protease inhibitors). When tacrolimus is used concurrently with other known nephrotoxic drugs, monitor renal function and tacrolimus blood concentrations, and adjust dose of both tacrolimus and/or concomitant medications during concurrent use *[see Adverse Reactions(6.1, 6.2) and Drug Interactions(7.2)].*

5.7 Neurotoxicity

Tacrolimus extended-release capsules may cause a spectrum of neurotoxicities. The most severe neurotoxicities include posterior reversible encephalopathy syndrome (PRES), delirium, seizure and coma; others include tremors, paresthesias, headache, mental status changes, and changes in motor and sensory functions *[see Adverse Reactions(6.1, 6.2)]* . As symptoms may be associated with tacrolimus whole blood trough concentrations at or above the recommended range, monitor for neurologic symptoms and consider dosage reduction or discontinuation of tacrolimus extended-release capsules if neurotoxicity occurs.

5.8 Hyperkalemia

Mild to severe hyperkalemia, which may require treatment, has been reported with tacrolimus including tacrolimus extended-release capsules. Concomitant use of agents associated with hyperkalemia (e.g., potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers) may increase the risk for hyperkalemia *[see Adverse Reactions(6.1)]* . Monitor serum potassium levels periodically during treatment.

5.9 Hypertension

Hypertension is a common adverse reaction of tacrolimus extended-release capsules therapy and may require antihypertensive therapy *[see Adverse Reactions(6.1)]* . Some antihypertensive drugs can increase the risk for hyperkalemia *[see Warnings and Precautions(5.8)]* . Calcium-channel blocking agents may increase tacrolimus blood concentrations and require dosage reduction of tacrolimus extended-release capsules *[see Drug Interactions(7.2)]* .

5.10 Risk of Rejection with Strong CYP3A Inducers and Risk of Serious Adverse Reactions with Strong CYP3A Inhibitors

The concomitant use of strong CYP3A inducers may increase the metabolism of tacrolimus, leading to lower whole blood trough concentrations and greater risk of rejection. In contrast, the concomitant use of strong CYP3A inhibitors may decrease the metabolism of tacrolimus, leading to higher whole blood trough concentrations and greater risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions(5.7, 5.11)]* . Therefore, adjust tacrolimus extended-release capsules dose and monitor tacrolimus whole blood trough concentrations when co-administering tacrolimus extended-release capsules with strong CYP3A inhibitors (e.g., including, but not limited to, telaprevir, boceprevir, ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin) or strong CYP3A inducers (e.g., including, but not limited to, rifampin, rifabutin) *[see Dosage and Administration(2.4) and Drug Interactions(7.2)]* . A rapid, sharp rise in tacrolimus levels has been reported after co-administration with a strong CYP3A4 inhibitor, clarithromycin, despite an initial reduction of tacrolimus dose. Early and frequent monitoring of tacrolimus whole blood trough levels is recommended *[see Drug Interactions (7.2)]* .

5.11 QT Prolongation

Tacrolimus extended-release capsules may prolong the QT/QTc interval and cause *Torsades de pointes*. Avoid tacrolimus extended-release capsules in patients with congenital long QT syndrome. Consider obtaining electrocardiograms and monitoring electrolytes (magnesium, potassium, calcium) periodically during treatment in patients with congestive heart failure, bradyarrhythmias, those taking certain antiarrhythmic medications or other products that lead to QT prolongation, and those with electrolyte disturbances (e.g., hypokalemia, hypocalcemia, or hypomagnesemia).

When co-administering tacrolimus extended-release capsules with other substrates and/or inhibitors of CYP3A, especially those that also have the potential to prolong the QT interval, a reduction in tacrolimus extended-release capsules dosage, monitoring of tacrolimus whole blood concentrations, and monitoring for QT prolongation is recommended *[see Dosage and Administration(2.4) and Drug Interactions(7.2)]* .

5.12 Immunizations

Whenever possible, administer the complete complement of vaccines before transplantation and treatment with tacrolimus extended-release capsules.

Avoid the use of live attenuated vaccines during treatment with tacrolimus extended-release capsules (e.g., intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines).

Inactivated vaccines noted to be safe for administration after transplantation may not be sufficiently immunogenic during treatment with tacrolimus extended-release capsules.

5.13 Pure Red Cell Aplasia

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. All of these patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease, or concomitant medications associated with PRCA. A mechanism for tacrolimus-induced PRCA has not been elucidated. If PRCA is diagnosed, consider discontinuation of tacrolimus extended-release capsules.

5.14 Thrombotic Microangiopathy (TMA) Including Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura

Cases of thrombotic microangiopathy (TMA), including hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP), have been reported in patients treated with tacrolimus extended-release capsules TMA may have a multifactorial etiology. Risk factors for TMA that can occur in transplant patients include, for example, severe infections, graft-versus-host disease (GVHD), Human Leukocyte Antigen (HLA) mismatch, the use of calcineurin inhibitors and mammalian target of rapamycin (mTOR) inhibitors. These risk factors may, either alone or combined, contribute to the risk of TMA.

In patients with signs and symptoms of TMA, consider tacrolimus as a risk factor. Concurrent use of tacrolimus and mTOR inhibitors may contribute to the risk of TMA.

5.15 Cannabidiol Drug Interactions

When cannabidiol and tacrolimus extended-release capsules are co-administered, closely monitor for an increase in tacrolimus blood levels and for adverse reactions suggestive of tacrolimus toxicity. A dose reduction of tacrolimus extended-release capsules should be considered as needed when tacrolimus extended-release capsules is co-administered with cannabidiol *[see Dosage and Administration (2.4)and Drug Interactions (7.3)]* .

6 ADVERSE REACTIONS

The following clinically significant adverse drug reactions are discussed in greater detail in other sections of labeling:

- Lymphoma and Other Malignancies *[see Warnings and Precautions(5.1)]*
- Serious Infections *[seeWarnings and Precautions(5.2)]*
- Increased Mortality in Female Liver Transplant Patients *[see Warnings and Precautions(5.3)]*
- New Onset Diabetes after Transplant *[see Warnings and Precautions(5.5)]*
- Nephrotoxicity due to Tacrolimus Extended-Release Capsules and Drug Interactions

[see Warnings and Precautions(5.6)]
- Neurotoxicity *[see Warnings and Precautions(5.7)]*
- Hyperkalemia *[see Warnings and Precautions(5.8)]*
- Hypertension *[see Warnings and Precautions(5.9)]*
- QT Prolongation *[see Warnings and Precautions(5.11)]*
- Pure Red Cell Aplasia *[see Warnings and Precautions(5.13)]*
- Thrombotic Microangiopathy, Including Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura *[see Warnings and Precautions (5.14)]*

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 patients were treated with tacrolimus extended-release capsules (N=214) or tacrolimus immediate-release product (N=212) and concomitant immunosuppressants (median duration of exposure of 12 months) in a randomized, open-label, active-controlled trial of mostly U.S. patients (Study 1) *[see Clinical Studies(14.1)]* . The types of adverse reactions seen in Study 1 were similar to the adverse reactions seen in Study 2 [non-U.S. trial in kidney transplant patients treated with tacrolimus extended-release capsules (N=331) or tacrolimus immediate-release product (N=336) and concomitant immunosuppressants] *[see Clinical Studies(14.2)]* .

In Study 1, the proportion of patients who discontinued treatment due to adverse reactions was 9% and 11% in the tacrolimus extended-release capsules and tacrolimus immediate-release treatment groups, respectively, through 12 months of treatment. The most common adverse reactions leading to discontinuation in tacrolimus extended-release capsules-treated patients were related to infections or renal/urinary disorders.

Infections
The overall incidence of infections, serious infections, and infections with identified etiology reported in patients treated with the tacrolimus extended-release capsules or tacrolimus immediate-release product in Study 1 are shown in Table 2.

Table 2: Percentage of Patients with Infections in Study 1 *Through One Year Post-Kidney Transplant

	Tacrolimus extended-release capsules, MMF, steroids, basiliximab induction N=214	**Tacrolimus immediate-release product, MMF, steroids, basiliximab induction N=212**
All Infections	69%	69%
Respiratory Infections	34%	31%
Urinary Tract Infections	16%	25%
Cytomegalovirus Infections	10%	11%
Bacterial Infections	8%	12%

Gastroenteritis	7%	3%
Polyomavirus Infections	3%	5%
Serious Infections	22%	23%

* Study 1 was not designed to support comparative claims of tacrolimus extended-release capsules compared to tacrolimus immediate-release product for the adverse reactions reported in this table.

New Onset Diabetes After Transplant (NODAT)

The incidence of new onset diabetes after transplantation (defined by the composite occurrence of ≥ 2 fasting plasma glucose values that were more than 126 mg/dL at ≥ 30 days apart, insulin use for ≥ 30 consecutive days, oral hypoglycemic use for ≥ 30 consecutive days, and/or HbA_{1C} ≥ 6.5%) is summarized in Table 3below for Study 1 through one year post-transplant *[see Warnings and Precautions(5.5)]* .

Table 3: Percentage of Patients with NODAT Through One Year Post-Kidney Transplant in Study 1 *

	Tacrolimus extended-release capsules, MMF, steroids, basiliximab induction N=162	**Tacrolimus immediate-release product, MMF, steroids, basiliximab induction N=151**
Composite NODAT	36%	35%
≥ 2 Fasting Plasma Glucose Values ≥ 126 mg/dL ≥ 30 days apart	26%	23%
HbA_{1C} ≥ 6.5%	19%	22%
Oral hypoglycemic use ≥ 30 consecutive days	14%	9%
Insulin use ≥ 30 consecutive days	6%	8%

* Study 1 was not designed to support comparative claims of tacrolimus extended-release capsules compared to tacrolimus immediate-release product for the adverse reactions reported in this table.

Hyperkalemia

In Study 1 *[see Clinical Studies(14.1)]* , 73 of 214 (34.1%) patients on tacrolimus extended-release capsules had a serum potassium level greater than 5.4 up to 6.4 mEq/L, and 8 out of 214 (3.7%) patients had a serum potassium level greater than 6.4 mEq/L *[see Warnings and Precautions(5.8)]* .

Common Adverse Reactions

The most common (≥ 30%) adverse reactions observed with tacrolimus extended-release capsules in Study 1 were: diarrhea, constipation, nausea, peripheral edema, tremor, and anemia. The incidence of adverse reactions that occurred in ≥ 15% of

tacrolimus extended-release capsules-treated patients compared to tacrolimus immediate-release product through one year of treatment in Study 1 is shown by treatment groups in Table 4.

Table 4: Adverse Reactions (≥ 15%) in Kidney Transplant Patients Through One Year Post-Transplant in Study 1 *

	Tacrolimus extended-release capsules, MMF, steroids, basiliximab induction N=214	**Tacrolimus immediate-release product, MMF, steroids, basiliximab induction N=212**
Diarrhea	45%	44%
Constipation	40%	32%
Nausea	36%	35%
Peripheral Edema	36%	34%
Tremor	35%	34%
Anemia	33%	29%
Hypertension	28%	30%
Vomiting	25%	25%
Hypomagnesemia	24%	27%
Insomnia	24%	28%
Hypophosphatemia	23%	28%
Headache	22%	24%
Hyperkalemia	20%	23%
Increased Blood Creatinine	19%	23%
Fatigue	16%	10%
Leukopenia	16%	16%
Hyperlipidemia	16%	17%
Hyperglycemia	16%	18%

* Study 1 was not designed to support comparative claims of tacrolimus extended-release capsules compared to tacrolimus immediate-release for the adverse reactions reported in this table.

Less Frequently Reported Adverse Reactions (less than 15% in tacrolimus extended-release capsules-treated patients) by System Organ Class

The following adverse reactions were reported in clinical studies of kidney transplant patients who were treated with tacrolimus extended-release capsules, MMF, and steroids (Studies 1 and 2):

- Blood and Lymphatic System Disorders: Hemolytic anemia, leukocytosis, neutropenia, thrombocytopenia, thrombotic microangiopathy
- Cardiac Disorders: Atrial fibrillation, atrial flutter, tachycardia
- Ear Disorders: Tinnitus

- Eye Disorders: Vision blurred, conjunctivitis
- Gastrointestinal Disorders: Abdominal distension, abdominal pain, aphthous stomatitis, dyspepsia, esophagitis, flatulence, gastritis, gastroesophageal reflux disease
- General Disorders and Administration Site Conditions: Anasarca, asthenia, edema, pyrexia
- Hepatobiliary Disorders: Abnormal hepatic function, cholestasis, hepatitis (acute and chronic), hepatotoxicity
- Infections and Infestations: Condyloma acuminatum, tinea versicolor
- Injury: Fall
- Investigations: Increased blood lactate dehydrogenase, increased blood urea, increased hepatic enzyme
- Metabolism and Nutrition Disorders: Anorexia, hyperphosphatemia, hyperuricemia, hypokalemia, hyponatremia, metabolic acidosis
- Musculoskeletal and Connective Tissue Disorders: Arthralgia, osteopenia, osteoporosis
- Neoplasms: Kaposi’s sarcoma
- Nervous System Disorders: Convulsion, dizziness, hypoesthesia, neurotoxicity, paresthesia, peripheral neuropathy
- Psychiatric Disorders: Agitation, anxiety, confusional state, depression, hallucination, mood swings, nightmare
- Renal and Urinary Disorders: Anuria, oliguria, proteinuria, renal failure, renal tubular necrosis, toxic nephropathy
- Respiratory, Thoracic and Mediastinal Disorders: Acute respiratory distress syndrome, dyspnea, pulmonary edema, productive cough
- Skin and Subcutaneous Tissue Disorders: Acne, alopecia, dermatitis, hyperhidrosis, hypotrichosis, pruritus, rash
- Vascular Disorders: Deep vein thrombosis, flushing

Pediatrics

Pediatric use information is approved for Astellas Pharma US, Inc.'s ASTAGRAF XL (tacrolimus extended-release capsules). However, due to Astellas Pharma US, Inc.'s marketing exclusivity rights, this drug product is not labeled with that information.

6.2 Postmarketing Experience

The following adverse reactions have been reported from marketing experience with tacrolimus in the U.S. and outside the U.S. 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. These reactions have been chosen for inclusion due to either their seriousness, frequency of reporting or causal connection to tacrolimus extended-release capsules:

- Blood and Lymphatic System Disorders: Agranulocytosis, disseminated intravascular coagulation, hemolytic uremic syndrome, febrile neutropenia, pancytopenia, pure red cell aplasia *[see Warnings and Precautions(5.13)]* , coagulopathy, thrombotic thrombocytopenic purpura, prolonged activated partial thromboplastin time, decreased blood fibrinogen
- Cardiac Disorders: Cardiac arrest, myocardial infarction, ventricular fibrillation, congestive cardiac failure, hypertrophic cardiomyopathy, pericardial effusion, angina

pectoris, supraventricular extrasystoles, supraventricular tachycardia, bradycardia, *Torsades de pointes*, QT prolongation
- Ear Disorders: Hearing loss
- Eye Disorders: Blindness, optic neuropathy, optic atrophy, photophobia
- Gastrointestinal Disorders: Gastrointestinal hemorrhage, gastrointestinal perforation, pancreatitis, peritonitis, stomach ulcer, intestinal obstruction, ascites, colitis, ileus, impaired gastric emptying, dysphagia
- Hepatobiliary Disorders: Hepatic failure, hepatic necrosis, cirrhosis, cholangitis, venoocclusive liver disease, bile duct stenosis, hepatic steatosis, jaundice
- Hypersensitivity Reactions: Hypersensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria
- Immune System Disorders: Graft versus host disease (acute and chronic)
- Investigations: Increased international normalized ratio
- Metabolism and Nutrition Disorders: Hypoproteinemia
- Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis, myalgia, polyarthritis, pain in extremity including Calcineurin-Inhibitor Induced Pain Syndrome (CIPS)
- Neoplasms: Lymphoma including EBV-associated lymphoproliferative disorder, hepatosplenic T-cell lymphoma, PTLD *[see Warnings and Precautions(5.1)]* , leukemia, melanoma
- Nervous System Disorders: Cerebral infarction, progressive multifocal leukoencephalopathy (PML) sometimes fatal *[see Warnings and Precautions(5.2)]* , posterior reversible encephalopathy syndrome (PRES) *[see Warnings and Precautions(5.7)]* , coma, status epilepticus, quadriplegia, flaccid paralysis, hemiparesis, aphasia, syncope, carpal tunnel syndrome, nerve compression, mutism, dysarthria, somnolence
- Psychiatric Disorders: Mental status changes
- Renal and Urinary Disorders: Hemorrhagic cystitis, hematuria, urinary retention, urinary incontinence
- Respiratory, Thoracic and Mediastinal Disorders: Interstitial lung disease, pulmonary hypertension, lung infiltration, rhinitis allergic, hiccups
- Skin and Subcutaneous Tissue Disorders: Hyperpigmentation, photosensitivity
- Vascular Disorders: Hemorrhage

7 DRUG INTERACTIONS

7.1 Mycophenolic Acid

When tacrolimus extended-release capsules is prescribed with a given dose of a mycophenolic acid (MPA) product, exposure to MPA is higher with tacrolimus extended-release capsules co-administration than with cyclosporine co-administration with MPA, because cyclosporine interrupts the enterohepatic recirculation of MPA while tacrolimus does not. Monitor for MPA-associated adverse reactions and reduce the dose of concomitantly administered mycophenolic acid products as needed.

7.2 Effects of Other Drugs on Tacrolimus Extended-Release Capsules

Table 5displays the effects of other drugs on tacrolimus extended-release capsules.

Table 5: Effects of Other Drugs/Substances on Tacrolimus Extended-Release Capsules [*]

Drug/Substance Class or Name	Drug Interaction Effect	Recommendations
Grapefruit or grapefruit juice [†]	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions(5.7, 5.10, 5.11)]* .	Avoid grapefruit or grapefruit juice.
Alcohol	May increase the rate of tacrolimus release and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions(5.7, 5.10, 5.11)]* .	Avoid alcoholic beverages.
Strong CYP3A Inducers [‡]: Antimycobacterials (e.g., rifampin, rifabutin), anticonvulsants (e.g., phenytoin, carbamazepine and phenobarbital), St John's wort	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection *[see Warnings and Precautions(5.10)]* .	Increase tacrolimus extended-release capsules dose and monitor tacrolimus whole blood trough concentrations *[see Dosage and Administration(2.3, 2.4) and Clinical Pharmacology(12.3)]* .
Strong CYP3A Inhibitors [‡]: Protease inhibitors (e.g., nelfinavir, telaprevir, boceprevir, ritonavir), azole antifungals (e.g., voriconazole, posaconazole, itraconazole, ketoconazole), antibiotics (e.g., clarithromycin, troleandomycin, chloramphenicol), nefazodone, letermovir, *Schisandra sphenanthera*extracts	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation). A rapid, sharp rise in tacrolimus levels may occur early, despite an immediate reduction of tacrolimus dose *[see Warnings and Precautions(5.7, 5.10, 5.11)]* .	Reduce tacrolimus extended-release capsules dose (for voriconazole and posaconazole, give one-third of the original dose) and adjust dose based on tacrolimus whole blood trough concentrations *[see Dosage and Administration(2.3, 2.4) and Clinical Pharmacology(12.3)]* . Early and frequent monitoring of tacrolimus whole blood trough levels should start within 1-3 days and continue monitoring as necessary

		[see Warnings and Precautions (5.10)] .
Mild or Moderate CYP3A Inhibitors: Clotrimazole, antibiotics (e.g., verapamil, diltiazem, nifedipine, nicardipine), amiodarone, danazol, ethinyl estradiol, cimetidine, lansoprazole and omeprazole	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions(5.7, 5.10, 5.11)]* .	Monitor tacrolimus whole blood trough concentrations and reduce tacrolimus extended-release capsules dose if needed *[see Dosage and Administration(2.3, 2.4) and Clinical Pharmacology(12.3)]* .
Other drugs, such as: Magnesium and aluminum hydroxide antacids Metoclopramide	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions(5.7, 5.10, 5.11)]* .	Monitor tacrolimus whole blood trough concentrations and reduce tacrolimus extended-release capsules dose if needed *[see Dosage and Administration(2.3, 2.4) and Clinical Pharmacology(12.3)]* .
Mild or Moderate CYP3A Inducers Methylprednisolone, prednisone	May decrease tacrolimus whole blood trough concentrations.	Monitor tacrolimus whole blood trough concentrations and adjust tacrolimus extended-release capsules dose if needed *[see Dosage and Administration(2.3, 2.4)]* .
Caspofungin	May decrease tacrolimus whole blood trough concentrations.	Monitor tacrolimus whole blood trough concentrations and adjust tacrolimus extended-release capsules dose if needed *[see Dosage and Administration (2.3, 2.4)]* .

* Tacrolimus extended-release capsules dosage adjustment recommendation based on observed effect of co-administered drug on tacrolimus exposures [see Clinical Pharmacology (12.3)] , literature reports of altered tacrolimus exposures, or the other drug's known CYP3A inhibitor/inducer status.

† High dose or double strength grapefruit juice is a strong CYP3A inhibitor; low dose or single strength grapefruit juice is a moderate CYP3A inhibitor.

‡ Strong CYP3A inhibitor/inducer, based on reported effect on exposures to tacrolimus along with supporting in vitro CYP3A inhibitor/inducer data, or based on drug-drug interaction studies with midazolam (sensitive CYP3A probe substrate).

Direct Acting Antiviral (DAA) Therapy

The pharmacokinetics of tacrolimus may be impacted by changes in liver function during DAA therapy, related to clearance of HCV virus. Close monitoring and potential dose adjustment of tacrolimus extended-release capsules is warranted to ensure continued efficacy and safety *[see Dosage and Administration (2.3, 2.4)]* .

7.3 Cannabidiol

The blood levels of tacrolimus may increase upon concomitant use with cannabidiol. When cannabidiol and tacrolimus extended-release capsules are co-administered, closely monitor for an increase in tacrolimus blood levels and for adverse reactions suggestive of tacrolimus toxicity. A dose reduction of tacrolimus extended-release capsules should be considered as needed when tacrolimus extended-release capsules is co-administered with cannabidiol *[see Dosage and Administration (2.4)and Warnings and Precautions (5.15)]* .

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy registry that monitors pregnancy outcomes in women exposed to tacrolimus extended-release capsules during pregnancy. The Transplantation Pregnancy Registry International (TPRI) is a voluntary pregnancy exposure registry that monitors outcomes of pregnancy in female transplant recipients and those fathered by male transplant recipients exposed to immunosuppressants including tacrolimus. Healthcare providers are encouraged to advise their patients to register by contacting the Transplantation Pregnancy Registry International at 1-877-955-6877 or https://www.transplantpregnancyregistry.org/.

Risk Summary

Tacrolimus can cause fetal harm when administered to a pregnant woman. Data from postmarketing surveillance and TPRI suggest that infants exposed to tacrolimus *in utero*are at a risk of prematurity, birth defects/congenital anomalies, low birth weight, and fetal distress *[see Human Data].*Advise pregnant women of the potential risk to the fetus.

Administration of oral tacrolimus to pregnant rabbits and rats throughout the period of organogenesis was associated with maternal toxicity/lethality, and an increased incidence of abortion, malformation and embryofetal death at clinically relevant doses [0.5 the maximum recommended clinical dose (0.2 mg/kg/day), on a mg/m ^{2}basis]. Administration of oral tacrolimus to pregnant rats after organogenesis and throughout lactation produced maternal toxicity, effects on parturition, reduced pup viability and reduced pup weight at clinically relevant doses (0.8 the maximum recommended clinical dose, on a mg/m ^{2}basis). Administration of oral tacrolimus to rats prior to mating, and throughout gestation and lactation produced maternal toxicity/lethality, marked effects on parturition, embryofetal loss, malformations, and reduced pup viability at clinically relevant doses (0.8 times the maximum recommended clinical dose, on a mg/m ^{2}basis). Interventricular septal defects, hydronephrosis, craniofacial malformations and skeletal effects were observed in offspring that died *[see Animal Data].*

The background risk of major birth defects and miscarriage in the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

Risks during pregnancy are increased in organ transplant recipients. The risk of premature delivery following transplantation is increased. Pre-existing hypertension and diabetes confer additional risk to the pregnancy of an organ transplant recipient. Pre-gestational and gestational diabetes are associated with birth defects/congenital anomalies, hypertension, low birth weight and fetal death.

Cholestasis of pregnancy (COP) was reported in 7% of liver or liver-kidney (LK) transplant recipients, compared with approximately 1% of pregnancies in the general population. However, COP symptoms resolved postpartum and no long-term effects on the offspring were reported.

Maternal Adverse Reactions

Tacrolimus extended-release capsules may increase hyperglycemia in pregnant women with diabetes (including gestational diabetes). Monitor maternal blood glucose levels regularly *[seeWarnings and Precautions(5.5)]* .

Tacrolimus extended-release capsules may exacerbate hypertension in pregnant women and increase pre-eclampsia. Monitor and control blood pressure *[seeWarnings and Precautions(5.8, 5.9)]* .

Fetal/Neonatal Adverse Reactions

Renal dysfunction, transient neonatal hyperkalemia and low birth weight have been reported at the time of delivery in infants of mothers taking tacrolimus extended-release capsules.

Labor or Delivery

There is an increased risk for premature delivery (less than 37 weeks) following transplantation and maternal exposure to tacrolimus extended-release capsules.

Data

Human Data

There are no adequate and well-controlled studies on the effects of tacrolimus in human pregnancy. Safety data from the TPRI and postmarketing surveillance suggest infants exposed to tacrolimus *in utero*have an increased risk for miscarriage, pre-term delivery (less than 37 weeks), low birth weight (less than 2,500 gram), birth defects/congenital anomalies and fetal distress.

TPRI reported 450 and 241 total pregnancies in kidney and liver transplant recipients exposed to tacrolimus, respectively. The TPRI pregnancy outcomes are summarized in Table 6. In the table below, the number of recipients exposed to tacrolimus concomitantly with mycophenolic acid (MPA) products during the preconception and first trimester periods is high (27% and 29% for kidney and liver transplant recipients, respectively). Because MPA products may also cause birth defects, the birth defect rate

may be confounded and this should be taken into consideration when reviewing the data, particularly for birth defects. Birth defects observed include cardiac malformations, craniofacial malformations, renal/urogenital disorders, skeletal abnormalities, neurological abnormalities and multiple malformations.

Table 6: TPRI-Reported Pregnancy Outcomes in Transplant Recipients with Exposure to Tacrolimus

	Kidney	Liver
Pregnancy Outcomes*	**462**	**253**
Miscarriage	24.5%	25%
Live births	**331**	**180**
Pre-term delivery (less than 37 weeks)	49%	42%
Low birth weight (less than 2,500 gram)	42%	30%
Birth defects	8% †	5%

* Includes multiple births and terminations.
† Birth defect rate confounded by concomitant MPA products exposure in over half of offspring with birth defects.

Additional information reported by TPRI in pregnant transplant patients receiving tacrolimus included diabetes during pregnancy in 9% of kidney recipients and 13% of liver recipients and hypertension during pregnancy in 53% of kidney recipients and 16.2% of liver recipients.

Animal Data

Administration of oral tacrolimus to pregnant rabbits throughout organogenesis produced maternal toxicity and abortion at 0.32 mg/kg (0.5 times the maximum recommended clinical dose [0.2 mg/kg/day], on a mg/m ^{2}basis). At 1 mg/kg (1.6 times the maximum recommended clinical dose), embryofetal lethality and fetal malformations (ventricular hypoplasia, interventricular septal defect, bulbous aortic arch, stenosis of ductus arteriosus, omphalocele, gallbladder agenesis, skeletal anomalies) were observed. Administration of 3.2 mg/kg oral tacrolimus (2.6 times the maximum recommended clinical dose) to pregnant rats throughout organogenesis produced maternal toxicity/lethality, embryofetal lethality and decreased fetal body weight in the offspring of C-sectioned dams; and decreased pup viability and interventricular septal defect in offspring of dams that delivered.

In a peri-/postnatal development study, oral administration of tacrolimus to pregnant rats during late gestation (after organogenesis) and throughout lactation produced maternal toxicity, effects on parturition, and reduced pup viability at 3.2 mg/kg (2.6 times the maximum recommended clinical dose); among these pups that died early, an increased incidence of kidney hydronephrosis was observed. Reduced pup weight was observed at 1 mg/kg (0.8 times the maximum recommended clinical dose).

Administration of oral tacrolimus to rats prior to mating, and throughout gestation and lactation produced maternal toxicity/lethality, embryofetal loss and reduced pup viability at 3.2 mg/kg (2.6 times the maximum recommended clinical dose range). Interventricular septal defects, hydronephrosis, craniofacial malformations and skeletal

effects were observed in offspring that died. Effects on parturition (incomplete delivery of nonviable pups) were observed at 1 mg/kg (0.8 times the maximum recommended clinical dose) *[see Nonclinical Toxicology(13.1)].*

8.2 Lactation

Risk Summary

Controlled lactation studies have not been conducted in humans; however, tacrolimus has been reported to be present in human milk. The effects of tacrolimus on the breastfed infant, or on milk production, have not been assessed. Tacrolimus is excreted in rat milk and in peri-/postnatal rat studies; exposure to tacrolimus during the postnatal period was associated with developmental toxicity in the offspring at clinically relevant doses *[see Pregnancy(8.1) and Nonclinical Toxicology(13.1)]* .

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for tacrolimus extended-release capsules and any potential adverse effects on the breastfed child from tacrolimus extended-release capsules or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Tacrolimus extended-release capsules can cause fetal harm when administered to pregnant women. Advise female and male patients of reproductive potential to speak to their healthcare provider on family planning options including appropriate contraception prior to starting treatment with tacrolimus extended-release capsules *[see Use in Specific Populations(8.1) and Nonclinical Toxicology(13.1)]* .

Infertility

Based on findings in animals, male and female fertility may be compromised by treatment with tacrolimus extended-release capsules *[see Nonclinical Toxicology(13.1)].*

8.4 Pediatric Use

Pediatric use information is approved for Astellas Pharma US, Inc.'s ASTAGRAF XL (tacrolimus extended-release capsules). However, due to Astellas Pharma US, Inc.'s marketing exclusivity rights, this drug product is not labeled with that information.

8.5 Geriatric Use

Clinical studies of tacrolimus extended-release capsules did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In Studies 1 and 2, 29 patients were 65 years of age and older, and 3 patients were 75 years of age and over *[see Clinical Studies(14)]* . 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 Renal Impairment

The pharmacokinetics of tacrolimus in patients with renal impairment was similar to that in healthy subjects with normal renal function. However, due to its potential for nephrotoxicity, monitoring of renal function in patients with renal impairment is recommended; tacrolimus dosage should be reduced if indicated *[see Warnings and Precautions(5.6) and Clinical Pharmacology(12.3)]* .

8.7 Hepatic Impairment

The mean clearance of tacrolimus was substantially lower in patients with severe hepatic impairment (mean Child-Pugh score: more than 10) compared to healthy subjects with normal hepatic function *[see Clinical Pharmacology(12.3)]* . With greater tacrolimus whole blood trough concentrations in patients with severe hepatic impairment, there is a greater risk of adverse reactions and dosage reduction is recommended *[see Dosage and Administration(2.3)].*For patients with moderate hepatic impairment, monitor tacrolimus whole blood trough concentrations. For patients with mild hepatic impairment, no dosage adjustments are needed.

8.8 Race or Ethnicity

African-American patients may need to be titrated to higher dosages to attain comparable trough concentrations compared to Caucasian patients *[see Dosage and Administration(2.3), Clinical Pharmacology(12.3), and Clinical Studies(14)].*

African-American and Hispanic patients are at increased risk for new onset diabetes after transplant. Monitor blood glucose concentrations and treat appropriately *[see Warnings and Precautions(5.5)].*

10 OVERDOSAGE

Postmarketing cases of overdose with tacrolimus have been reported. Overdosage adverse reactions included:

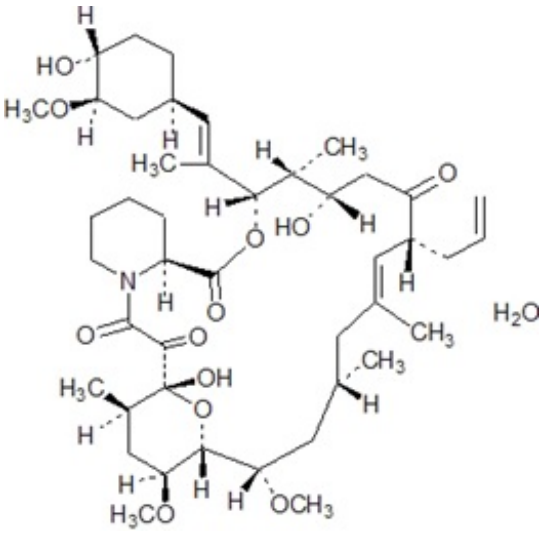
- nervous system disorders (tremor, headache, confusional state, balance disorders, encephalopathy, lethargy and somnolence)
- gastrointestinal disturbances (nausea, vomiting, and diarrhea)
- abnormal renal function (increased blood urea nitrogen and elevated serum creatinine)
- urticaria
- hypertension
- peripheral edema, and
- infections [one fatal postmarketing case of bilateral pneumopathy and CMV infection was attributed to tacrolimus (extended-release) overdose].

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.

11 DESCRIPTION

Tacrolimus is the active ingredient in tacrolimus extended-release capsules. Tacrolimus is a calcineurin-inhibitor immunosuppressant produced by *Streptomyces tsukubaensis*. Chemically, tacrolimus is designated as [3 *S*– [3 *R**[*E*(1 *S**, 3 *S**, 4 *S**)], 4 *S**, 5 *R**, 8 *S**, 9 *E*, 12 *R**, 14 *R**, 15 *S**, 16 *R**, 18 *S**, 19 *S**, 26a *R**]] – 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 – methoxycyclo – hexyl) – 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 an empirical 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.

Tacrolimus extended-release capsules is available for oral administration as hard gelatin capsules containing the equivalent of 0.5 mg, 1 mg or 5 mg of anhydrous tacrolimus, USP. Inactive ingredients include ethylcellulose NF, hypromellose USP, magnesium stearate NF and lactose monohydrate NF. The ingredients are directly proportional across all capsule strengths. The capsule shell contains gelatin NF, ferric oxide red NF, ferric oxide yellow NF, and titanium dioxide USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin (a ubiquitous mammalian intracellular enzyme) is then formed and the phosphatase activity of calcineurin is inhibited. Such inhibition prevents the dephosphorylation and translocation of various factors such as the nuclear factor of activated T-cells (NF-AT), and nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB).

Tacrolimus inhibits the expression and/or production of several cytokines that include interleukin (IL)-1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, gamma interferon, tumor necrosis factor-alpha, and granulocyte macrophage colony-stimulating factor. Tacrolimus also inhibits IL-2 receptor expression and nitric oxide release, induces

apoptosis and production of transforming growth factor-beta that can lead to immunosuppressive activity. The net result is the inhibition of T-lymphocyte activation and proliferation as well as T-helper-cell-dependent B-cell response (i.e., immunosuppression).

12.3 Pharmacokinetics

Table 7summarizes the pharmacokinetic (PK) parameters of tacrolimus following oral administration of tacrolimus extended-release capsules in healthy subjects and in kidney transplant patients. Whole blood tacrolimus concentrations in these PK studies were measured using validated HPLC/MS/MS assays.

Table 7: Pharmacokinetic Parameters of Tacrolimus Extended-Release Capsules (Given Once Daily) in Healthy Subjects and in Kidney Transplant Patients (Under Fasted Conditions)

Population	Tacrolimus Extended-Release Capsules Dose*	Day†	PK Parameters of Tacrolimus Extended-Release Capsules			
			C_{max}‡ (ng/mL)	T_{max}§ (hr)	AUC_{24}‡ (ng•hr/mL)	C_{24}¶ (ng/mL)
Healthy Subjects (N=24)	4 mg 4 mg	Day 1 Day 10	6.2 ± 2.1 11.6 ± 3.4	2 [1 to 5] 2 [1 to 3]	74 ± 22 155 ± 46	2.3 ± 0.8 4.7 ± 1.5
Adult Kidney De novo # (N=17)	0.2 mg/kg 0.19 mg/kg 0.18 mg/kg 0.18 mg/kg	Day 1 Day 3 Day 7 Day 14	26 ± 13.7 31 ± 13.9 32.2 ± 10.2 32.7 ± 9	3 [2 to 24] 2 [0.5 to 2] 2 [1 to 6] 2 [1 to 4]	372 ± 202 437 ± 175 405 ± 117 412 ± 109	12.1 ± 7.2 13.5 ± 5.6 11.4 ± 4 11.2 ± 3.9
Adult Kidney (6 months or greater post-transplant) (N=60)	5.2 mg/day Þ	Day 14 Þ	16.1 ± 5.3	2 [1 to 6]	222 ± 64	6.7 ± 1.9 ß

* Healthy adult subjects (actual administered dose of tacrolimus extended-release capsules); adult de novo kidney transplant patients (actual group mean dose of tacrolimus extended-release capsules).
† Day of tacrolimus extended-release capsules treatment and PK profiling.
‡ Arithmetic means ± S.D.
§ Median [range].
¶ Tacrolimus trough concentration before the next dose.
# "De novo" refers to immunosuppression starting at the time of transplantation; data from PK substudy of Study 2.
Þ Same daily dose of tacrolimus extended-release capsules for 14-day period.
ß Correlation coefficient of AUC 24 to C min r = 0.88.

In de novo adult kidney transplant patients, the tacrolimus systemic exposure, as assessed by AUC_{24}, for tacrolimus extended-release capsules 0.2 mg/kg once daily on Day 1 post-transplant was 18% (Ratio [SD]: 0.822 [1.647]) lower when compared with Prograf (tacrolimus immediate-release) 0.2 mg/kg/day given twice daily. By Day 3 post-

transplant, the AUC $_{24}$was similar between the two formulations. On Day 14 (steady state), the AUC $_{24}$for tacrolimus extended-release capsules was 21% (Ratio [SD]: 1.207 [1.326]) higher than that of Prograf (tacrolimus immediate-release), at comparable trough concentrations (C $_{24}$).

Due to intersubject variability in tacrolimus PK, individualization of dosing regimen is necessary for optimal therapy *[see Dosage and Administration(2.3, 2.4)]* .

Pharmacokinetic data indicate that whole blood concentrations rather than plasma concentrations serve as the more appropriate sampling compartment to describe tacrolimus PK.

Absorption

In healthy subjects, the administration of escalating tacrolimus extended-release capsules doses ranging from 1.5 mg to 10 mg resulted in dose-proportional increases in tacrolimus AUC and C $_{24h}$, and no change in elimination half-life.

Food Effects

The presence of a meal affects the absorption of tacrolimus; the rate and extent of absorption is greatest under fasted conditions. In 24 healthy subjects, administration of tacrolimus extended-release capsules immediately following a high-fat meal (150 protein calories, 250 carbohydrate calories, and 500 to 600 fat calories) reduced the C $_{max}$, AUC $_{t}$, and AUC $_{inf}$of tacrolimus by approximately 25% compared with fasting values. Food delayed the median T $_{max}$from 2 hours in the fasted state to 4 hours in the fed state; however, the terminal half-life remained 36 hours regardless of dosing conditions. The time when a meal is consumed also affected tacrolimus bioavailability. In 24 healthy subjects, when tacrolimus extended-release capsules was administered 1.5 hours after consumption of a high-fat breakfast, tacrolimus exposure was decreased approximately 35%. Administration of tacrolimus extended-release capsules 1 hour prior to a high-fat breakfast reduced tacrolimus exposure by 10%. Tacrolimus extended-release capsules should be taken, preferably on an empty stomach, at least 1 hour before a meal or at least 2 hours after a meal.

Chronopharmacokinetic Effect

In 23 healthy subjects, a diurnal effect on the absorption of tacrolimus was observed. Evening dosing of tacrolimus extended-release capsules reduced AUC $_{inf}$by 35% relative to morning dosing. Tacrolimus extended-release capsules should be taken consistently at the same time every morning.

Distribution

The plasma protein binding of tacrolimus is approximately 99% and is independent of concentration over a range of 5 ng/mL 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 in which tacrolimus was administered as tacrolimus immediate-release, the ratio of whole blood concentration to plasma concentration averaged 35 (range 12 to 67).

Elimination

Metabolism

The desired pharmacological activity of tacrolimus is primarily due to the parent drug. Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P-450 system (CYP3A4 and CYP3A5). 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

In a mass balance study of orally-administered radiolabeled tacrolimus to 6 healthy subjects, the mean recovery of the radiolabel was 94.9 ± 30.7%. Fecal elimination accounted for 92.6 ± 30.7% and urinary elimination accounted for 2.3 ± 1.1% of the total radiolabel administered. 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 the mean clearance of tacrolimus was 0.172 ± 0.088 L/hr/kg.

The elimination half-life of tacrolimus after oral administration of 4 mg tacrolimus extended-release capsules daily for 10 days was 38 ± 3 hours in 24 healthy subjects.

Specific Populations

Pediatric Patients

Pediatric use information is approved for Astellas Pharma US, Inc.'s ASTAGRAF XL (tacrolimus extended-release capsules). However, due to Astellas Pharma US, Inc.'s marketing exclusivity rights, this drug product is not labeled with that information.

Patients with Renal Impairment

Tacrolimus pharmacokinetics following a single administration of tacrolimus immediate-release injection (administered as a continuous IV infusion) 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 mean clearance of tacrolimus in patients with renal dysfunction given tacrolimus IV was similar to that in healthy subjects given tacrolimus IV and in healthy subjects given oral tacrolimus immediate-release *[see Use in Specific Populations(8.6)]* .

Patients with Hepatic Impairment

Tacrolimus pharmacokinetics have been determined in six patients with mild hepatic impairment (mean Child-Pugh score: 6.2) following single oral administration of tacrolimus immediate-release. The mean clearance of tacrolimus in patients with mild hepatic impairment was not substantially different from that in healthy subjects. Tacrolimus pharmacokinetics were studied in six patients with severe hepatic impairment (mean Child-Pugh score: more than 10). The mean clearance was substantially lower in patients with severe hepatic impairment *[see Dosage and Administration(2.3) and Use in Specific Populations(8.7)].*

Racial or Ethnic Groups

The pharmacokinetics of tacrolimus was studied following single oral administration of

tacrolimus immediate-release (5 mg) in 10 African-American, 12 Latino-American, and 12 Caucasian healthy subjects *[see Dosage and Administration(2.2), Use in Specific Populations(8.8) and Clinical Studies(14)]:*

- The mean (± SD) tacrolimus C_{max} in African-Americans (23.6 ± 12.1 ng/mL) was lower than in Caucasians (40.2 ± 12.6 ng/mL) and Latino-Americans (36.2 ± 15.8 ng/mL).
- 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 lower than in Caucasians (19 ± 5.8%).
- There was no significant difference in mean terminal half-life among the three ethnic groups (range from approximately 25 to 30 hours).

Male and Female Patients

A formal trial to evaluate the effect of gender on tacrolimus pharmacokinetics has not been conducted; however, there was no difference in total mg daily dosages between male and female patients receiving tacrolimus extended-release capsules in the kidney transplant trials. A retrospective comparison of pharmacokinetics in healthy subjects, and in kidney transplant patients indicated no gender-based differences.

Drug Interaction Studies

Because tacrolimus is metabolized mainly by CYP3A enzymes, drugs or substances known to inhibit these enzymes and/or are known CYP3A substrates may increase tacrolimus whole blood concentrations. Drugs known to induce CYP3A enzymes may decrease tacrolimus whole blood concentrations *[see Warnings and Precautions(5.10) and Drug Interactions(7.2)]* .

Figure 1 and Figure 2 summarize the PK data from drug interaction studies of tacrolimus extended-release capsules or tacrolimus immediate-release capsules. These studies assessed the effect of co-administered drugs on tacrolimus PK in healthy subjects. Dosing adjustments, when using drugs that inhibit or increase CYP3A enzymes, may be necessary *[see Drug Interactions(7.2)]* .

Figure 1: Effect of Co-administered Drugs on the Pharmacokinetics of Tacrolimus (when Given as Tacrolimus Extended-Release Capsules)

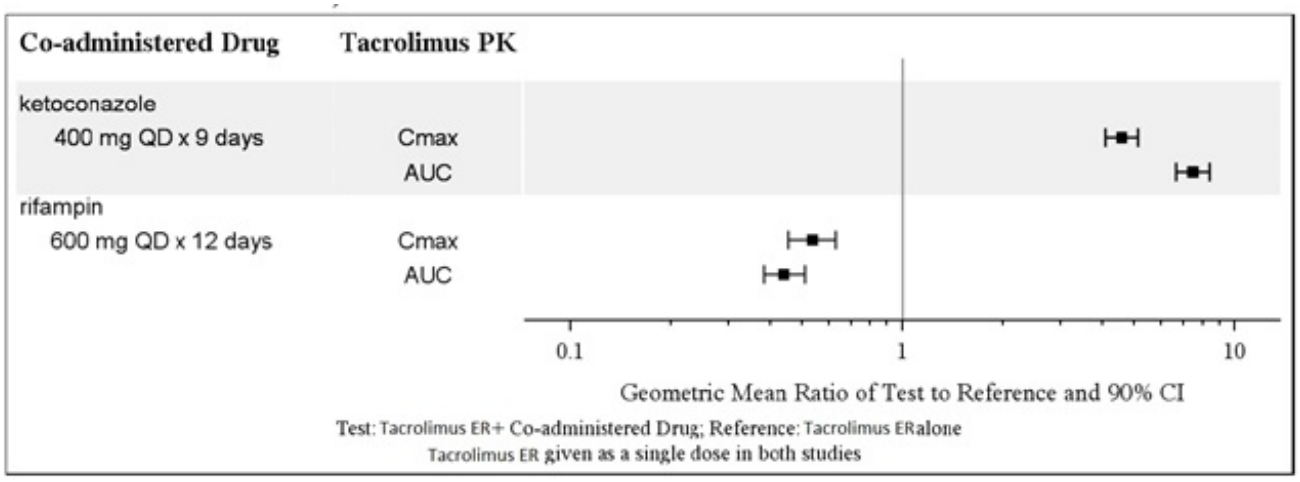
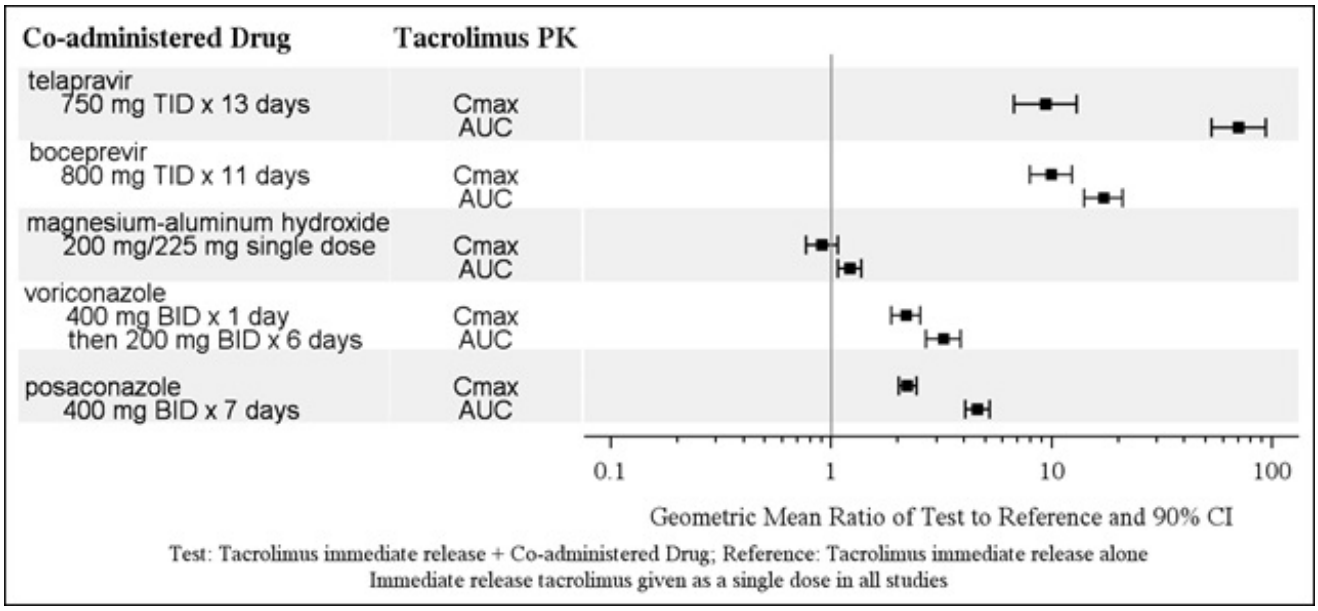


Figure 2: Effect of Co-administered Drugs on the Pharmacokinetics of Tacrolimus (when Given as Immediate-Release Tacrolimus)



Other Drug Interaction Studies

- *Caspofungin*(see complete prescribing information for CANCIDAS): Caspofungin reduced the blood AUC $_{0\text{-}12}$of tacrolimus by approximately 20%, peak blood concentration (C $_{max}$) by 16%, and 12-hour blood concentration (C $_{12hr}$) 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 (7.2)]* . The mechanism of interaction has not been confirmed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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 (0.49 times the AUC at the maximum clinical dose of 0.2 mg/kg/day) and in the rat was 5 mg/kg/day (0.14 times the AUC at the maximum clinical dose of 0.2 mg/kg/day) *[see Warnings and Precautions(5.1)]* .

A 104-week dermal carcinogenicity study was performed in mice with tacrolimus ointment (0.03% to 3%), equivalent to tacrolimus doses of 1.1mg/kg/day to 118 mg/kg/day or 3.3 mg/m ^{2}/day 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; 2.4-fold the human exposure in stable adult kidney transplant patients more than 6 months post-transplant). 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 are limited; doses of tacrolimus were administered that likely induced immunosuppression in these animals, impairing their immune system's ability to inhibit unrelated carcinogenesis.

Mutagenesis

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.

Impairment of Fertility

Tacrolimus subcutaneously administered to male rats at paternally toxic doses of 2 mg/kg/day [1.6 times the maximum recommended clinical dose (0.2 mg/kg/day) on a mg/m ^{2}basis] or 3 mg/kg/day (2.4 times the maximum recommended clinical dose) resulted in a dose-related decrease in sperm count.

Tacrolimus administered orally at 1 mg/kg (0.8 times the maximum clinical dose) 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- and post-implantation loss and increased numbers of undelivered and nonviable pups. When administered at 3.2 mg/kg (2.6 times the maximum 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 Tacrolimus Extended-Release Capsules with Basiliximab Induction

Study 1 was a 12-month, randomized, open-label trial of tacrolimus extended-release capsules (N=214) compared to active-control of tacrolimus (Prograf) immediate-release (N=212), conducted primarily in the U.S. in patients who were a recipient of a primary or retransplanted non-HLA-identical living or deceased donor kidney transplant. All patients received basiliximab induction and concomitant mycophenolate mofetil (MMF) and corticosteroids. The study population was 17 to 77 years of age, the mean age was 48 years; 64% were male and 36% were female; 73% were Caucasian, 22% were African-American, 2% were Asian, and 3% were categorized as other races. Living donors provided 49% of the organs and 51% of patients received a kidney transplant from a deceased donor with a mean cold ischemia time of 19 hours. The most frequent diseases leading to transplantation were balanced between the groups and included nephrosclerosis/hypertensive nephropathy, diabetic nephropathy, glomerulonephritis, and polycystic kidney disease. In the study, 97% of patients had no previous transplant and 3% had a previous transplant.

Study Medications

Tacrolimus Extended-Release Capsules or Control [Prograf (tacrolimus) capsules]

The initial dose of tacrolimus extended-release capsules was administered prior to reperfusion or within 48 hours after completion of the transplant procedure. The protocol-defined initial post-operative daily doses were 0.15 to 0.2 mg per kg given as a single dose in the morning for tacrolimus extended-release capsules and 0.075 to 0.1 mg per kg twice daily for control. The tacrolimus extended-release capsules and control dosage was then adjusted on the basis of safety and efficacy and a target whole blood tacrolimus trough concentration range of 7 ng/mL to 16 ng/mL for the first 90 days post-transplant and 5 ng/mL to 15 ng/mL thereafter.

The average recorded starting tacrolimus daily dose, given any time up to day 2 post-transplant, was higher for tacrolimus extended-release capsules than for control (0.14 mg per kg per day versus 0.1 mg per kg per day). Thereafter, to achieve comparable mean tacrolimus trough concentrations, on average 15% higher total mean daily doses of tacrolimus were required for tacrolimus extended-release capsules than for control.

Tacrolimus whole blood trough concentrations were monitored on Day 3, Day 7, Day 10, Day 14, and Day 21, then Month 1, Month 2, Month 4, Month 6, Month 8, Month 10, and Month 12. Table 10shows the tacrolimus whole blood trough concentrations measured at protocol-specified time points for tacrolimus extended-release capsules. Approximately 80% of tacrolimus extended-release capsules-treated patients maintained tacrolimus whole trough blood concentrations between 5 ng/mL to 17 ng/mL during Month 1 through Month 2 and between 4 ng/mL to 12 ng/mL from Month 3 through Month 12.

Table 10: Observed Tacrolimus Whole Blood Trough Concentrations in Tacrolimus Extended-Release Capsules-Treated Kidney Transplant Patients in Study 1

Scheduled Visit	**Tacrolimus Whole Blood Trough Concentrations (ng/mL)*** **[Median (10 thto 90 thPercentile)]**
Day 3	9.6 (4.9 to 20.2)
Day 7	9.1 (4.4 to 16.8)
Day 14	10 (5.7 to 16.9)
Month 1	10.5 (5.6 to 17.1)
Month 2	9.4 (6.1 to 14.2)
Month 6	7.7 (4.4 to 11.5)
Month 12	7.2 (3.8 to 10.4)

* Immunoassay was used in most laboratories.

African-American patients required higher tacrolimus extended-release capsules dosages to attain similar trough concentrations as Caucasian patients (see Table 11).

Table 11: Tacrolimus Extended-Release Capsules Dosages and Mean Whole Blood Trough Concentrations in African-American and Caucasian Kidney Transplant Patients in Study 1

Time After Transplant	Caucasian Patients N=160		African-American Patients N=41	
	Dose (mg/kg)	Mean Trough Concentration (ng/mL)	Dose (mg/kg)	Mean Trough Concentration (ng/mL)
Day 7	0.14	10.65	0.14	7.78
Month 1	0.14	11.11	0.17	10.92
Month 6	0.1	7.95	0.13	8.42
Month 12	0.09	7.53	0.12	7.33

MMF

The initial dose of MMF was 1 gram administered orally or intravenously prior to or within 48 hours of completion of the transplant procedure. Subsequent MMF was administered orally 1 gram twice daily or up to 1.5 grams twice daily in African-American patients. Dose-equivalent three times daily or four times daily dosing was permitted if MMF tolerability was a concern.

The MMF dosages administered by time period in tacrolimus extended-release capsules-treated patients are shown in Table 12. The MMF dosage was reduced to less than 2 grams per day by month 12 in 56% of tacrolimus extended-release capsules-treated patients. Approximately 57% of the MMF dose reductions were because of adverse reactions in the tacrolimus extended-release capsules group *[see Adverse Reactions(6.1)]* .

Table 12: Proportion of Patients Who Received 2 grams (or less than or more than 2 grams) of MMF by Time Period in Tacrolimus Extended-Release Capsules-Treated Patients in Study 1

Time period (Days)	Patients on MMF	Time-averaged MMF dosage*		
	N	Less than 2 grams per day	2 grams per day	Greater than 2 grams per day
1 to 30	211	30%	64%	6%
31 to 90	208	38%	57%	5%
91 to 180	205	49%	48%	3%
181 to 365	201	51%	47%	3%

* Time-averaged MMF dosage is the total MMF dosage per day divided by the duration of treatment. A time-averaged MMF dosage of 2 grams per day means that the MMF dosage was not reduced in those patients during the time period.

Basiliximab Induction

All patients were administered 2 doses of basiliximab induction therapy (20 mg intravenously) with the first dose on Day 0 before skin closure and the second dose between Day 3 and Day 5.

Steroids

All patients were administered an intravenous bolus of 500 to 1,000 mg of methylprednisolone (or an equivalent steroid dose) on Day 0 followed by oral administration of 200 mg methylprednisolone (or an equivalent dose of steroid) on Day 1 and subsequent tapering to achieve a targeted mean prednisone dose of 5 to 10 mg/day after the first 3 months.

Efficacy Results

The efficacy failure rate, defined as the percentage of patients with biopsy-proven acute rejection (BPAR), graft failure, death, and/or lost to follow at 12 months, is shown in Table 13for the intent-to-treat population, as well as the rates of the individual events.

Table 13: Incidence of BPAR, Graft Loss, Death or Lost to Follow-up at 12 Months in Kidney Transplant Patients in Study 1

	Tacrolimus extended-release capsules + MMF, steroids, basiliximab induction (N=214)	**Prograf + MMF, steroids, basiliximab induction (N=212)**
Efficacy Failure	30 (14%)	32 (15.1%)
Treatment Difference (95% CI *)	-1.1% (-7.8%, +5.6%)	
Efficacy Failure Endpoints		
Biopsy-Proven Acute Rejection	22 (10.3%)	16 (7.5%)
Graft Loss	5 (2.3%)	9 (4.2%)
Death	3 (1.4%)	9 (4.2%)
Lost to follow-up	3 (1.4%)	4 (1.9%)

* 95% confidence interval calculated using normal approximation.

Glomerular Filtration Rate

The estimated mean glomerular filtration rates, using the Modification of Diet in Renal Disease (MDRD) formula, by treatment group at Month 12 in the intent-to-treat population is shown in Table 14.

Table 14: Estimated Glomerular Filtration Rate (mL/min/1.73m ^{2}) by MDRD Formula at 12 Months Post-Transplant in Study 1

	Tacrolimus extended-release capsules + MMF, steroids, basiliximab induction	**Prograf + MMF, steroids, basiliximab induction (N=202)**

	(N=201)	
Month 1 Baseline Mean (SD)	56 (20)	56 (21)
Month 12 LOCF *	58 (21)	56 (23)
Mean (Standard deviation)	+2.3 (-1.2, +5.8)	
Mean Difference Tacrolimus Extended-Release Capsules minus Prograf (tacrolimus immediate-release) †		

* Last observation carried forward (LOCF); patients who died, lost the graft, or were lost to follow-up are imputed as zeroes.
† Results from analysis of covariance model with Month 1 baseline as a covariate.

14.2 Clinical Study of Tacrolimus Extended-Release Capsules without Induction

Study 2 was a 12-month, randomized, double-blind trial of tacrolimus extended-release capsules (N=331) compared to active control of tacrolimus (Prograf) immediate-release (N=336), in non-U.S. patients who received a primary or retransplanted non-HLA-identical living or deceased donor kidney transplant. This trial was designed to remain double-blind until the last patient enrolled had completed 24 weeks on study treatment. Patients with a high immunologic risk defined as a panel reactive antibody (PRA) grade more than 50% in the previous 6 months and/or with a previous graft survival of less than 12 months due to immunologic reasons were excluded, as were patients of donor kidneys with cold ischemia time more than 30 hours, or donor kidneys from a non heart-beating donor. The patient treatment assignments remained blinded for 12 months for 96% of the patients participating in the trial.

All patients received concomitant MMF and corticosteroids without induction. The population was 18 to 65 years of age; the mean age was 48 years; 63% of the study population was male; 82% were Caucasian, 5% were African-American, 2% were Asian, and 11% were categorized as other races. Living donors provided 27% of the organs and 73% of patients received a kidney transplant from a deceased donor with a mean cold ischemia time of 17 hours. The most frequent diseases leading to transplantation were balanced between the groups and included nephrosclerosis/hypertensive nephropathy, diabetic nephropathy, glomerulonephritis, and polycystic kidney disease.

Study Medication

Tacrolimus Extended-Release Capsules or Control [Prograf (tacrolimus) capsules]

The protocol-specified initial preoperative dose for both tacrolimus extended-release capsules and control was 0.1 mg per kg given orally in one dose within 12 hours prior to reperfusion, given at any time of the day. The initial post-operative tacrolimus daily dose (0.2 mg per kg per day) was given orally in one dose, preferably in the morning for tacrolimus extended-release capsules, and was given as 0.1 mg/kg twice daily for control. Subsequent doses of tacrolimus extended-release capsules and control were adjusted on the basis of clinical evidence of efficacy, occurrence of adverse events and according to whole blood tacrolimus trough concentration target ranges of 10 ng/mL to 15 ng/mL for the first 28 days post-transplant, 5 ng/mL to 15 ng/mL from Day 29 to Day 168, 5 ng/mL to 10 ng/mL thereafter.

The actual tacrolimus doses on Day 0 (0.1 mg per kg per day preoperative) and Day 1 (0.2 mg per kg per day post-operative) were comparable between tacrolimus extended-

release capsules and control. Thereafter, to achieve comparable mean tacrolimus trough concentrations, on average, 25% higher total mean daily doses of tacrolimus were required for tacrolimus extended-release capsules than for control.

Tacrolimus whole blood trough concentrations were monitored on Day 1, Day 3, Day 7, Day 14, then Month 1, Month 2, Month 3, Month 6, Month 11, Month 12, and then every 3 months.

Table 15 shows the tacrolimus whole blood trough concentrations measured at protocol-specified time points for tacrolimus extended-release capsules. Approximately 80% of tacrolimus extended-release capsules-treated patients maintained tacrolimus whole trough blood concentrations between 6 ng/mL to 20 ng/mL during Month 1 through Month 2, and between 6 ng/mL to 14 ng/mL from Month 3 through Month 12.

Table 15: Observed Tacrolimus Whole Blood Trough Concentrations for Tacrolimus Extended-Release Capsules Kidney Transplant Patients Evaluated in Study 2

Scheduled Visit	Tacrolimus Whole Blood Trough Concentrations (ng/mL)* [Median (10 thto 90 thPercentile)]
Day 3	13.8 (6.5 to 25.5)
Day 7	10.1 (5.5 to 17.3)
Day 14	10.8 (6.7 to 17.9)
Month 1	12 (7.5 to 17.6)
Month 2	11.1 (6.6 to 17.3)
Month 6	9.2 (5.7 to 13.5)
Month 12	8 (5.1 to 13.8)

* Immunoassay was used in most laboratories.

MMF

The initial dose of MMF was 1 gram orally twice daily starting preoperatively and given for the first 14 days of the study. Thereafter the MMF dose was reduced to 0.5 grams twice daily to be maintained throughout the study.

The MMF dosages administered by time period in tacrolimus extended-release capsules-treated patients are shown in Table 16. The MMF dosage was reduced to 0.5 grams twice daily starting after Day 14 in the majority of patients.

Table 16: Distribution (%) of Tacrolimus Extended-Release Capsules-Treated Patients by Average Daily Dosage of MMF Received by Time Period in Study 2

Time period (Days)	Patients on MMF	Time-averaged MMF dosage*,†		
	N	Less than 1 gram per day	1 gram to less than 2 grams per day	2 grams per day
1 to 30	331	1%	78%	21%
31 to 90	303	8%	87%	6%
91 to	281	12%	85%	3%

180	281	12%	85%	3%
181 to 365	258	15%	83%	2%

* Time-averaged MMF dosage is the total MMF dosage per day divided by the duration of treatment. A time-averaged MMF dosage of 2 grams per day means that the MMF dosage was not reduced in those patients during the time period.
† One patient had a time-averaged dose during the first and last period of more than 2 gram/day.

Steroids

An intravenous (IV) bolus of up to 1,000 mg methylprednisolone (or equivalent) was administered perioperatively (Day 0) with a second IV bolus of 125 mg being administered 1 day after reperfusion (Day 1). On Day 2, oral prednisone was started at 20 mg per day. Thereafter, the dose of oral prednisone (or equivalent) was tapered to a dose of 0 to 5 mg/day.

No Antibody Induction

Antibody induction therapy was not allowed.

Efficacy Results

The efficacy failure rate, defined as the percentage of patients with biopsy-proven acute rejection (BPAR), graft failure, death, and/or lost to follow at 12 months, is shown in Table 17for the intent-to-treat population, as well as the rates of the individual events. About 1% of randomized patients were not transplanted and were not included in the ITT analysis.

Table 17: Incidence of BPAR, Graft Loss, Death or Lost to Follow-up at 12 Months in Kidney Transplant Patients in Study 2

	Tacrolimus extended-release capsules + MMF and steroids (N=331)	**Prograf + MMF and steroids (N=336)**
Efficacy Failure	93 (28.1%)	78 (23.2%)
Treatment Difference (95% CI *)	+4.9% (-1.7%, +11.5%)	
Efficacy Failure Endpoints		
Biopsy-Proven Acute Rejection	68 (20.5%)	54 (16.1%)
Graft loss	28 (8.5%)	24 (7.1%)
Death	10 (3%)	8 (2.4%)
Lost to follow-up	4 (1.2%)	7 (2.1%)

* 95% confidence interval calculated using normal approximation.

Glomerular Filtration Rate

The estimated mean glomerular filtration rates, using the Modification of Diet in Renal

Disease (MDRD) formula, by treatment group at Month 12 in the intent-to-treat population in Study 2 is shown in Table 18.

Table 18: Estimated Glomerular Filtration Rate (mL/min/1.73m ^{2}) by MDRD Formula at 12 Months Post-Kidney Transplant in Study 2

	Tacrolimus extended-release capsules + MMF and steroids (N=287)	Prograf + MMF and steroids (N=300)
Month 1 Baseline Mean (SD)	51 (19)	52 (20)
Month 12 LOCF *	52 (20)	55 (19)
Mean (Standard deviation)		
Mean Difference Tacrolimus Extended-Release Capsules minus Prograf (tacrolimus immediate-release) †	-1.8 (-4.6, +0.8)	

* Last observation carried forward (LOCF); patients who died, lost the graft or were lost to follow-up are imputed as zeroes.
† Results from analysis of covariance model with Month 1 baseline as a covariate.

16 HOW SUPPLIED/STORAGE AND HANDLING

Tacrolimus extended-release capsules are supplied as listed in Table 19.

Table 19: Strengths of Tacrolimus Extended-Release Capsules

0.5 mg	Oblong capsule with opaque yellowish pink cap and opaque light orange body. Capsule is branded with dull red “SD-TC” on capsule body and dull red “0.5 mg” on the capsule cap. • Blister carton packed with an aluminum foil bag containing 5 blister cards of 10 capsules on each card. (NDC 71432-2001-1).
1 mg	Oblong capsule with opaque light yellow cap and opaque light orange body. Capsule is branded with dull red “SD-TC” on capsule body and dull red “1 mg” on the capsule cap. • Blister carton packed with an aluminum foil bag containing 5 blister cards of 10 capsules on each card. (NDC 71432-2002-1)
5 mg	Oblong capsule with an opaque red-orange cap and opaque orange body. Capsule is branded with dull red “SD-TC” on capsule body and dull red “5 mg” on the capsule cap. • Blister carton packed with an aluminum foil bag containing 5 blister cards of 10 capsules on each card. (NDC 71432-2003-1)

Store and Dispense

Store at 25°C (77°F); excursions permitted from 15° to 30°C (59° to 86°F) [See USP

Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

17.1 Administration

Advise patients or caregivers to:

- Inspect their tacrolimus extended-release capsules medicine when they receive a new prescription and before taking it. If the appearance of the capsule is not the same as usual, or if dosage instructions have changed, advise patients to contact their healthcare provider as soon as possible to make sure that they have the right medicine. Other tacrolimus products cannot be substituted for tacrolimus extended-release capsules *[see Warnings and Precautions(5.4)].*
- Take tacrolimus extended-release capsules at the same time every day to achieve consistent blood concentrations.
- Take tacrolimus extended-release capsules in the morning, on an empty stomach at least 1 hour before or at least 2 hours after breakfast, to achieve maximum possible blood concentrations of the drug.
- Swallow capsule whole with liquid. Do not chew, divide or crush capsule.
- Avoid alcoholic beverages, grapefruit, and grapefruit juice while on tacrolimus extended-release capsules *[see Dosage and Administration(2.1) and Drug Interactions(7.2)].*
- Take a missed dose of tacrolimus extended-release capsules as soon as possible but not more than 14 hours after the scheduled time (i.e., for a missed 8 AM dose, take by 10 PM). Beyond the 14-hour timeframe, instruct the patient to wait until the usual scheduled time the following morning to take the next scheduled dose. Do not take 2 doses at the same time.

17.2 Development of Lymphoma and Other Malignancies

Inform patients that they are at an 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 using a broad spectrum sunscreen with a high protection factor *[see Warnings and Precautions(5.1)]* .

17.3 Increased Risk of Infection

Inform patients that they are at an 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 such as fever, sweats or chills, cough or flu-like symptoms, muscle aches, or warm, red, painful areas of the skin *[see Boxed Warning and Warnings and Precautions(5.2)]* .

17.4 New Onset Diabetes after Transplant

Inform patients that tacrolimus extended-release 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(5.5)]* .

17.5 Nephrotoxicity

Inform patients that tacrolimus extended-release 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(5.6)]* .

17.6 Neurotoxicity

Inform patients that they are at risk of developing adverse neurologic reactions including seizure, altered mental status, and tremor. Advise patients to contact their physician should they develop vision changes, delirium, or tremors *[see Warnings and Precautions(5.7)]* .

17.7 Hyperkalemia

Inform patients that tacrolimus extended-release 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(5.8)]* .

17.8 Hypertension

Inform patients that tacrolimus extended-release capsules can cause high blood pressure which may require treatment with anti-hypertensive therapy *[see Warnings and Precautions(5.9)]* . Advise patients to monitor their blood pressure.

17.9 Thrombotic Microangiopathy

Inform patients that tacrolimus extended-release capsules can cause blood clotting problems. The risk of this occurring increases when patients take tacrolimus extended-release capsules and sirolimus or everolimus concomitantly, or when patients develop certain infections. Advise them to seek medical attention promptly if they develop fever, petequiae or bruises, fatigue, confusion, jaundice, oliguria *[see Warnings and Precautions (5.14)]* .

17.10 Drug Interactions

Instruct patients to tell their healthcare providers when they start or stop taking any medicines, including prescription and nonprescription medicines, herbal and dietary supplements. Some medications could alter tacrolimus concentrations in the blood and thus may require the adjustment of the dosage of tacrolimus extended-release capsules. Advise patients to avoid grapefruit, grapefruit juice and alcoholic beverages *[see Warnings and Precautions(5.10, 5.15) and Drug Interactions(7)]* .

17.11 Pregnancy, Lactation and Infertility

Inform women of childbearing potential that tacrolimus extended-release capsules can harm the fetus. Instruct male and female patients to discuss with their healthcare provider family planning options including appropriate contraception. Also, discuss with pregnant patients the risks and benefits of breastfeeding their infant *[see Use in Specific Populations(8.1, 8.2, 8.3)].*

Encourage female transplant patients who become pregnant and male patients who have fathered a pregnancy, exposed to immunosuppressants including tacrolimus, to

enroll in the voluntary Transplantation Pregnancy Registry International. To enroll or register, patients can call the toll free number 1-877-955-6877 or https://www.transplantpregnancyregistry.org/*[see Use in Specific Populations(8.1)]* .

Based on animal studies, tacrolimus extended-release capsules may affect fertility in males and females *[see Nonclinical Toxicology(13.1)].*

17.12 Immunizations

Inform patients that tacrolimus extended-release capsules can interfere with the usual response to immunizations and that they should avoid live vaccines *[see Warnings and Precautions(5.12)].*

Manufactured by:

Chengdu Suncadia Medicine Co., Ltd.

Chengdu, Sichuan 610000, China

Distributed by:

eVenus Pharmaceutical Laboratories, Inc.

506 Carnegie Center, Suite 100,

Princeton, NJ 08540 USA

Product of China

Revised: January 2024

Rev.05

MEDICATION GUIDE
Tacrolimus [ta-KROE-li-mus] Extended-Release Capsules

Read this Medication Guide before you start taking tacrolimus extended-release capsules and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment. If you have any questions about tacrolimus extended-release capsules, ask your healthcare provider or pharmacist.

What is the most important information I should know about tacrolimus extended-release capsules?
Tacrolimus extended-release capsules can cause serious side effects, including:

- **Increased risk of cancer.**People who take tacrolimus extended-release capsules have an increased risk of getting some kinds of cancer, including skin and lymph gland cancer (lymphoma).
- **Increased risk of infection.** Tacrolimus extended-release capsules is a medicine that affects your immune system. Tacrolimus extended-release capsules can lower the ability of your immune system to fight infections. Serious infections can happen in people receiving tacrolimus extended-release capsules that can cause death. **Call your healthcare provider 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

- **Increased risk of death in females who have had a liver transplant.** You should not take tacrolimus extended-release capsules if you have had a liver transplant without talking to your healthcare provider.

What is tacrolimus extended-release capsules?

- Tacrolimus extended-release capsules is a prescription medicine used with other medicines to help prevent organ rejection in people who have had a kidney transplant.
- Tacrolimus extended-release capsules is an extended-release capsule and is not the same as tacrolimus immediate-release capsules, tacrolimus for oral suspension or tacrolimus extended-release tablets. Your healthcare provider should decide what medicine is right for you.

Who should not take tacrolimus extended-release capsules?

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

What should I tell my healthcare provider before taking tacrolimus extended-release capsules?

Before you take tacrolimus extended-release capsules tell your healthcare provider if you:

- plan to receive any live vaccines. Ask your healthcare provider if you are not sure if your vaccine is a live vaccine.
- have or have had liver, kidney, or heart problems **or** any other medical conditions.
- are pregnant or plan to become pregnant. Tacrolimus extended-release capsules may harm your unborn baby.

o If you are able to become pregnant, you should use effective birth control before and during treatment with tacrolimus extended-release capsules. Talk to your healthcare provider before starting treatment with tacrolimus extended-release capsules about birth control methods that may be right for you.
o Males who have female partners that are able to become pregnant should also use effective birth control before and during treatment with tacrolimus extended-release capsules. Talk to your healthcare provider before starting treatment with tacrolimus extended-release capsules about birth control methods that may be right for you.
o There is a pregnancy registry for females who become pregnant and males who have fathered a pregnancy during treatment with tacrolimus extended-release capsules. The purpose of this registry is to collect information about your health and of your baby. To enroll in this voluntary registry, call 1-877-955-6877 or go to https://www.transplantpregnancyregistry.org/.

- are breastfeeding or plan to breastfeed. Tacrolimus extended-release capsules passes into your breast milk. You and your healthcare provider should decide if you will breastfeed while taking tacrolimus extended-release capsules.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, natural, herbal or nutritional

supplements. Tacrolimus extended-release capsules may affect the way other medicines work, and other medicines may affect how tacrolimus extended-release capsules works.

Especially tell your healthcare provider if you take:

- sirolimus (RAPAMUNE): You should not take tacrolimus extended-release capsules if you take sirolimus
- cyclosporine (GENGRAF, NEORAL, and SANDIMMUNE)
- medicines called aminoglycosides that are used to treat bacterial infections
- ganciclovir (CYTOVENE IV, VALCYTE)
- amphotericin B (ABELCET, AMBISOME)
- cisplatin
- antiviral medicines called nucleoside reverse transcriptase inhibitors
- antiviral medicines called protease inhibitors
- water pill (diuretic)
- medicine to treat high blood pressure
- nelfinavir (VIRACEPT)
- telaprevir (INCIVEK)
- boceprevir
- ritonavir (KALETRA, NORVIR, TECHNIVIE, VIEKIRA PAK, VIEKIRA XR)
- letermovir (PREVYMIS)
- ketoconazole
- itraconazole (ONMEL, SPORANOX)
- voriconazole (VFEND)
- caspofungin (CANCIDAS)
- clarithromycin (BIAXIN, BIAXIN XL, PREVPAC)
- rifampin (RIFADIN, RIFAMATE, RIFATER, RIMACTANE)
- rifabutin (MYCOBUTIN)
- amiodarone (NEXTERONE, PACERONE)
- cannabidiol (EPIDIOLEX)

Ask your healthcare provider or pharmacist if you are not sure if you take any of the medicines listed above. Tacrolimus extended-release capsules may affect the way other medicines work, and other medicines may affect how tacrolimus extended-release capsules works.

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

How should I take tacrolimus extended-release capsules?

- Take tacrolimus extended-release capsules exactly as your healthcare provider tells you to take it.
- Your healthcare provider may change your dose if needed. **Do not**stop taking or change your dose of tacrolimus extended-release capsules without talking to your healthcare provider.
- Take tacrolimus extended-release capsules whole. Do not break, crush, chew, or dissolve tacrolimus extended-release capsules before swallowing. If you cannot swallow tacrolimus extended-release capsules whole, tell your healthcare provider.
- Take tacrolimus extended-release capsules at the same time each morning, preferably on an empty stomach at least 1 hour before, or at least 2 hours after, you have eaten a meal.
- If you miss your dose of tacrolimus extended-release capsules, it should be taken as soon as possible, but no longer than 14 hours after your regularly scheduled time. If

it is longer than 14 hours, the missed dose should be skipped and the next dose should be taken the following morning at your regularly scheduled time. **Do not**take 2 doses at the same time.
- If you take too much tacrolimus extended-release capsules, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking tacrolimus extended-release capsules?
- Live vaccines such as flu vaccine through your nose, measles, mumps, rubella, polio by mouth, BCG (TB vaccine), yellow fever, chicken pox (varicella) or typhoid.
- Exposure to sunlight and UV light such as tanning machines. Wear protective clothing and use a sunscreen.
- You should not eat grapefruit or drink grapefruit juice while taking tacrolimus extended-release capsules.
- You should not drink alcohol when taking tacrolimus extended-release capsules.

What are the possible side effects of tacrolimus extended-release capsules?
Tacrolimus extended-release capsules may cause serious side effects, including:
- **See "What is the most important information I should know about tacrolimus extended-release capsules?"**
- **Problems from medication errors such as graft rejection and other serious reactions.**People who take tacrolimus extended-release capsules have sometimes been given the wrong medicine because some medicines have the same ingredient (tacrolimus) as tacrolimus extended-release capsules. Serious reactions have happened including graft rejection. **Check your tacrolimus extended-release capsules when you get a new prescription to make sure you have received the right medicine.**

o Call your healthcare provider right away if you think you were given the wrong medicine.
o Ask your healthcare provider or pharmacist if you are not sure what tacrolimus extended-release capsules should look like.
- **high blood sugar (diabetes).**Your healthcare provider may do certain tests to check for diabetes while you take tacrolimus extended-release capsules. Call your healthcare provider right away if you have:

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

- **kidney problems.**Kidney problems are serious and common side effects of tacrolimus extended-release capsules. Your healthcare provider may do certain tests to check your kidney function while you take tacrolimus extended-release capsules.
- **nervous system problems.**Nervous system problems are a serious and common side effect of tacrolimus extended-release capsules. Call your healthcare provider or go to the nearest hospital emergency room right away if you get any of these symptoms while taking tacrolimus extended-release capsules. These could be signs of serious nervous system problems:

o confusion	o numbness and tingling	o seizures
o changes in alertness	o headache	o vision changes

o muscle tremors

- **high levels of potassium in your blood.**Your healthcare provider may do certain tests to check your potassium level while you take tacrolimus extended-release capsules.
- **high blood pressure.**High blood pressure is a serious and common side effect of tacrolimus extended-release capsules. Your healthcare provider will monitor your blood pressure while you take tacrolimus extended-release capsules and may ask you to check your blood pressure at home.
- **changes in the electrical activity of your heart (QT prolongation).**
- **severe low blood cell count (anemia).**
- **blood clotting problems:**Tell your healthcare provider right away if you have fever and bruising under the skin that may appear as red dots, with or without unexplained tiredness, confusion, yellowing of the skin or eyes, decreased urination. When taken with sirolimus or everolimus, the risk of developing these symptoms may increase.

The most common side effects of tacrolimus extended-release capsules arediarrhea, constipation, nausea, swelling of the hands, ankles, or legs, and tremors (shaking of the body).
These are not all the possible side effects of tacrolimus extended-release capsules. For more information, ask your healthcare provider or pharmacist.
Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store tacrolimus extended-release capsules?

- Store tacrolimus extended-release capsules at room temperature between 68°F to 77°F (20°C to 25°C).
- Safely throw away medicine that is out of date or no longer needed.
- **Keep tacrolimus extended-release capsules and all medicines out of reach of children.**

General information about the safe and effective use of tacrolimus extended-release capsules.

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use tacrolimus extended-release capsules for a condition for which it was not prescribed. Do not give tacrolimus extended-release capsules to other people, even if they have the same symptoms that you have. It may harm them.
- This Medication Guide summarizes the most important information about tacrolimus extended-release capsules. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about tacrolimus extended-release capsules that is written for health professionals.

What are the ingredients in tacrolimus extended-release capsules?
Active ingredient:tacrolimus.
Inactive ingredients:

- **The capsule contains:**ethylcellulose NF, hypromellose USP, magnesium stearate NF, and lactose monohydrate NF
- **The capsule shell contains:**gelatin NF, ferric oxide red NF, ferric oxide yellow NF, and titanium dioxide USP

Manufactured by:
Chengdu Suncadia Medicine Co., Ltd.
Chengdu, Sichuan 610000, China
Distributed by:
eVenus Pharmaceutical Laboratories, Inc.
506 Carnegie Center, Suite 100,
Princeton, NJ 08540 USA
Rev. 05

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Revised: 01/2024

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL – 0.5 MG CARTON LABEL

NDC 71432- **2001**-1

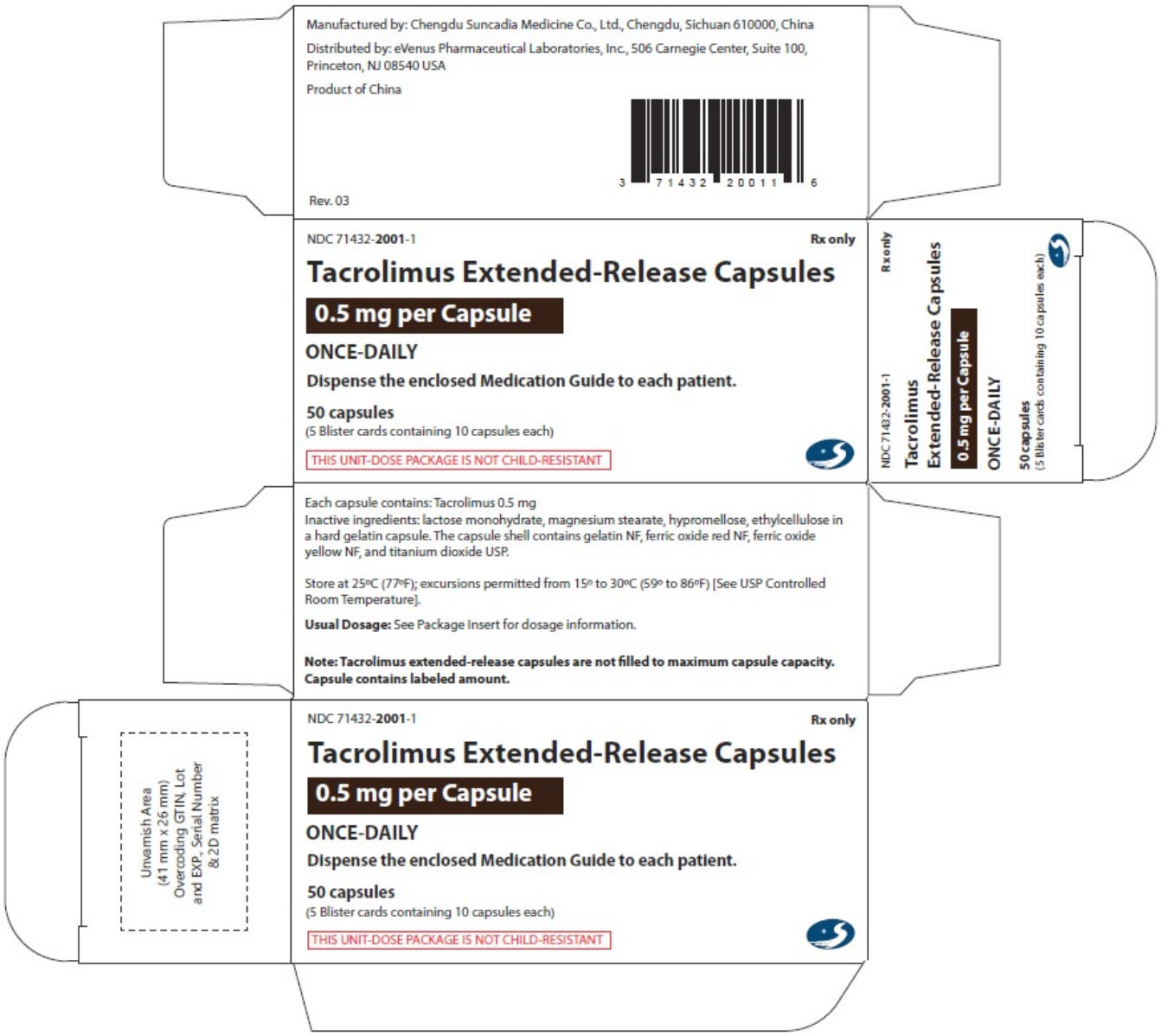
Tacrolimus Extended-Release Capsules

0.5 mg per Capsule

ONCE-DAILY

50 capsules (5 Blister cards containing 10 capsules each)

Rx Only



PACKAGE/LABEL PRINCIPAL DISPLAY PANEL – 1 MG CARTON LABEL

NDC 71432- **2002**-1

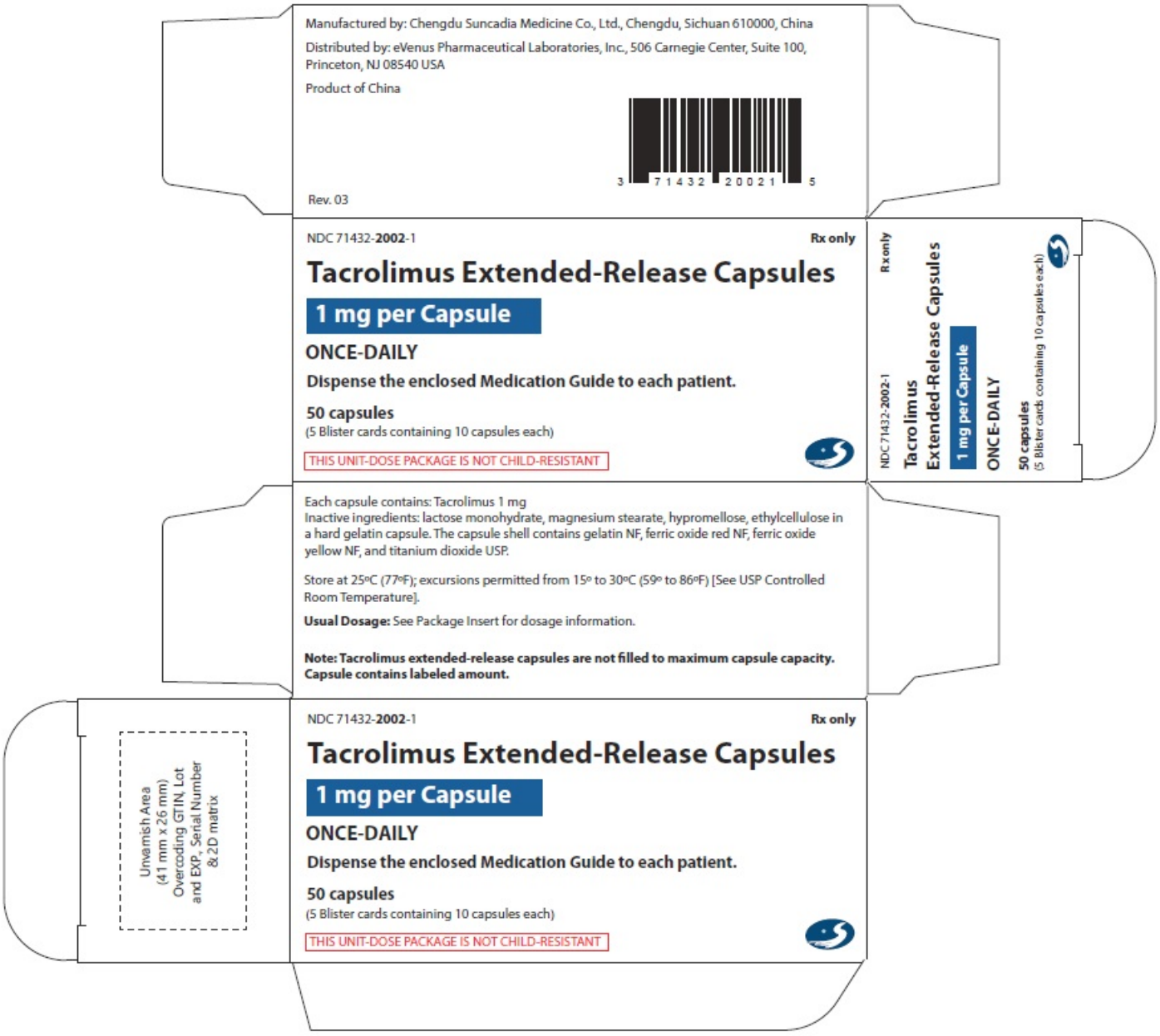
Tacrolimus Extended-Release Capsules

1 mg per Capsule

ONCE-DAILY

50 capsules (5 Blister cards containing 10 capsules each)

Rx Only



PACKAGE/LABEL PRINCIPAL DISPLAY PANEL – 5 MG CARTON LABEL

NDC 71432- **2003**-1

Tacrolimus Extended-Release Capsules

5 mg per Capsule

ONCE-DAILY

50 capsules (5 Blister cards containing 10 capsules each)

Rx Only

TACROLIMUS

tacrolimus extended-release capsules capsule, coated, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:71432-2001
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
TACROLIMUS (UNII: WM0HAQ4WNM) (TACROLIMUS ANHYDROUS - UNII:Y5L2157C4J)	TACROLIMUS ANHYDROUS	0.5 mg

Product Characteristics			
Color	pink (Opaque yellowish pink) , orange (Opaque Light orange)	**Score**	no score
Shape	CAPSULE (Oblong capsule)	**Size**	11mm
Flavor		**Imprint Code**	SD;TC;0;5;mg
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:71432-2001-1	1 in 1 CARTON	01/25/2024	
1		5 in 1 BAG		
1		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA215012	01/25/2024	

TACROLIMUS

tacrolimus extended-release capsules capsule, coated, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:71432-2002
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
TACROLIMUS (UNII: WM0HAQ4WNM) (TACROLIMUS ANHYDROUS - UNII:Y5L2157C4J)	TACROLIMUS ANHYDROUS	1 mg

Product Characteristics			
Color	yellow (Opaque light yellow) , orange (Opaque light orange)	**Score**	no score
Shape	CAPSULE (Oblong capsule)	**Size**	14mm
Flavor		**Imprint Code**	SD;TC;1;mg
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:71432-2002-1	1 in 1 CARTON	01/25/2024	
1		5 in 1 BAG		
1		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA215012	01/25/2024	

TACROLIMUS

tacrolimus extended-release capsules capsule, coated, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:71432-2003
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
TACROLIMUS (UNII: WM0HAQ4WNM) (TACROLIMUS ANHYDROUS - UNII:Y5L2157C4J)	TACROLIMUS ANHYDROUS	5 mg

Product Characteristics			
Color	orange (Opaque red-orange) , orange (Opaque orange)	**Score**	no score
Shape	CAPSULE (Oblong capsule)	**Size**	21mm
Flavor		**Imprint Code**	SD;TC;5;mg
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:71432-2003-1	1 in 1 CARTON	01/25/2024	
1		5 in 1 BAG		
1		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA215012	01/25/2024	

Labeler - Chengdu Suncadia Medicine Co., Ltd. (421325179)

Registrant - Chengdu Suncadia Medicine Co., Ltd. (421325179)

Establishment

Name	Address	ID/FEI	Business Operations
Chengdu Suncadia Medicine Co., Ltd.		421325179	manufacture(71432-2002, 71432-2001, 71432-2003)

Revised: 2/2024 Chengdu Suncadia Medicine Co., Ltd.