

**ASTAGRAF XL- tacrolimus extended-release capsules capsule, coated, extended release**  
**Astellas Pharma US, Inc.**

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use ASTAGRAF XL® safely and effectively. See full prescribing information for ASTAGRAF XL.

ASTAGRAF XL (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 ASTAGRAF XL or other immunosuppressants that may lead to hospitalization or death (5.1, 5.2).
- Increased mortality in female liver transplant patients with ASTAGRAF XL. Not approved for use in liver transplantation (5.3).

----- **INDICATIONS AND USAGE** -----

ASTAGRAF XL is a calcineurin-inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in kidney transplant patients in combination with other immunosuppressants (1)

Limitation of Use:

- Not interchangeable or substitutable with other tacrolimus products (1, 5.4)

----- **DOSAGE AND ADMINISTRATION** -----

- Take consistently every morning at 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)

<b>Recommended ASTAGRAF XL starting dosages</b> (patients with severe hepatic impairment may require a lower starting dosage) (2.2)	
With MMF, steroids, and <u>basiliximab induction</u>	0.15 to 0.2 mg/kg prior to reperfusion or within 48 hours of completion of transplant procedure (may delay timing until renal function recovers)
With MMF and steroids; <u>without basiliximab induction</u>	<u>First Dose</u> (pre-operative): 0.1 mg/kg as a single dose within 12 hours prior to reperfusion <u>Second Dose</u> (post-operative): 0.2 mg/kg at least 4 hours after pre-operative dose and within 12 hours after reperfusion.

MMF = mycophenolate mofetil

<b>ASTAGRAF XL Target Whole Blood Trough Concentrations (2.3)</b>	
<b>Time Period</b>	<b>Tacrolimus Target Whole Blood Trough Concentrations</b>
During Month 1	7 to 15 ng/mL with basiliximab induction 10 to 15 ng/mL without basiliximab induction
Months 2 to 6	5 to 15 ng/mL
> 6 Months	5 to 10 ng/mL

- African-Americans may need to be titrated to higher dosages to achieve the target tacrolimus concentrations (2.3)
- Assess tacrolimus whole blood trough concentrations at least two times on separate days during the first week after initiation of dosing and after a dosage change, a change in co-administration of CYP3A4 inducers and/or inhibitors, or a change in renal or hepatic function (2.4)

----- **DOSAGE FORMS AND STRENGTHS** -----

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

----- **CONTRAINDICATIONS** -----

Known hypersensitivity to tacrolimus (4)

----- **WARNINGS AND PRECAUTIONS** -----

- Graft rejection and other serious adverse reactions due to medication errors: Instruct patients or caregivers to recognize appearance of ASTAGRAF XL capsules (5.4)
- New onset diabetes after transplant: Monitor blood glucose (5.5)
- Nephrotoxicity (acute and/or chronic) due to ASTAGRAF XL and 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 ASTAGRAF XL (5.7)
- Hyperkalemia: Risk may be increased with other agents associated with hyperkalemia; monitor serum potassium levels (5.8)
- Hypertension: May require antihypertensive therapy (5.9)
- QT prolongation: Consider obtaining electrocardiograms and monitoring electrolytes in patients at high risk (5.11)
- Pure red cell aplasia: Consider discontinuation (5.13)

----- **ADVERSE REACTIONS** -----

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

**To report SUSPECTED ADVERSE REACTIONS, contact Astellas Pharma US, Inc. at 1-800-727-7003 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://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 (2.2, 5.10, 7.1)
- See Full Prescribing Information for clinically significant drug interactions (7.1, 7.2)

See 17 for **PATIENT COUNSELING INFORMATION** and **Medication Guide**.

Revised: 12/2015

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## **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 ASTAGRAF XL<sup>®</sup> 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 ASTAGRAF XL. ASTAGRAF XL is not approved for use in liver transplantation [see Warnings and Precautions (5.3)].**

## **1 INDICATIONS AND USAGE**

ASTAGRAF XL is indicated for the prophylaxis of organ rejection in kidney transplant patients in combination with other immunosuppressants.

### Limitation of Use

ASTAGRAF XL extended-release capsules are not interchangeable or substitutable with other tacrolimus extended-release or immediate-release products [see *Warnings and Precautions (5.4)*].

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Administration Instructions

- Take ASTAGRAF XL 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)*].
- Swallow ASTAGRAF XL capsules whole with liquid; do not chew, divide, or crush the capsules.
- If a dose is missed, take the dose up to 14 hours after the scheduled time (i.e., for a missed 8:00 AM dose, take by 10:00 PM). Beyond the 14-hour time frame, wait until the usual scheduled time the following morning to take the next regular daily dose.
- Avoid eating grapefruit or drinking grapefruit juice or alcoholic beverage while taking ASTAGRAF XL [see *Drug Interactions (7.2)*].

### 2.2 Recommended Starting Dosage

Table 1 includes the recommended starting ASTAGRAF XL dosages. Due to the reduced clearance and prolonged half-life, patients with severe hepatic impairment (Child-Pugh  $\geq 10$ ) may require a lower starting dosage of ASTAGRAF XL [see *Clinical Pharmacology (12.3)*].

**Table 1: Recommended Starting Dosage of ASTAGRAF XL with or without Basiliximab Induction**

Concomitant Medications	Starting Dosages of ASTAGRAF XL
With MMF, steroids, and <b>basiliximab induction</b>	Administer 0.15 to 0.2 mg/kg prior to reperfusion or within 48 hours of the completion of the transplant procedure (timing may be delayed until renal function has recovered).
With MMF and steroids; <b>Without basiliximab induction</b>	<ul style="list-style-type: none"><li>• First Dose (pre-operative): Administer 0.1 mg/kg as a single dose within 12 hours prior to reperfusion.</li><li>• Second Dose (post-operative): Administer 0.2 mg/kg at least 4 hours after the pre-operative dose and within 12 hours after reperfusion.</li></ul>

MMF = mycophenolate mofetil

### 2.3 Dosage Adjustments

Titrate the ASTAGRAF XL dosage based on clinical assessments of rejection and tolerability and to achieve target trough concentration ranges (see Table 2) [see *Dosage and Administration (2.4)* and *Warnings and Precautions (5.6, 5.7, 5.11)*].

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

**Table 2: Recommended Target Tacrolimus Whole Blood Trough Concentrations in Kidney Transplant Patients**

<b>Time Period Post Transplant</b>	<b>Tacrolimus Target Whole Blood Trough Concentrations</b>
During Month 1	7 to 15 ng/mL (with basiliximab induction) 10 to 15 ng/mL (without basiliximab induction)
Months 2 to 6	5 to 15 ng/mL
> 6 Months	5 to 10 ng/mL

For observed tacrolimus concentrations see *Clinical Studies (14)*.

## 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 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 ASTAGRAF XL 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

ASTAGRAF XL CAPSULES:

- 0.5 mg: light yellow cap and orange body branded with red “✦ 647” on the capsule body and “0.5 mg” on the capsule cap.
- 1 mg: white cap and orange body branded with red “✦ 677” on the capsule body and “1 mg” on the capsule cap.
- 5 mg: grayish-red cap and orange body branded with red “✦ 687” on the capsule body and “5 mg” on the capsule cap.

## 4 CONTRAINDICATIONS

ASTAGRAF XL 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 ASTAGRAF XL, 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.

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. Monitor EBV serology during treatment.

## 5.2 Serious Infections

Immunosuppressants, including ASTAGRAF XL, 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), and
- 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 ASTAGRAF XL or tacrolimus immediate-release product, mortality at 12 months was 10% higher among the 76 female patients (18%) treated with ASTAGRAF XL compared to the 64 female patients (8%) treated with tacrolimus immediate-release product. ASTAGRAF XL is not approved for the prophylaxis of organ rejection in patients who received a liver transplant.

## 5.4 Graft Rejection and other Serious Adverse Reactions due to Medication Errors

Medication errors, including substitution and dispensing errors, between tacrolimus immediate-release products and ASTAGRAF XL (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. ASTAGRAF XL is not interchangeable or substitutable with tacrolimus immediate-release products or tacrolimus extended-release products. Instruct patients and caregivers to recognize the appearance of ASTAGRAF XL capsules [see *Dosage Forms and Strengths (3)*].

## 5.5 New Onset Diabetes after Transplant

ASTAGRAF XL 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 ASTAGRAF XL and Drug Interactions

ASTAGRAF XL, like other calcineurin-inhibitors, can cause acute or chronic nephrotoxicity. Consider dosage reduction in patients with elevated serum creatinine and tacrolimus whole blood trough concentrations greater than the recommended range.

The risk for nephrotoxicity may increase when ASTAGRAF XL 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) [see *Drug Interactions (7.2)*]. Monitor renal function and consider dosage reduction if nephrotoxicity occurs.

## 5.7 Neurotoxicity

ASTAGRAF XL 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 ASTAGRAF XL if neurotoxicity occurs.

### **5.8 Hyperkalemia**

Mild to severe hyperkalemia, which may require treatment, has been reported with tacrolimus including ASTAGRAF XL. 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 ASTAGRAF XL 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 ASTAGRAF XL [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 ASTAGRAF XL dose and monitor tacrolimus whole blood trough concentrations when coadministering ASTAGRAF XL with strong CYP3A inhibitors (e.g., telaprevir, boceprevir, ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin) or strong CYP3A inducers (e.g., rifampin, rifabutin) [see *Dosage and Administration (2.4)* and *Drug Interactions (7.2)*].

### **5.11 QT Prolongation**

ASTAGRAF XL may prolong the QT/QTc interval and cause Torsade de Pointes. Avoid ASTAGRAF XL 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 coadministering ASTAGRAF XL with other substrates and/or inhibitors of CYP3A, especially those that also have the potential to prolong the QT interval, a reduction in ASTAGRAF XL dosage, monitoring of tacrolimus whole blood concentrations, and monitoring for QT prolongation is recommended [see *Drug Interactions (7.2)*].

### **5.12 Immunizations**

Whenever possible, administer the complete complement of vaccines before transplantation and treatment with ASTAGRAF XL.

Avoid the use of live attenuated vaccines during treatment with ASTAGRAF XL (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 ASTAGRAF XL.

### **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 ASTAGRAF XL.

## 6 ADVERSE REACTIONS

### 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 ASTAGRAF XL (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 ASTAGRAF XL (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 ASTAGRAF XL and tacrolimus immediate-release treatment groups, respectively, through 12 months of treatment. The most common adverse reactions leading to discontinuation in ASTAGRAF XL-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 ASTAGRAF XL or tacrolimus immediate-release product in Study 1 are shown in Table 3.

**Table 3: Percentage of Patients with Infections in Study 1<sup>a</sup> Through One Year Post-Renal Transplant**

	<b>ASTAGRAF XL, MMF, steroids, basiliximab induction N=214</b>	<b>Tacrolimus immediate-release product, MMF, steroids, basiliximab induction N=212</b>
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%

<sup>a</sup> Study 1 was not designed to support comparative claims of ASTAGRAF XL 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  $\geq 2$  fasting plasma glucose values that were  $> 126$  mg/dL at  $\geq 30$  days apart, insulin use for  $\geq 30$  consecutive days, oral hypoglycemic use for  $\geq 30$  consecutive days, and/or  $HbA_{1C} \geq 6.5\%$ ) is



summarized in Table 4 below for Study 1 through one year post-transplant [see *Warnings and Precautions* (5.5)].

**Table 4: Percentage of Patients with NODAT Through 1 Year Post-Renal Transplant in Study 1<sup>a</sup>**

	<b>ASTAGRAF XL, MMF, steroids, basiliximab induction N=162</b>	<b>Tacrolimus immediate- release product, MMF, steroids, basiliximab induction N=151</b>
Composite NODAT	36%	35%
≥ 2 Fasting Plasma Glucose Values ≥ 126 mg/dL ≥ 30 days apart	26%	23%
HbA <sub>1C</sub> ≥ 6.5%	19%	22%
Oral hypoglycemic use ≥ 30 consecutive days	14%	9%
Insulin use ≥ 30 consecutive days	6%	8%

<sup>a</sup> Study 1 was not designed to support comparative claims of ASTAGRAF XL compared to tacrolimus immediate-release product for the adverse reactions reported in this table.

#### Hyperkalemia

In Study 1 [see *Clinical Studies* (14.1)], 73 out of 214 (34.1%) patients on ASTAGRAF XL 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.

#### Common Adverse Reactions

The most common (≥ 30%) adverse reactions observed with ASTAGRAF XL in Study 1 were: diarrhea, constipation, nausea, peripheral edema, tremor, and anemia. The incidence of adverse reactions that occurred in ≥ 15% of ASTAGRAF XL-treated patients compared to tacrolimus immediate-release product through one year of treatment in Study 1 is shown by treatment groups in Table 5.

**Table 5: Adverse Reactions (≥ 15%) in Kidney Transplant Patients Through One Year Post Transplant in Study 1a**

	<b>ASTAGRAF XL, MMF, steroids, basiliximab induction N=214</b>	<b>Tacrolimus immediate-release product, MMF, steroids, basiliximab induction N=212</b>
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%

<sup>a</sup> Study 1 was not designed to support comparative claims of ASTAGRAF XL compared to tacrolimus immediate-release for the adverse reactions reported in this table.

### Less Frequently Reported Adverse Reactions (< 15% in ASTAGRAF XL-treated patients) by System Organ Class

The following adverse reactions were reported in clinical studies of kidney transplant patients who were treated with ASTAGRAF XL, 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

## **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.

*Blood and Lymphatic System Disorders:* Agranulocytosis, disseminated intravascular coagulation, hemolytic uremic syndrome, 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, Torsade de Pointes, QT prolongation

*Ear Disorders:* Hearing loss

*Eye Disorders:* Blindness, 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:* Hypoproteinaemia

*Musculoskeletal and Connective Tissue Disorders:* Rhabdomyolysis, myalgia, polyarthrititis

*Neoplasms:* Lymphoma including EBV-associated lymphoproliferative disorder, hepatosplenic T-cell lymphoma, PTLN [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 ASTAGRAF XL is prescribed with a given dose of a mycophenolic acid (MPA) product, exposure to MPA is higher with ASTAGRAF XL coadministration than with cyclosporine coadministration 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 ASTAGRAF XL

Table 6 displays the effects of other drugs on ASTAGRAF XL.

**Table 6: Effects of Other Drugs/Substances on ASTAGRAF XL<sup>a</sup>**

<b>Drug/Substance Class or Name</b>	<b>Drug Interaction Effect</b>	<b>Recommendations</b>
Grapefruit or grapefruit juice <sup>b</sup>	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) [see <i>Warnings and Precautions (5.7, 5.10, 5.11)</i> ]	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 <i>Warnings and Precautions (5.7, 5.10, 5.11)</i> ]	Avoid alcoholic beverages
Strong CYP3A Inducers <sup>c</sup> : 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 <i>Warnings and Precautions (5.10)</i> ]	Increase ASTAGRAF XL dose and monitor tacrolimus whole blood trough concentrations [see <i>Dosage and Administration (2.3, 2.4) and Clinical Pharmacology (12.3)</i> ]
Strong CYP3A Inhibitors <sup>c</sup> : Protease inhibitors (e.g., nelfinavir, telaprevir, boceprevir, ritonavir), azole antifungals (e.g., voriconazole, posaconazole, itraconazole, ketoconazole), antibiotics (e.g., clarithromycin, troleandomycin, chloramphenicol), nefazodone, schisandra sphenanthera extracts	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) [see <i>Warnings and Precautions (5.7, 5.10, 5.11)</i> ]	Reduce ASTAGRAF XL dose (for voriconazole and posaconazole, give one-third of the original dose) and adjust dose based on tacrolimus whole blood trough concentrations [see <i>Dosage and Administration (2.3, 2.4) and Clinical Pharmacology (12.3)</i> ]
Mild or Moderate CYP3A Inhibitors: Clotrimazole, antibiotics (e.g., erythromycin, fluconazole), calcium channel blockers (e.g., verapamil, diltiazem, nifedipine, nocardipine), 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 <i>Warnings and Precautions (5.7, 5.10, 5.11)</i> ]	Monitor tacrolimus whole blood trough concentrations and reduce ASTAGRAF XL dose if needed [see <i>Dosage and Administration (2.3, 2.4) and Clinical Pharmacology (12.3)</i> ]
Other drugs, such as:	May increase tacrolimus whole	Monitor tacrolimus whole

Magnesium and aluminum hydroxide antacids  Metoclopramide	blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) [see <i>Warnings and Precautions</i> (5.7, 5.10, 5.11)]	blood trough concentrations and reduce ASTAGRAF XL dose if needed [see <i>Dosage and Administration</i> (2.3, 2.4) and <i>Clinical Pharmacology</i> (12.3)]
Mild or Moderate CYP3A Inducers Methylprednisolone, prednisone	May decrease tacrolimus concentrations	Monitor tacrolimus whole blood trough concentrations and adjust ASTAGRAF XL dose if needed [see <i>Dosage and Administration</i> (2.3, 2.4)]

<sup>a</sup> ASTAGRAF XL dosage adjustment recommendation based on observed effect of coadministered 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

<sup>b</sup> High dose or double strength grapefruit juice is a *strong* CYP3A inhibitor; low dose or single strength grapefruit juice is a *moderate* CYP3A inhibitor

<sup>c</sup> 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)

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### ***Pregnancy Category C***

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

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

In pregnant rabbits, tacrolimus at oral doses of 0.32 and 1.0 mg/kg (0.5 and 1.6 times the maximum clinical dose based on body surface area, respectively) was associated with maternal toxicity as well as an increased incidence of abortions. At the 1 mg/kg dose, fetal rabbits showed an increased incidence of malformations (ventricular hypoplasia, interventricular septal defect, bulbous aortic arch, stenosis of ductus arteriosus, interrupted ossification of vertebral arch, vertebral and rib malformations, omphalocele, and gallbladder agenesis) and developmental variations. In pregnant rats, tacrolimus at oral doses of 3.2 mg/kg (2.6 times the maximum clinical dose) was associated with maternal toxicity, an increase in late resorptions, decreased numbers of live births, and decreased pup weight and viability. Tacrolimus, given orally to pregnant rats after organogenesis and during lactation at 1.0 and 3.2 mg/kg (0.8 and 2.6 times the maximum recommended clinical dose, respectively) was associated with reduced pup weights and pup viability (3.2 mg/kg only); among the high dose pups that died early, an increased incidence of kidney hydronephrosis was observed.

### 8.3 Nursing Mothers

Tacrolimus is present in breast milk. Because of the potential for serious adverse drug reactions in nursing infants from ASTAGRAF XL, a decision should be made whether to discontinue nursing or to discontinue ASTAGRAF XL, taking into account the importance of drug to the mother.

### 8.4 Pediatric Use

The safety and effectiveness of ASTAGRAF XL in pediatric patients less than 16 years of age have not been established.

### **8.5 Geriatric Use**

Clinical studies of ASTAGRAF XL 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: > 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 (2.2)*]. 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**

African-American patients may need to be titrated to higher dosages to attain comparable trough concentrations compared to Caucasian patients [see *Dosage and Administration (2.2)*, *Clinical Pharmacology (12.3)*, and *Clinical Studies (14)*].

## **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)
- urticarial
- 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

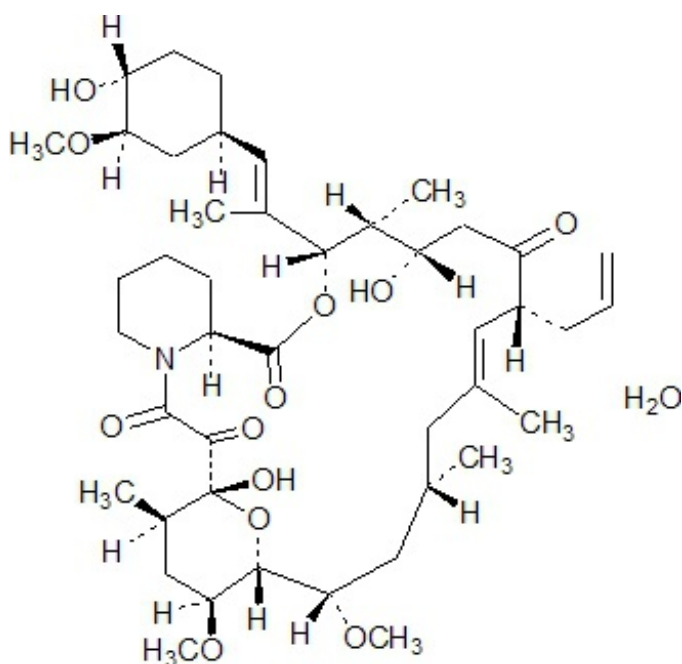
overdoses, but experience has not been sufficient to warrant recommending its use. General supportive measures and treatment of specific symptoms should be followed in all cases of overdose.

## 11 DESCRIPTION

ASTAGRAF XL, a calcineurin-inhibitor immunosuppressant, is available for oral administration as hard gelatin capsules (tacrolimus extended-release 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, titanium dioxide USP, ferric oxide NF, and sodium lauryl sulfate.

Tacrolimus is the active ingredient in ASTAGRAF XL. Tacrolimus is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. Chemically, tacrolimus is designated as [3S – [3R\*[E(1S\*, 3S\*, 4S\*)], 4S\*, 5R\*, 8S\*, 9E, 12R\*, 14R\*, 15S\*, 16R\*, 18S\*, 19S\*, 26aR\*]] – 5, 6, 8, 11, 12, 13, 14, 15, 16, 17, 18, 19, 24, 25, 26, 26a – hexadecahydro – 5, 19 – dihydroxy – 3 – [2 – (4 – hydroxy – 3 – 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<sub>44</sub>H<sub>69</sub>NO<sub>12</sub>•H<sub>2</sub>O 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.

## 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 (an ubiquitous mammalian intracellular enzyme) is then formed and the phosphatase activity of calcineurin 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 7 summarizes the pharmacokinetic (PK) parameters of tacrolimus following oral administration of ASTAGRAF XL in healthy subjects and in kidney transplant patients. Whole blood tacrolimus concentrations in these pharmacokinetic studies were measured using validated HPLC/MS/MS assays.

**Table 7: Pharmacokinetic Parameters of ASTAGRAF XL (Given Once Daily) in Healthy Subjects and in Kidney Transplant Patients (Under Fasted Conditions)**

Population	ASTAGRAF XL Dose <sup>a</sup>	Day <sup>b</sup>	Pharmacokinetic Parameters of ASTAGRAF XL			
			C <sub>max</sub> <sup>c</sup> (ng/mL)	T <sub>max</sub> <sup>d</sup> (hr)	AUC <sub>24</sub> <sup>c</sup> (ng·hr/mL)	C <sub>24</sub> <sup>f</sup> (ng/mL)
Healthy Subjects (n=24)	4 mg	Day 1	6.2 ± 2.1	2.0 [1.0-5.0]	74 ± 22	2.3 ± 0.8
	4 mg	Day 10	11.6 ± 3.4	2.0 [1.0-3.0]	155 ± 46	4.7 ± 1.5
Adult Kidney <i>De novo</i> <sup>e</sup> (n=17)	0.20 mg/kg	Day 1	26.0 ± 13.7	3.0 [2-24]	372 ± 202	12.1 ± 7.2
	0.19 mg/kg	Day 3	31.0 ± 13.9	2.0 [0.5-2.0]	437 ± 175	13.5 ± 5.6
	0.18 mg/kg	Day 7	32.2 ± 10.2	2.0 [1-6]	405 ± 117	11.4 ± 4.0
	0.18 mg/kg	Day 14	32.7 ± 9.0	2.0 [1-4]	412 ± 109	11.2 ± 3.9
Adult Kidney (6 months or greater post-transplant) (n=60)	5.2 mg/day <sup>g</sup>	Day 14 <sup>g</sup>	16.1 ± 5.3	2.0 [1.0 - 6.0]	222 ± 64	6.7 ± 1.9 <sup>h</sup>

<sup>a</sup> Healthy adult subjects (actual administered dose of ASTAGRAF XL); Adult *de novo* kidney transplant patients (actual group mean dose of ASTAGRAF XL)

<sup>b</sup> Day of ASTAGRAF XL treatment and PK profiling

<sup>c</sup> Arithmetic means ± S.D.

<sup>d</sup> Median [range]

<sup>e</sup> “De novo” refers to immunosuppression starting at the time of transplantation; data from PK substudy of Study 2

<sup>f</sup> Tacrolimus trough concentration before the next dose

<sup>g</sup> Same daily dose of ASTAGRAF XL for 14-day period

<sup>h</sup> Correlation coefficient of AUC<sub>24</sub> to C<sub>min</sub> r = 0.88

In *de novo* adult kidney transplant patients, the tacrolimus systemic exposure, as assessed by AUC<sub>24</sub>, for ASTAGRAF XL 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<sub>24</sub> was similar between the two formulations. On Day 14 (steady state), the AUC<sub>24</sub> for ASTAGRAF XL was 21% (Ratio [SD]: 1.207 [1.326]) higher than that of PROGRAF (tacrolimus immediate-release), at comparable trough concentrations (C<sub>24</sub>).

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



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

### **Absorption**

In healthy subjects, the administration of escalating ASTAGRAF XL 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 ASTAGRAF XL 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 ASTAGRAF XL was administered 1.5 hours after consumption of a high-fat breakfast, tacrolimus exposure was decreased approximately 35%. Administration of ASTAGRAF XL 1 hour prior to a high-fat breakfast reduced tacrolimus exposure by 10%. ASTAGRAF XL 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 ASTAGRAF XL reduced  $AUC_{inf}$  by 35% relative to morning dosing. ASTAGRAF XL 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 5-50 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).

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

### **Excretion**

In a mass balance study of orally-administered radiolabeled tacrolimus to 6 healthy subjects, the mean recovery of the radiolabel was  $94.9 \pm 30.7\%$ . Fecal elimination accounted for  $92.6 \pm 30.7\%$  and urinary elimination accounted for  $2.3 \pm 1.1\%$  of the total radiolabel administered. The elimination half-life based on radioactivity was  $31.9 \pm 10.5$  hours, whereas it was  $48.4 \pm 12.3$  hours based on tacrolimus concentrations. The mean clearance of radiolabel was  $0.226 \pm 0.116$  L/hr/kg and the mean clearance of tacrolimus was  $0.172 \pm 0.088$  L/hr/kg.

The elimination half-life of tacrolimus after oral administration of 4 mg ASTAGRAF XL daily for 10 days was  $38 \pm 3$  hours in 24 healthy subjects.

### **Specific Populations**

#### **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  $3.9 \pm 1.6$  and  $12.0 \pm 2.4$  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 *Dosage and Administration (2.2)* and *Use in Specific Populations (8.6)*].

### 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 6 patients with severe hepatic impairment (mean Pugh score: > 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)*].

### Race

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 ( $\pm$  SD) tacrolimus  $C_{\max}$  in African-Americans ( $23.6 \pm 12.1$  ng/mL) was lower than in Caucasians ( $40.2 \pm 12.6$  ng/mL) and Latino-Americans ( $36.2 \pm 15.8$  ng/mL).
- Mean  $AUC_{0-\infty}$  tended to be lower in African-Americans ( $203 \pm 115$  ng hr/mL) than Caucasians ( $344 \pm 186$  ng hr/mL) and Latino-Americans ( $274 \pm 150$  ng hr/mL).
- The mean ( $\pm$  SD) absolute oral bioavailability (F) in African-Americans ( $12 \pm 4.5\%$ ) and Latino-Americans ( $14 \pm 7.4\%$ ) was lower than in Caucasians ( $19 \pm 5.8\%$ ).
- There was no significant difference in mean terminal half-life among the three ethnic groups (range from approximately 25 to 30 hours).

### Gender

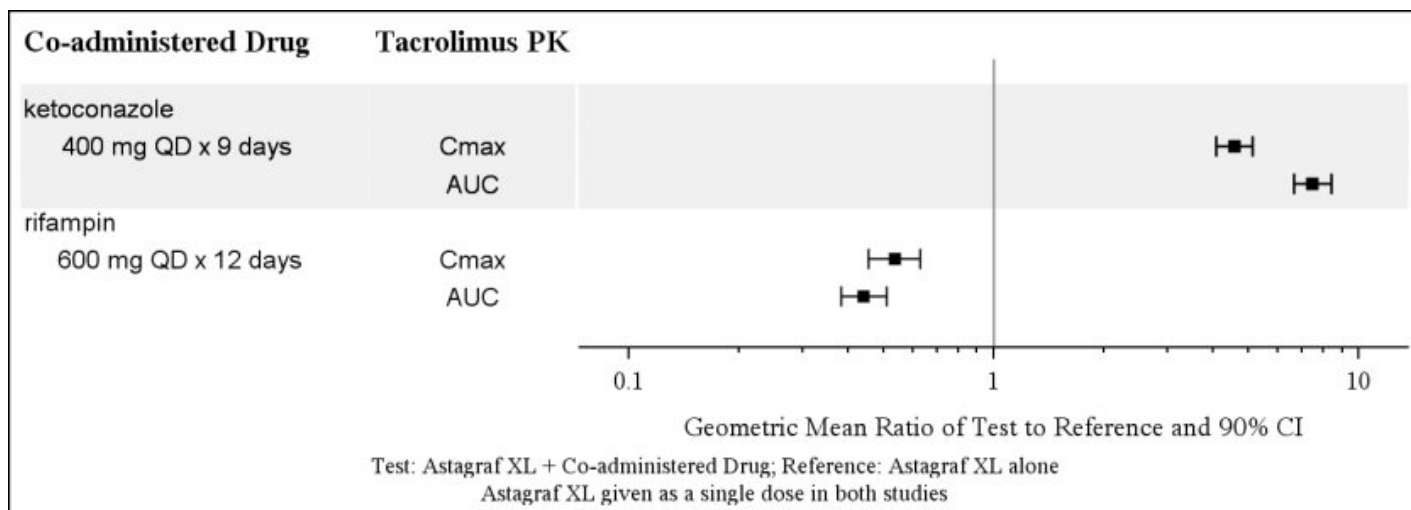
A formal trial to evaluate the effect of gender on tacrolimus pharmacokinetics has not been conducted; however, there was no difference in total mg daily dosages between male and female patients receiving ASTAGRAF XL in the kidney transplant trials. A retrospective comparison of pharmacokinetics in healthy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

### ***Drug Interactions***

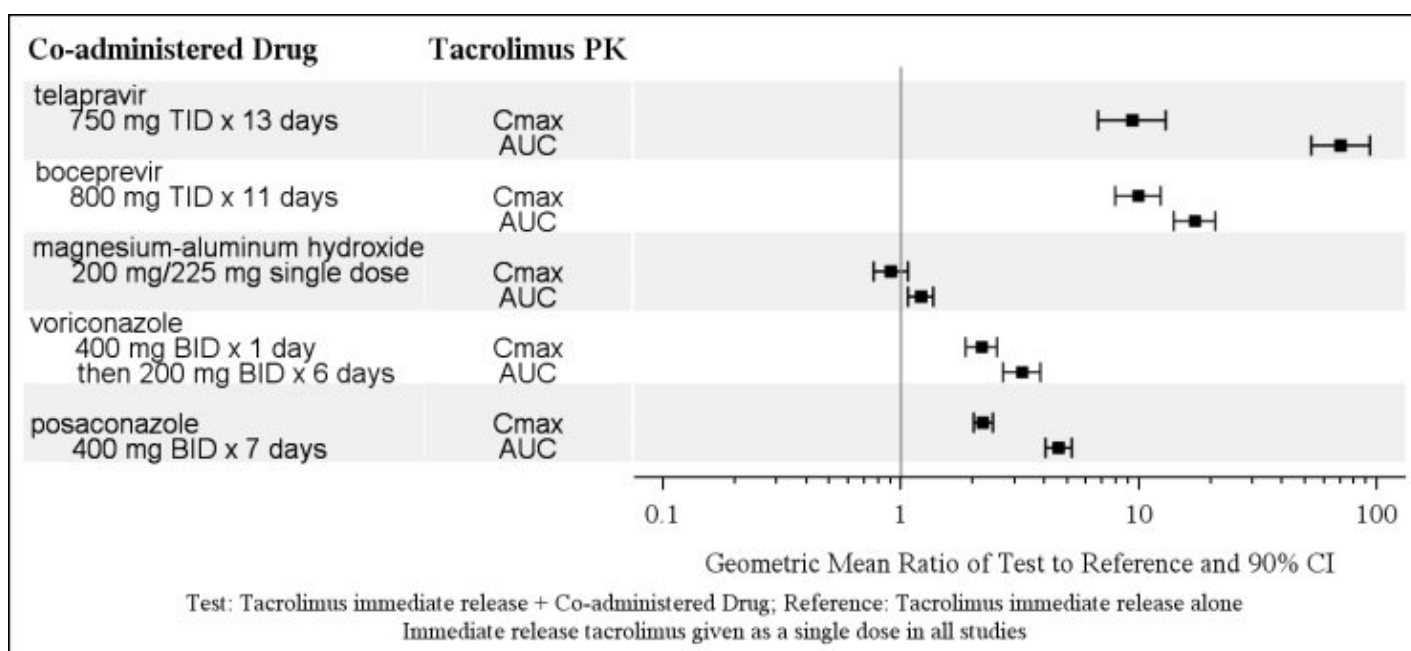
Because tacrolimus is metabolized mainly by CYP3A enzymes, drugs or substances known to inhibit these enzymes and/or are known CYP3A substrates may increase tacrolimus whole blood concentrations. Drugs known to induce CYP3A enzymes may decrease tacrolimus whole blood concentrations [see *Warnings and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

Figures 1 and 2 summarize the PK data from drug interaction studies of ASTAGRAF XL or tacrolimus immediate-release capsules. These studies assessed the effect of co-administered drugs on tacrolimus PK in healthy subjects. For the clinical recommendations, see *Drug Interactions (7.2)*.

**Figure 1: Effect of Co-administered Drugs on the Pharmacokinetics of Tacrolimus (when Given as ASTAGRAF XL)**



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



## 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 *Boxed Warning, Warnings and Precautions (5.1)*].

A 104-week dermal carcinogenicity study was performed in mice with tacrolimus ointment (0.03%-3%), equivalent to tacrolimus doses of 1.1-118 mg/kg/day or 3.3-354 mg/m<sup>2</sup>/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 renal transplant patients > 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 given orally at 1 mg/kg (0.8 times the maximum clinical dose based on body surface area) to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryoletality and adverse effects on female reproduction. Effects on female reproductive function (parturition) and embryoletal effects were indicated by a higher rate of pre-implantation loss and increased numbers of undelivered and nonviable pups. When given at 3.2 mg/kg (2.6 times the maximum clinical dose 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 ASTAGRAF XL with Basiliximab Induction**

Study 1 was a 12-month, randomized, open-label trial of ASTAGRAF XL (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 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 Medication

##### *ASTAGRAF XL or Control [PROGRAF (tacrolimus) capsules]*

The initial dose of ASTAGRAF XL 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 0.20 mg per kg given as a single dose in the morning for ASTAGRAF XL and 0.075 to 0.10 mg per kg twice daily for control. The ASTAGRAF XL and control dosage was then adjusted on the basis of safety and efficacy and a target whole blood tacrolimus trough concentration range of 7 to 16 ng/mL for the first 90 days post-transplant and 5 to 15 ng/mL thereafter.

The average recorded starting tacrolimus daily dose, given any time up to day 2 post-transplant, was higher for ASTAGRAF XL than for control (0.14 mg per kg per day versus 0.10 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 ASTAGRAF XL than for control.

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

**Table 8: Observed Tacrolimus Whole Blood Trough Concentrations in ASTAGRAF XL-Treated Kidney Transplant Patients in Study 1**

Scheduled Visit	Tacrolimus Whole Blood Trough Concentrations (ng/mL)* Median (10 <sup>th</sup> to 90 <sup>th</sup> Percentile)
Day 3	9.6 (4.9 to 20.2)
Day 7	9.1 (4.4 to 16.8)
Day 14	10.0 (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 ASTAGRAF XL dosages to attain similar trough concentrations as Caucasian patients (see Table 9).

**Table 9: ASTAGRAF XL 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	0.10	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 ASTAGRAF XL-treated patients are shown in Table 10. The MMF dosage was reduced to less than 2 grams per day by month 12 in 56% of ASTAGRAF XL-treated patients. Approximately 57% of the MMF dose reductions were because of adverse reactions in the ASTAGRAF XL group [see Adverse Reactions (6.1)].

**Table 10: Proportion of Patients Who Received 2 grams (or less than or more than 2 grams) of MMF by Time Period in ASTAGRAF XL-treated Patients in Study 1**

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

<sup>a</sup> 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 days 3 and 5.

### *Steroids*

All patients were administered an intravenous bolus of 500 to 1000 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 11 for the intent-to-treat population, as well as the rates of the individual events.

**Table 11: Incidence of BPAR, Graft Loss, Death or Lost to Follow-up at 12 Months in Kidney Transplant Patients in Study 1**

	ASTAGRAF XL + MMF, steroids, basiliximab induction (N=214)	PROGRAF + MMF, steroids, basiliximab induction (N=212)
Efficacy Failure	30 (14.0%)	32 (15.1%)
Treatment Difference (95% CI <sup>a</sup> )	-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%)

<sup>a</sup> 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 12.

**Table 12: Estimated Glomerular Filtration Rate (mL/min/1.73m<sup>2</sup>) by MDRD Formula at 12 Months Post-Transplant in Study 1**

	<b>ASTAGRAF XL + MMF, steroids, basiliximab induction (n=201)</b>	<b>PROGRAF + MMF, steroids, basiliximab induction (n=202)</b>
Month 1 Baseline Mean (SD)	56 (20)	56 (21)
Month 12 LOCF <sup>a</sup>		
Mean (Standard deviation)	58 (21)	56 (23)
Mean Difference XL minus PROGRAF (tacrolimus immediate-release) <sup>b</sup>	<b>+2.3 (-1.2, +5.8)</b>	

<sup>a</sup> Last observation carried forward (LOCF); patients who died, lost the graft or were lost to follow-up are imputed as zeroes

<sup>b</sup> Results from analysis of covariance model with Month 1 Baseline as a covariate

## 14.2 Clinical Study of ASTAGRAF XL without Induction

Study 2 was a 12-month, randomized, double-blind trial of ASTAGRAF XL (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 > 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 > 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

#### *ASTAGRAF XL or Control [PROGRAF (tacrolimus) capsules]*

The protocol specified initial pre-operative dose for both ASTAGRAF XL 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 ASTAGRAF XL, and was given as 0.1 mg/kg twice daily for control. Subsequent doses of ASTAGRAF XL 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 to 15 ng/mL for the first 28 days post-transplant, 5 to 15 ng/mL from Day 29 to Day 168, 5 to 10 ng/mL thereafter.

The actual tacrolimus doses on day 0 (0.1 mg per kg per day pre-operative) and day 1 (0.2 mg per kg per day post-operative) were comparable between ASTAGRAF XL and control. Thereafter, to achieve comparable mean tacrolimus trough concentrations, on average, 25% higher total mean daily doses of tacrolimus were required for ASTAGRAF XL than for control.

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

Table 13 shows the tacrolimus whole blood trough concentrations measured at protocol-specified time points for ASTAGRAF XL. Approximately 80% of ASTAGRAF XL-treated patients maintained

tacrolimus whole trough blood concentrations between 6 to 20 ng/mL during months 1 through 2 and between 6 to 14 ng/mL from months 3 through 12.

**Table 13: Observed Tacrolimus Whole Blood Trough Concentrations for ASTAGRAF XL Kidney Transplant Patients Evaluated in Study 2**

Scheduled Visit	Tacrolimus Whole Blood Trough Concentrations (ng/mL)* [Median (10 <sup>th</sup> to 90 <sup>th</sup> Percentile)]
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	12.0 (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	8.0 (5.1 to 13.8)

\* Immunoassay was used in most laboratories

#### *MMF*

The initial dose of MMF was 1 gram orally twice daily starting pre-operatively 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 ASTAGRAF XL-treated patients are shown in Table 14. The MMF dosage was reduced to 0.5 grams twice daily starting after day 14 in the majority of patients.

**Table 14: Distribution (%) of ASTAGRAF XL-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 <sup>a,b</sup>		
	N	Less than 1 gram per day	1 gram to less than 2 grams per day	2 grams per day
1-30	331	1%	78%	21%
31-90	303	8%	87%	6%
91-180	281	12%	85%	3%
181-365	258	15%	83%	2%

<sup>a</sup> 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.

<sup>b</sup> One patient had a time-averaged dose during the first and last period of > 2 gm/day.

#### *Steroids*

An intravenous (IV) bolus of up to 1000 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 15 for 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 15: Incidence of BPAR, Graft Loss, Death or Lost to Follow-up at 12 Months in Kidney Transplant Patients in Study 2**

	<b>ASTAGRAF XL + MMF and steroids (N=331)</b>	<b>PROGRAF + MMF and steroids (N=336)</b>
Efficacy Failure	93 (28.1%)	78 (23.2%)
Treatment Difference (95% CI <sup>a</sup> )	+4.9% (-1.7%, +11.5%)	
<b>Efficacy Failure Endpoints</b>		
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%)

<sup>a</sup> 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 16.

**Table 16: Estimated Glomerular Filtration Rate (mL/min/1.73m<sup>2</sup>) by MDRD Formula at 12 Months Post-Kidney Transplant in Study 2**

	<b>ASTAGRAF XL + MMF and steroids (N=287)</b>	<b>PROGRAF + MMF and steroids (N=300)</b>
Month 1 Baseline Mean (SD)	51 (19)	52 (20)
Month 12 LOCF <sup>a</sup>		
Mean (Standard deviation)	52 (20)	55 (19)
Mean Difference XL minus PROGRAF (tacrolimus immediate- release) <sup>b</sup>	<b>-1.8 (-4.6, +0.8)</b>	


<sup>a</sup> Last observation carried forward (LOCF); patients who died, lost the graft or were lost to follow-up are imputed as zeroes



<sup>b</sup> Results from analysis of covariance model with Month 1 Baseline as a covariate.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

ASTAGRAF XL (tacrolimus) extended-release capsules are supplied in short, square bottles as well as in blister cartons (see Table 17).

**Table 17: Strengths of ASTAGRAF XL**

Oblong capsule with a light yellow cap and orange body. Capsule is branded with red “ 
---

0.5 mg	<p>647” on capsule body and “0.5 mg” on capsule cap. Both bottle and blister packaging are branded with matching brown stripes.</p> <ul style="list-style-type: none"> <li>• 30-count in short, square bottles with brown caps (NDC 0469-0647-73)</li> <li>• Blister cartons containing 5 blister cards of 10 capsules on each card (NDC 0469-0647-11).</li> </ul>
1 mg	<p>Oblong capsule with a white cap and orange body. Capsule is branded with red “ 677” on capsule body and “1 mg” on capsule cap. Both bottle and blister packaging are branded with matching blue stripes.</p> <ul style="list-style-type: none"> <li>• 30-count in short, square bottles with blue caps (NDC 0469-0677-73)</li> <li>• Blister cartons containing 5 blister cards of 10 capsules on each card (NDC 0469-0677-11).</li> </ul>
5 mg	<p>Oblong capsule with a grayish-red cap and orange body. Capsule is branded with red “ 687” on capsule body and “5 mg” on capsule cap. Both bottle and blister packaging are branded with matching orange stripes.</p> <ul style="list-style-type: none"> <li>• 30-count in short, square bottles with orange caps (NDC 0469-0687-73)</li> <li>• Blister cartons containing 5 blister cards of 10 capsules on each card (NDC 0469-0687-11).</li> </ul>

## Store and Dispense

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

## 17 PATIENT COUNSELING INFORMATION

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

### Administration

Advise patients to:

- Inspect their ASTAGRAF XL 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 ASTAGRAF XL [see *Warnings and Precautions (5.4)*].
- Take ASTAGRAF XL at the same time every day to achieve consistent blood concentrations.
- Take ASTAGRAF XL in the morning, preferably 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 beverage, grapefruit and grapefruit juice while on ASTAGRAF XL [see *Dosage and Administration (2.1) and Drug Interactions (7.2)*].
- Take a missed dose of ASTAGRAF XL 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.

### 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 use a sunscreen with a high protection factor [see *Boxed Warning and Warnings and Precautions (5.1)*].

### 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 [see *Boxed Warning and Warnings and Precautions (5.2)*].

### New Onset Diabetes After Transplant

Inform patients that ASTAGRAF XL 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)*].

### Nephrotoxicity

Inform patients that ASTAGRAF XL 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)*].

### 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)*].

### Hyperkalemia

Inform patients that ASTAGRAF XL 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)*].

### Hypertension

Inform patients that ASTAGRAF XL can cause high blood pressure which may require treatment with anti-hypertensive therapy [see *Warnings and Precautions (5.9)*].

### Drug Interactions

Instruct patients to tell their healthcare providers when they start or stop taking any concomitant medications, including prescription and non-prescription medicines, herbal and dietary supplements. Some medications could alter tacrolimus concentrations in the blood and thus may require the adjustment of the dosage of ASTAGRAF XL [see *Warnings and Precautions (5.10) and Drug Interactions (7)*].

### Immunizations

Inform patients that ASTAGRAF XL can interfere with the usual response to immunizations and that they should avoid live vaccines [see *Warnings and Precautions (5.12)*].

## **Product of Japan**

Manufactured by:

**Astellas Ireland Co., Limited**

Killorglin, County Kerry, Ireland

Marketed by:

**Astellas Pharma US, Inc.**

Northbrook, IL 60062

ASTAGRAF XL<sup>®</sup> is a registered trademark of Astellas Pharma Inc.

PROGRAF<sup>®</sup> is a registered trademark of Astellas Pharma Inc.

14E029-AST

**MEDICATION GUIDE**  
**ASTAGRAF XL® [as' tah graf ex el']**  
**(tacrolimus)**  
**extended-release capsules**

**What is the most important information I should know about ASTAGRAF XL?**

**ASTAGRAF XL can cause serious side effects, including:**

- **Increased risk of cancer.** People who take ASTAGRAF XL have an increased risk of getting some kinds of cancer, including skin and lymph gland cancer (lymphoma).
- **Increased risk of infection.** ASTAGRAF XL is a medicine that affects your immune system. ASTAGRAF XL can lower the ability of your immune system to fight infections. Serious infections can happen in people receiving ASTAGRAF XL that can cause death. **Call your doctor right away if you have symptoms of an infection such as:**
  - fever
  - cough or flu-like symptoms
  - warm, red, or painful areas on
  - sweats or chills
  - muscle aches
  - your skin
- **Increased risk of death in females who have had a liver transplant.** You should not take ASTAGRAF XL if you have had a liver transplant without talking to your doctor.

**What is ASTAGRAF XL?**

- ASTAGRAF XL is a prescription medicine used with other medicines to help prevent organ rejection in people who have had a kidney transplant.
- ASTAGRAF XL is an extended-release capsule and is not the same as tacrolimus immediate-release capsules. Your doctor should decide what medicine is right for you.

**Who should not take ASTAGRAF XL?**

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

**Before you take ASTAGRAF XL tell your doctor if you:**

- plan to receive any live vaccines. Ask your doctor 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. ASTAGRAF XL may harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. ASTAGRAF XL can pass into your breast milk. You and your doctor should decide if you will take ASTAGRAF XL or breastfeed. You should not do both.

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

**How should I take ASTAGRAF XL?**

- Take ASTAGRAF XL exactly as your doctor tells you to take it.

- Your doctor may change your dose if needed. **Do not** stop taking or change your dose of ASTAGRAF XL without talking to your doctor.
- Take ASTAGRAF XL capsules whole. Do not break, crush, chew, or dissolve ASTAGRAF XL capsules before swallowing. If you cannot swallow ASTAGRAF XL capsules whole, tell your doctor.
- Take ASTAGRAF XL 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 ASTAGRAF XL, 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 ASTAGRAF XL, call your doctor or go to the nearest hospital emergency room right away.

### What should I avoid while taking ASTAGRAF XL?

- 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 ASTAGRAF XL.
- You should not drink alcohol when taking ASTAGRAF XL.

### What are the possible side effects of ASTAGRAF XL?

#### ASTAGRAF XL may cause serious side effects, including:

- **See “What is the most important information I should know about ASTAGRAF XL?”**
- **graft rejection and other serious reactions.** People who take ASTAGRAF XL have sometimes been given the wrong medicine because some medicines have the same ingredient (tacrolimus) as ASTAGRAF XL. Serious reactions have happened including graft rejection. **Check your ASTAGRAF XL when you get a new prescription to make sure you have received the right medicine.**
  - Call your doctor right away if you think you were given the wrong medicine
  - Ask your doctor or pharmacist if you are not sure what ASTAGRAF XL should look like.
- **high blood sugar (diabetes).** Your doctor may do certain tests to check for diabetes while you take ASTAGRAF XL. Call your doctor right away if you have:
 

<input type="checkbox"/> frequent urination	<input type="checkbox"/> confusion	<input type="checkbox"/> fruity smell on your breath
<input type="checkbox"/> increased thirst or hunger	<input type="checkbox"/> drowsiness	<input type="checkbox"/> nausea, vomiting, or stomach pain
<input type="checkbox"/> blurred vision	<input type="checkbox"/> loss of appetite	
- **kidney problems.** Your doctor may do certain tests to check your kidney function.
- **nervous system problems.** Call your doctor or go to the nearest hospital emergency room right away if you get any of the these symptoms while taking ASTAGRAF XL. These could be signs of serious nervous system problems:
 

<input type="checkbox"/> confusion	<input type="checkbox"/> numbness and tingling	<input type="checkbox"/> seizures
<input type="checkbox"/> changes in alertness	<input type="checkbox"/> headache	<input type="checkbox"/> vision changes
<input type="checkbox"/> muscle tremors		
- **high levels of potassium in your blood.** Your doctor may do certain tests to check your potassium level while you take ASTAGRAF XL.

- **high blood pressure.** Your doctor will monitor your blood pressure while you take ASTAGRAF XL.
- **changes in the electrical activity of your heart (QT prolongation).**

**The most common side effects of ASTAGRAF XL** are diarrhea, constipation, nausea, swelling of the hands, ankles, or legs, and tremors (shaking of the body).

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

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

#### **How should I store ASTAGRAF XL?**

- Store ASTAGRAF XL 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 ASTAGRAF XL and all medicines out of reach of children.**

#### **General information about the safe and effective use of ASTAGRAF XL.**

- This Medication Guide summarizes the most important information about ASTAGRAF XL. If you would like more information, talk to your doctor. You can ask your pharmacist or doctor for information about ASTAGRAF XL that is written for health professionals.

#### **What are the ingredients in ASTAGRAF XL?**

**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, titanium dioxide USP, ferric oxide NF, and sodium lauryl sulfate

Manufactured by: **Astellas Ireland Co., Limited**, Killorglin, County Kerry, Ireland

Marketed by: **Astellas Pharma US, Inc.**, Northbrook, IL 60062

ASTAGRAF XL<sup>®</sup> is a registered trademark of Astellas Pharma Inc.

14E029-AST-MG

This Medication Guide has been approved by the U.S. Food and Drug Administration  
12/2015

Issued:

**PACKAGE/LABEL PRINCIPAL DISPLAY PANEL – 0.5 mg bottle label**

NDC 0469-0647-73

**Astagraf XL<sup>®</sup>**  
(tacrolimus extended-release capsules)

**0.5 mg**

**ONCE-DAILY**

Swallow capsule whole.  
Do not cut, crush, or chew capsule.  
**30 Capsules**

Store at 25°C (77°F); excursions  
15°C-30°C (59°F-86°F)  
Dosage: See Package Insert for  
dosage information **Rx only**

**Note: Astagraf XL capsules are not  
filled to maximum capsule capacity.  
Capsule contains labeled amount.**

Product of Japan  
Manufactured by: **Astellas Ireland Co., Ltd.**  
Killorglin, County Kerry, Ireland  
Marketed by: **Astellas Pharma US, Inc.**   
Northbrook, IL 60062  
14C017-AST **064773**



NDC 0469-0647-73

**Astagraf XL<sup>®</sup>**  
(tacrolimus extended-release capsules)

**0.5 mg**

**ONCE-DAILY**

Swallow capsule whole.  
Do not cut, crush, or chew capsule.

**30 Capsules**

**PACKAGE/LABEL PRINCIPAL DISPLAY PANEL – 1 mg bottle label**

NDC 0469-0677-73

**Astagraf XL<sup>®</sup>**  
(tacrolimus extended-release capsules)

**1 mg**

**ONCE-DAILY**

Swallow capsule whole.  
Do not cut, crush, or chew capsule.  
**30 Capsules**

Store at 25°C (77°F); excursions  
15°C-30°C (59°F-86°F)  
Dosage: See Package Insert for  
dosage information **Rx only**

**Note: Astagraf XL capsules are not  
filled to maximum capsule capacity.  
Capsule contains labeled amount.**

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Marketed by: **Astellas Pharma US, Inc.**   
Northbrook, IL 60062  
14C017-AST **067773**



NDC 0469-0677-73

**Astagraf XL<sup>®</sup>**  
(tacrolimus extended-release capsules)

**1 mg**

**ONCE-DAILY**

Swallow capsule whole.  
Do not cut, crush, or chew capsule.

**30 Capsules**

**PACKAGE/LABEL PRINCIPAL DISPLAY PANEL – 5 mg bottle label**

NDC 0469-0687-73

**Astagraf XL<sup>®</sup>**  
 (tacrolimus extended-release capsules)

**5 mg**

**ONCE-DAILY**

Swallow capsule whole.  
 Do not cut, crush, or chew capsule.  
**30 Capsules**

Store at 25°C (77°F); excursions  
 15°C-30°C (59°F-86°F)  
 Dosage: See Package Insert for  
 dosage information

Rx only

**Note: Astagraf XL capsules are not  
 filled to maximum capsule capacity.  
 Capsule contains labeled amount.**

Product of Japan  
 Manufactured by: **Astellas Ireland Co., Ltd.**  
 Killorglin, County Kerry, Ireland  
 Marketed by: **Astellas Pharma US, Inc.**  
 Northbrook, IL 60062



14C017-AST

068773



143417

NDC 0469-0687-73

**Astagraf XL<sup>®</sup>**  
 (tacrolimus extended-release capsules)

**5 mg**

**ONCE-DAILY**

Swallow capsule whole.  
 Do not cut, crush, or chew capsule.

**30 Capsules**

**ASTAGRAF XL**

tacrolimus extended-release capsules capsule, coated, extended release

**Product Information**

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:0469-0647
<b>Route of Administration</b>	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**

<b>Color</b>	YELLOW, ORANGE	<b>Score</b>	no score
<b>Shape</b>	CAPSULE	<b>Size</b>	11mm
<b>Flavor</b>		<b>Imprint Code</b>	
<b>Contains</b>			

**Packaging**

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0469-0647-73	1 in 1 CARTON		
1		30 in 1 BOTTLE; Type 0: Not a Combination Product		



2	NDC:0469-0647-11	5 in 1 CARTON		
2		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		
<b>Marketing Information</b>				
<b>Marketing Category</b>	<b>Application Number or Monograph Citation</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>	
NDA	NDA204096	07/19/2013		

**ASTAGRAF XL**  
tacrolimus extended-release capsules capsule, coated, extended release

<b>Product Information</b>			
<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:0469-0677
<b>Route of Administration</b>	ORAL		

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

<b>Product Characteristics</b>			
<b>Color</b>	WHITE, ORANGE	<b>Score</b>	no score
<b>Shape</b>	CAPSULE	<b>Size</b>	14mm
<b>Flavor</b>		<b>Imprint Code</b>	
<b>Contains</b>			

<b>Packaging</b>				
<b>#</b>	<b>Item Code</b>	<b>Package Description</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
1	NDC:0469-0677-73	1 in 1 CARTON		
1		30 in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:0469-0677-11	5 in 1 CARTON		
2		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

<b>Marketing Information</b>				
<b>Marketing Category</b>	<b>Application Number or Monograph Citation</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>	
NDA	NDA204096	07/19/2013		

**ASTAGRAF XL**  
tacrolimus extended-release capsules capsule, coated, extended release

Product Information				
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0469-0687	
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	GRAY, RED, ORANGE	Score	no score	
Shape	CAPSULE	Size	22mm	
Flavor		Imprint Code		
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0469-0687-73	1 in 1 CARTON		
1		30 in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:0469-0687-11	5 in 1 CARTON		
2		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	
NDA	NDA204096	07/19/2013		

**Labeler** - Astellas Pharma US, Inc. (605764828)

### Establishment

Name	Address	ID/FEI	Business Operations
Astellas Ireland Co., Ltd.		985098269	ANALYSIS(0469-0647, 0469-0677, 0469-0687) , MANUFACTURE(0469-0647, 0469-0677, 0469-0687)

### Establishment

Name	Address	ID/FEI	Business Operations
Astellas Pharma Tech Co., Ltd.		691336904	ANALYSIS(0469-0647, 0469-0677, 0469-0687) , MANUFACTURE(0469-0647, 0469-0677, 0469-0687)