ASTAGRAF XL™
(tacrolimus extended-release capsules)

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: 2013

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

See full prescribing information for complete boxed warning

- **Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe ASTAGRAF XL (5.1)**
- **Increased susceptibility to infection and the possible development of malignancies may result from immunosuppression (5.2, 5.3, 5.6, 5.7)**
- **Use in liver transplantation is not recommended due to increased mortality rate in female liver transplant recipients (5.4)**

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

ASTAGRAF XL is a calcineurin-inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in patients receiving a kidney transplant with mycophenolate mofetil (MMF) and corticosteroids, with or without basiliximab induction (1.1)

Limitations of use (1.2):

- Not interchangeable with tacrolimus immediate-release capsules
- Do not use simultaneously with cyclosporine

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

Recommended Initial Oral Dose and Observed Whole Blood Tacrolimus Trough Concentrations in Kidney Transplant Patients (2.1, 2.4)

Treatment Regimen	Oral Dose	Observed Whole Blood Trough Concentrations[a]
With basiliximab induction[b]	0.15 mg/kg/day	Day 1 to 60: 5-17 ng/mL Month 3 to 12: 4-12 ng/mL
Without induction[c]	Pre-operative: 0.1 mg/kg/day Post-operative: 0.2 mg/kg/day	Day 1 to 60: 6-20 ng/mL Month 3 to 12: 6-14 ng/mL

[a] 10th - 90th percentile (14).
[b] Give first dose prior to or within 48 hours after transplant completion; may delay therapy initiation until renal function has recovered (2.2).
[c] Give preoperative dose within 12 hours prior to reperfusion, and first post-operative dose within 12 hours after reperfusion but not less than 4 hours after pre-operative dose (2.1)

- Take once daily in the morning, preferably on an empty stomach; do not take with an alcoholic beverage or grapefruit juice; do not chew, divide or crush capsules (2.4, 7)
- Monitoring of whole blood tacrolimus trough concentrations is recommended (2.5)

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

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

----------CONTRAINDICATIONS----------

- ASTAGRAF XL is contraindicated in patients with hypersensitivity to tacrolimus (4).

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

- Medication errors have been reported including unintentional substitution between immediate-release tacrolimus and ASTAGRAF XL (extended-release) tacrolimus formulations (5.5)
- New Onset Diabetes After Transplant: Monitor blood glucose (5.8)
- Nephrotoxicity (acute and/or chronic): Monitor renal function; reduce the dose; use caution with other nephrotoxic drugs (5.9)
- Neurotoxicity, Risk of Posterior Reversible Encephalopathy Syndrome (PRES): Monitor for neurologic abnormalities; reduce or discontinue immunosuppression (5.10)
- Hyperkalemia: Monitor serum potassium levels; use caution with other agents that increase potassium (5.11)
- Hypertension: May require antihypertensive therapy; monitor relevant drug-drug interactions (5.12)
- Use with Sirolimus: Not recommended; increased risk of serious adverse reactions in liver and heart transplant recipients (5.13)
- Use with Strong CYP3A Inhibitors and Inducers: Adjust tacrolimus dose and monitor trough concentrations and for occurrence of adverse reactions, including QT prolongation (5.14, 7)
- Immunizations: Avoid use of live vaccines (5.15)
- Pure Red Cell Aplasia: Consider discontinuation (5.16)

----------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 Astellas Pharma US, Inc. at 1-800-727-7003 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Mycophenolic Acid Products: Monitor for MPA-related adverse reactions and adjust MMF or MPA-dose as needed (7.1)
- CYP3A Inhibitors: Increased tacrolimus concentrations; monitor concentrations and adjust tacrolimus dose as needed with concomitant use (5.14, 7)
- CYP3A Inducers: Decreased tacrolimus concentrations; monitor concentrations and adjust tacrolimus dose as needed with concomitant use (5.14, 7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data may cause fetal harm (8.1)
- Nursing Mothers: Discontinue drug or nursing (8.3)
- Renal Impairment: If nephrotoxicity develops, reduce doses (2.2, 8.6)
- Hepatic Impairment: Lower doses below the recommended starting dose may be required (2.3, 8.7)
- Race: African-Americans may need higher doses (2.1, 8.8, 14)

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

Revised: 07/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

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

- **Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe ASTAGRAF XL. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient [*see Warnings and Precautions (5.1)*].**

Malignancies and Serious Infections

- **Increased susceptibility to infection and the possible development of malignancies such as lymphoma and skin cancer may result from immunosuppression [*see Warnings and Precautions (5.2, 5.3, 5.6, 5.7)*].**

Mortality in Liver Transplantation

- **Increased mortality in female transplant recipients was observed in a clinical trial of liver transplantation. Use in liver transplantation is not recommended [*see Warnings and Precautions (5.4)*].**

1 INDICATIONS AND USAGE

1.1 Prophylaxis of Organ Rejection in Kidney Transplant

ASTAGRAF XL is indicated for the prophylaxis of organ rejection in patients receiving a kidney transplant. It is recommended that ASTAGRAF XL be used concomitantly with mycophenolate mofetil (MMF) and corticosteroids, with or without basiliximab induction [*see Clinical Studies (14)*]. Therapeutic drug monitoring is recommended for all patients receiving ASTAGRAF XL [*see Dosage and Administration (2.5)*].

1.2 Limitations of Use

- ASTAGRAF XL extended-release capsules are not interchangeable or substitutable with tacrolimus immediate-release capsules.
- ASTAGRAF XL should not be used simultaneously with cyclosporine.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Adult Kidney Transplant Recipients

Initial dosage recommendations for adult patients after kidney transplantation are presented in Table 1. Dosing of ASTAGRAF XL should be titrated based on clinical assessments of rejection and tolerability, and to maintain trough concentration ranges as noted in Table 1. Frequent monitoring of tacrolimus trough concentrations is recommended in the early post-transplant period to ensure adequate drug exposure [*see Dosage and Administration (2.5)*].

ASTAGRAF XL extended-release capsules are not interchangeable or substitutible with tacrolimus immediate-release capsules.

With Basiliximab Induction
When used with basiliximab induction. MMF, and corticosteroids, the initial dose of ASTAGRAF XL should be administered prior to or within 48 hours of the completion of the transplant procedure, but may be delayed until renal function has recovered.

Without Induction
When used with MMF and corticosteroids, the pre-operative dose of ASTAGRAF XL should be given as one dose within 12 hours prior to reperfusion; the initial post-operative dose should be given not less than 4 hours after the pre-operative dose and within 12 hours after reperfusion.

Table 1. Recommended Initial Oral Dose and Observed Whole Blood Trough Concentrations in Kidney Transplant Patients

Treatment Regimen	Oral Dose	Observed Whole Blood Trough Concentrations[a]
With basiliximab induction	0.15 mg/kg/day	Day 1 to 60: 5-17 ng/mL Month 3 to 12: 4-12 ng/mL
Without induction	Pre-operative: 0.1 mg/kg/day Post-operative: 0.2 mg/kg/day	Day 1 to 60: 6-20 ng/mL Month 3 to 12: 6-14 ng/mL

a)10th - 90th percentile; see also Clinical Studies (14) for description of immunosuppressive regimens.

African-American kidney transplant patients may require higher doses of ASTAGRAF XL to attain comparable trough concentrations compared to Caucasian patients [*see Clinical Pharmacology (12.3), Clinical Studies (14)*].

2.2 Patients with Renal Impairment

In kidney transplant patients with post-operative oliguria, the initial dose of ASTAGRAF XL should be administered no sooner than 6 hours and within 48 hours of transplantation, but may be delayed until renal function shows evidence of recovery.

Frequent monitoring of renal function is recommended. ASTAGRAF XL dosage should be reduced if nephrotoxicity develops.

2.3 Patients with Hepatic Impairment
Due to the reduced clearance and prolonged half-life, patients with severe hepatic impairment (Child Pugh ≥ 10) may require lower doses of ASTAGRAF XL. Frequent monitoring of blood concentrations is warranted.

2.4 Administration Instructions
ASTAGRAF XL is a once daily extended-release oral formulation of tacrolimus.

Intravenous administration of tacrolimus should be reserved only for initiation in patients unable to take oral therapy. Prograf Injection is administered as a continuous IV infusion. Conversion from intravenous Prograf to oral ASTAGRAF XL is recommended as soon as oral therapy can be tolerated. This usually occurs within 2 to 3 days. In patients receiving Prograf intravenous infusion, the first dose of oral ASTAGRAF XL therapy should be given 8-12 hours after discontinuing the Prograf IV infusion.

To ensure consistent and maximum possible drug exposure, ASTAGRAF XL capsules should be taken consistently every morning, preferably on an empty stomach at least 1 hour before a meal or at least 2 hours after a meal [*see Clinical Pharmacology (12.3)*].

ASTAGRAF XL should be swallowed whole and should not be chewed, divided, or crushed.

Patients should not eat grapefruit or drink grapefruit juice in combination with ASTAGRAF XL [*see Drug Interactions (7.2)*].

Patients should not take ASTAGRAF XL with an alcoholic beverage [*see Drug Interactions (7.3)*].

If a dose of ASTAGRAF XL is missed, the dose may be taken 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, the patient should wait until the usual scheduled time the following morning to take the next regular daily dose. It is not recommended to double the dose of ASTAGRAF XL to make up for the missed dose.

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

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

Methods commonly used for the assay of tacrolimus include high-performance liquid chromatography with tandem mass spectrometric detection (HPLC/MS/MS) and immunoassays. Immunoassays may react with metabolites as well as the parent compound. Therefore, assay results obtained with immunoassays may have a positive bias relative to results of HPLC/MS. The bias may depend upon the specific assay and laboratory. Comparison of the concentrations in published literature to patient concentrations using the current assays must be made with detailed knowledge of the assay methods and biological matrices employed. Whole blood is the matrix of choice and specimens should be collected into tubes containing ethylene diamine tetraacetic acid (EDTA) anti-coagulant. Heparin anti-coagulation is not recommended because of the tendency to form clots on storage. Samples which are not analyzed immediately should be stored at room temperature or in a refrigerator and assayed within 7 days; see assay instructions for specifics. If samples are to be kept longer, they should be deep frozen at -20°C. One study showed drug recovery >90% for samples stored at -20°C for 6 months, with reduced recovery observed after 6 months.

3 DOSAGE FORMS AND STRENGTHS
- 0.5 mg hard gelatin capsule with a light yellow cap and orange body branded with red " 647" on the capsule body and "0.5 mg" on the capsule cap.
- 1 mg hard gelatin capsule with a white cap and orange body branded with red " 677" on the capsule body and "1 mg" on the capsule cap.
- 5 mg hard gelatin capsule with a 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 hypersensitivity to tacrolimus.

5 WARNINGS AND PRECAUTIONS
5.1 Management of Immunosuppression
Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe ASTAGRAF XL. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physicians responsible for maintenance therapy should have complete information requisite for the follow-up of the patients [*see Boxed Warning*].

5.2 Lymphoma and Other Malignancies
Patients receiving immunosuppressants, including ASTAGRAF XL, are at increased risk of developing lymphomas and other malignancies, particularly of the skin [*see Boxed Warning*]. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

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

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

5.3 Serious Infections
Patients receiving immunosuppressants, including ASTAGRAF XL, are at increased risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections [*see Boxed Warning, Warnings and Precautions (5.6, 5.7)*]. These infections may lead to serious, including fatal, outcomes. Because of the danger of oversuppression of the immune system which can increase susceptibility to infection, combination immunosuppressant therapy should be used with caution.

5.4 Liver Transplant Recipients
In a clinical trial of 471 liver transplant recipients randomized to ASTAGRAF XL or Prograf, 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 Prograf. Use of ASTAGRAF XL in liver transplantation is not recommended [*see Boxed Warning*].

5.5 Medication Errors
ASTAGRAF XL extended-release capsules are not interchangeable or substitutable with tacrolimus immediate-release capsules. Medication and dispensing errors, including inadvertent or unintentional substitution between twice daily immediate-release and ASTAGRAF XL (once daily extended-release) tacrolimus formulations have been observed in postmarketing surveillance of ASTAGRAF XL in countries where it is approved and marketed. This has led to serious adverse events, including graft rejection, or other adverse reactions, which could be a consequence of either under- or over-exposure to tacrolimus [*see How Supplied (16)*].

Note that ASTAGRAF XL is supplied in short, square bottles as well as in blister cartons containing 5 blister cards of 10 capsules on each card, and contains the statement "ONCE DAILY" on its label.

5.6 Polyoma Virus Infections
Patients receiving immunosuppressants, including ASTAGRAF XL, are at increased risk for opportunistic infections, including polyoma virus infections. Polyoma virus infections in transplant patients may have serious, and sometimes fatal, outcomes. These include polyoma virus-associated nephropathy (PVAN), mostly due to BK virus infection, and JC virus-associated progressive multifocal leukoencephalopathy (PML), which have been observed in patients receiving ASTAGRAF XL [*see Adverse Reactions (6.2)*]. PVAN is associated with serious outcomes, including deteriorating renal function and kidney graft loss. Patient monitoring may help detect patients at risk for PVAN.

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

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

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

5.8 New Onset Diabetes after Transplant
ASTAGRAF XL was shown to cause new onset diabetes mellitus in clinical trials of kidney transplant patients [*see Adverse Reactions (6.1)*]. New onset diabetes after transplantation may be reversible in some patients. Black and Hispanic kidney transplant patients are at an increased risk [*see Use in Specific Populations (8.8)*]. Blood glucose concentrations should be monitored frequently in patients using ASTAGRAF XL.

5.9 Nephrotoxicity
ASTAGRAF XL, like other calcineurin-inhibitors, can cause acute or chronic nephrotoxicity, particularly when used in high doses. Acute nephrotoxicity is most often related to vasoconstriction of the afferent renal arteriole, is characterized by increasing serum creatinine, hyperkalemia, and/or a decrease in urine output, and is typically reversible. Chronic calcineurin-inhibitor nephrotoxicity is associated with increased serum creatinine, decreased kidney graft life, and characteristic histologic changes observed on renal biopsy; the changes associated with chronic calcineurin-inhibitor nephrotoxicity are typically progressive. Patients with impaired renal function should be monitored closely, as the dosage of ASTAGRAF XL may need to be reduced. In patients with persistent elevations of serum creatinine who are unresponsive to dosage adjustments, consideration should be given to changing to another immunosuppressive therapy.

Due to the potential for additive or synergistic impairment of renal function, care should be taken when administering ASTAGRAF XL with drugs that may be associated with renal dysfunction. These include, but are not limited to, aminoglycosides, ganciclovir, amphotericin B, cisplatin, nucleotide reverse transcriptase inhibitors (e.g., tenofovir) and protease inhibitors (e.g., ritonavir, indinavir). Similarly, care should be exercised when administering with CYP3A inhibitors such as antifungal drugs (e.g., ketoconazole), calcium channel blockers (e.g., diltiazem, verapamil), and macrolide antibiotics (e.g., clarithromycin, erythromycin, troleandomycin), which will result in increased tacrolimus whole blood concentrations due to inhibition of tacrolimus metabolism [*see Drug Interactions (7.4, 7.5, 7.6, 7.7)*].

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

Coma and delirium, in the absence of PRES, have also been associated with high plasma concentrations of tacrolimus. Seizures have occurred in patients receiving tacrolimus [*see Adverse Reactions (6.2)*]. Other less severe neurotoxicities, include tremors, parathesias, headache, and other changes in motor function, mental status, and sensory function have also been reported [*see Adverse Reactions (6.1)*]. Tremor and headache have been associated with high whole-blood concentrations of tacrolimus and may respond to dosage adjustment.

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

5.12 Hypertension
Hypertension is a common adverse effect of ASTAGRAF XL therapy and may require antihypertensive therapy [*see Adverse Reactions (6.1)*]. The control of blood pressure can be accomplished with any of the common antihypertensive agents, though careful consideration should be given prior to use of antihypertensive agents associated with hyperkalemia (e.g., potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers) *[see Warnings and Precautions (5.11)]*. Calcium-channel blocking agents may increase tacrolimus blood concentrations and therefore require dosage reduction of ASTAGRAF XL [*see Drug Interactions (7.6)*].

5.13 Use with Sirolimus
The use of ASTAGRAF XL with sirolimus is not recommended in kidney transplant patients. Use of sirolimus with tacrolimus in studies of *de novo* liver transplant recipients was associated with an excess mortality, graft loss and hepatic artery thrombosis (HAT). Use of sirolimus with tacrolimus in heart transplant patients was associated with an increased risk of renal function impairment, wound healing complications, and insulin-dependent post-transplant diabetes mellitus.

5.14 Use with CYP3A Inhibitors and Inducers Including Those That Prolong QT
When coadministering ASTAGRAF XL with strong CYP3A-inhibitors (e.g., telaprevir, boceprevir, ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin) and strong CYP3A inducers (e.g., rifampin, rifabutin) adjustments in the dosing regimen of tacrolimus and subsequent frequent monitoring of tacrolimus whole blood trough concentrations and tacrolimus-associated adverse reactions are recommended [*see Drug Interactions (7)*].

When coadministering ASTAGRAF XL with other substrates and/or inhibitors of CYP3A that also have the potential to prolong the QT interval, a reduction in tacrolimus dose, frequent monitoring of tacrolimus whole blood concentrations, and monitoring for QT prolongation is recommended. Use of tacrolimus with amiodarone has been reported to result in increased tacrolimus whole blood concentrations with or without concurrent QT prolongation.

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

5.16 Pure Red Cell Aplasia
Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. A mechanism for tacrolimus-induced PRCA has not been elucidated. All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease, or concomitant medications associated with PRCA. If PRCA is diagnosed, discontinuation of ASTAGRAF XL should be considered.

6 ADVERSE REACTIONS
The following serious and otherwise important adverse drug reactions are discussed in greater detail in other sections of labeling:
- Lymphoma and Other Malignancies [*see Warnings and Precautions (5.2)*]
- Serious Infections [*see Warnings and Precautions (5.3)*]
- Polyoma Virus Infections [*see Warnings and Precautions (5.6)*]
- Cytomegalovirus (CMV) Infections [*see Warnings and Precautions (5.7)*]
- New Onset Diabetes after Transplant [*see Warnings and Precautions (5.8)*]
- Nephrotoxicity [*see Warnings and Precautions (5.9)*]

- Neurotoxicity [*see Warnings and Precautions (5.10)*]
- Hyperkalemia [*see Warnings and Precautions (5.11)*]
- Hypertension [*see Warnings and Precautions (5.12)*]
- Pure Red Cell Aplasia [*see Warnings and Precautions (5.16)*]

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.

The data described below reflect exposure to ASTAGRAF XL in 545 renal transplant recipients exposed to ASTAGRAF XL for periods up to two years [*see Clinical Studies (14)*].

The most frequent diseases leading to transplantation were glomerulonephritis, polycystic kidney disease nephrosclerosis/hypertensive nephropathy, and diabetic nephropathy in both studies.

Study 1: With Basiliximab Induction

The proportion of patients who discontinued treatment due to adverse reactions was 9% in the ASTAGRAF XL arm and 11% in the Prograf control arm 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. The most common (≥ 30%) adverse reactions observed in the ASTAGRAF XL group were: diarrhea, constipation, nausea, peripheral edema, tremor and anemia.

Study 2: Without Induction

The proportion of patients who discontinued treatment due to adverse reactions was 13% in the ASTAGRAF XL arm and 11% in the Prograf control arm through 12 months of treatment. The most common adverse reactions leading to discontinuation in ASTAGRAF XL-treated patients were related to infections, graft dysfunction, renal vascular/ischemic conditions and diabetes. The most common (≥30%) adverse reaction observed in the ASTAGRAF XL group was anemia.

Information on selected significant adverse reactions observed during Studies 1 and 2 are summarized below.

New Onset Diabetes After Transplant (NODAT)

New onset diabetes after transplantation (defined by the composite occurrence of ≥ 2 fasting plasma glucose values that were > 126 mg/dL at ≥ 30 days apart, insulin use for ≥ 30 consecutive days, oral hypoglycemic use for ≥ 30 consecutive days, oral hypoglycemic use for ≥ 30 consecutive days, and/or HbA_{1c} ≥ 6.5%) is summarized in Table 2 below for Study 1 and Study 2 through one year post-transplant.

Table 2. Composite NODAT Through 1 Year Post-Transplant in Studies 1 and 2

	Study 1		Study 2	
	ASTAGRAF XL n (%) (N=162)	Prograf n (%) (N=151)	ASTAGRAF XL n (%) (N=288)	Prograf n (%) (N=299)
Composite NODAT	58 (36)	53 (35)	105 (37)	90 (30)
≥ 2 Fasting Plasma Glucose Values ≥ 126 mg/dL ≥ 30 days apart	42 (26)	35 (23)	51 (18)	47 (16)
Insulin use ≥ 30 consecutive days	10 (6)	12 (8)	29 (10)	29 (10)
Oral hypoglycemic use ≥ 30 consecutive days	22 (14)	13 (9)	20 (7)	23 (8)
HbA_{1c} ≥ 6.5%	31 (19)	33 (22)	48 (17)	39 (13)

Infections

Adverse reactions of infectious etiology were reported based on clinical assessment by physicians. The causative organisms for these reactions are identified when provided by the physician. The overall number of infections, serious infections, and select infections with identified etiology reported in patients treated with ASTAGRAF XL or the control in Studies 1 and 2 are shown in Table 3.

Table 3. Overall Infections and Select Infections by Treatment Group in Studies 1 and 2 Through One Year Post-Transplant

	Study 1		Study 2	
	ASTAGRAF XL n (%) (N=214)	Prograf n (%) (N=212)	ASTAGRAF XL n (%) (N=331)	Prograf n (%) (N=336)
All Infections	148 (69)	146 (69)	228 (69)	216 (64)
Serious Infections	48 (22)	49 (23)	79 (24)	64 (19)
Bacterial Infections	18 (8)	25 (12)	125 (38)	137 (41)
Respiratory Infections	73 (34)	65 (31)	75 (23)	74 (22)
Cytomegalovirus Infections	21 (10)	24 (11)	38 (12)	21 (6)
Polyomavirus Infections	6 (3)	10 (5)	7 (2)	1 (0)
Gastroenteritis	16 (7)	6 (3)	16 (5)	8 (2)

Studies 1 and 2 were not designed to support comparative claims for ASTAGRAF XL for the adverse reactions reported in this table.

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 ITT population in Studies 1 and 2 are shown in Table 4.

Table 4. Estimated Glomerular Filtration Rate (mL/min/1.73m²) by MDRD Formula at 12 Months Post-Transplant

	Study 1		Study 2	
	ASTAGRAF XL (n=201)	Prograf (n=202)	ASTAGRAF XL (n=287)	Prograf (n=300)
Month 1 Baseline Mean (SD)	56 (20)	56 (21)	51 (19)	52 (20)
Month 12 LOCF[a]				
Mean (Standard deviation)	58 (21)	56 (23)	52 (20)	55 (19)
Median (Min-Max)	56 (0, 177)	57 (0, 120)	54 (0, 116)	54 (0, 134)
Mean Difference XL-Prograf[b]	**+2.3 (-1.2, +5.8)**		**-1.8 (-4.6, +0.8)**	

a) Subject's last observation carried forward (LOCF) for missing data at Month 1; patients who died, lost the graft or were lost to follow-up are imputed as zeroes

b) Tacrolimus XL-Prograf treatment mean difference results of analysis of covariance model with Month 1 Baseline as a covariate.

The incidence of adverse reactions that occurred in ≥ 15% of ASTAGRAF XL-treated patients compared to control through one year of treatment in Studies 1 and 2 are shown in Table 5.

Table 5. Adverse Events Occurring in ≥ 15% of ASTAGRAF XL-Treated Kidney Transplant Patients Through One year Post Transplant in Studies 1 or 2[a]

	Study 1		Study 2	
Adverse Reactions	ASTAGRAF XL n (%) (N=214)	Prograf n (%) (N=212)	ASTAGRAF XL n (%) (N=331)	Prograf n (%) (N=336)
Anemia	70 (33)	61 (29)	103 (31)	87 (26)
Constipation	85 (40)	68 (32)	45 (14)	60 (18)
Diarrhea	96 (45)	94 (44)	88 (27)	103 (31)
Fatigue	34 (16)	22 (10)	7 (2)	6 (2)
Graft Dysfunction	29 (14)	45 (21)	57 (17)	56 (17)
Headache	46 (22)	50 (24)	39 (12)	33 (10)
Hyperglycemia	34 (16)	39 (18)	61 (18)	65 (19)
Hyperkalemia	43 (20)	49 (23)	50 (15)	49 (15)
Hyperlipidemia	35 (16)	36 (17)	23 (7)	28 (8)
Hypertension	59 (28)	63 (30)	80 (24)	76 (23)
Hypomagnesemia	52 (24)	57 (27)	9 (3)	12 (4)
Hypophosphatemia	50 (23)	59 (28)	15 (5)	22 (7)
Increased Blood Creatinine	40 (19)	49 (23)	54 (16)	63 (19)
Insomnia	52 (24)	60 (28)	29 (9)	34 (10)
Leukopenia	35 (16)	33 (16)	51 (15)	37 (11)
Nausea	76 (36)	75 (35)	51 (15)	42 (13)
Peripheral Edema	76 (36)	73 (34)	38 (12)	49 (15)
Tremor	75 (35)	73 (34)	58 (18)	58 (17)
Urinary Tract Infection	34 (16)	53 (25)	7 (2)	10 (3)
Urinary Tract Infection (bacterial)	1 (1)	6 (3)	86 (26)	102 (30)
Vomiting	53 (25)	53 (25)	42 (13)	43 (13)

a) Studies 1 and 2 were not designed to support comparative claims for ASTAGRAF XL for the adverse reactions reported in this table.

Less Frequently Reported Adverse Reactions (<15%) by System Organ Class

The following adverse reactions were also reported in clinical studies of kidney transplant recipients who were treated with ASTAGRAF XL.

Blood and Lymphatic System Disorders
Coagulopathy, hemolytic anemia, leukocytosis, neutropenia, pancytopenia, thrombocytopenia, thrombotic microangiopathy

Cardiac Disorders
Angina pectoris, atrial fibrillation, atrial flutter, bradycardia, cardiac arrest, congestive cardiac failure, hypertrophic cardiomyopathy, myocardial ischemia, myocardial infarction, pericardial effusion, tachycardia, ventricular extrasystoles

Ear Disorders
Hearing loss, otitis (media and externa), tinnitus

Eye Disorders
Vision blurred, conjunctivitis

Gastrointestinal Disorders
Abdominal distension, abdominal pain, aphthous stomatitis, ascites, colitis, dyspepsia, esophagitis, flatulence, gastritis, gastroesophageal reflux disease, gastrointestinal hemorrhage, ileus, impaired gastric emptying, pancreatitis, stomach ulcer

General Disorders and Administration Site Conditions
Anasarca, asthenia, edema

Hepatobiliary Disorders
Abnormal hepatic function, cholestasis, hepatitis (acute and chronic), hepatotoxicity

Infections and Infestations
Condyloma acuminatum, Epstein-Barr virus infection, tinea versicolor

Injury, Poisoning and Procedural Complications
Fall

Investigations
Abnormal electrocardiogram T wave, increased blood lactate dehydrogenase, increased blood urea,
increased hematocrit, increased hepatic enzyme, increased international normalized ratio, weight fluctuation

Metabolism and Nutrition Disorders
Anorexia, dehydration, fluid overload, hypercalcemia, hyperphosphatemia, hyperuricemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, hypoproteinemia, metabolic acidosis

Musculoskeletal and Connective Tissue Disorders
Arthralgia, osteopenia, osteoporosis

Neoplasms
Bladder cancer, Kaposi's sarcoma, non-melanoma skin cancer, papillary thyroid cancer

Nervous System Disorders
Aphasia, carpal tunnel syndrome, cerebral infarction, cerebral ischemia, convulsion, dizziness, hypoesthesia, neurotoxicity, paresthesia, peripheral neuropathy, somnolence, syncope

Psychiatric Disorders
Agitation, anxiety, confusional state, depression, hallucination, mental status changes, mood swings, nightmare

Renal and Urinary Disorders
Anuria, hematuria, oliguria, proteinuria, renal failure, renal graft dysfunction, renal tubular necrosis, toxic nephropathy, urinary incontinence, urinary retention

Respiratory, Thoracic and Mediastinal Disorders
Acute respiratory distress syndrome, allergic rhinitis, dyspnea, emphysema, hiccups, lung infiltration, pulmonary edema, productive cough, respiratory failure

Skin and Subcutaneous Tissue Disorders
Acne, alopecia, dermatitis, hyperhidrosis, hypotrichosis, pruritus, rash

Vascular Disorders
Deep vein thrombosis, flushing, hemorrhage, hypotension, orthostatic hypotension

6.2 Postmarketing Experience

The following adverse reactions have been reported from worldwide marketing experience with tacrolimus. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders
Agranulocytosis, decreased blood fibrinogen, disseminated intravascular coagulation, hemolytic uremic syndrome, prolonged activated partial thromboplastin time, pure red cell aplasia [*see Warnings and Precautions (5.16)*], thrombotic thrombocytopenic purpura

Cardiac Disorders
QT prolongation, supraventricular extrasystoles, supraventricular tachycardia, Torsade de Pointes, ventricular fibrillation

Eye Disorders
Blindness, photophobia, optic atrophy

Gastrointestinal Disorders
Dysphagia, gastrointestinal perforation, intestinal obstruction, peritonitis

General Disorders
Multi-organ failure

Hepatobiliary Disorders
Bile duct stenosis, cholangitis, cirrhosis, hepatic failure, hepatic necrosis, hepatic steatosis, jaundice, venoocclusive liver disease

Immune disorders
Graft versus host disease (acute and chronic)

Musculoskeletal and Connective Tissue Disorders
Myalgia, polyarthritis, rhabdomyolysis

Neoplasms
Lymphoma including EBV-associated lymphoproliferative disorder, hepatosplenic T-cell lymphoma, PTLD [*see Warnings and Precautions (5.2)*]; leukemia, melanoma

Nervous System Disorders
Coma, dysarthria, flaccid paralysis, hemiparesis, mutism, nerve compression, posterior reversible encephalopathy syndrome (PRES) [*see Warnings and Precautions (5.10)*], progressive multifocal leukoencephalopathy (PML) sometimes fatal [*see Warnings and Precautions (5.6)*], quadriplegia, status epilepticus

Renal and Urinary Disorders
Hemorrhagic cystitis

Respiratory, Thoracic and Mediastinal Disorders
Interstitial lung disease, pulmonary hypertension

Skin and Subcutaneous Tissue Disorders
Hyperpigmentation, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria

7 DRUG INTERACTIONS

Since tacrolimus is metabolized mainly by CYP3A enzymes, drugs or substances known to inhibit these enzymes may increase tacrolimus whole blood concentrations. Drugs known to induce CYP3A enzymes may decrease tacrolimus whole blood concentrations [*see Warnings and Precautions (5.14), Clinical Pharmacology (12.3)*].

7.1 Mycophenolic Acid Products

With a given dose of mycophenolic acid (MPA) products, 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. Clinicians should monitor for MPA associated adverse events and reduce the dose of concomitantly administered mycophenolic acid products, if needed.

7.2 Grapefruit Juice

Grapefruit juice inhibits CYP3A-enzymes resulting in increased tacrolimus whole blood trough concentrations, and patients should avoid eating grapefruit or drinking grapefruit juice in combination with ASTAGRAF XL [*see Dosage and Administration (2.4)*].

7.3 Alcohol

Consumption of alcohol with ASTAGRAF XL may increase the rate of release of tacrolimus and/or adversely alter the pharmacokinetic properties and the effectiveness and safety of ASTAGRAF XL. Therefore, alcoholic beverages should not be consumed with ASTAGRAF XL [*see Dosage and Administration (2.4)*].

7.4 Protease Inhibitors

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

7.5 Antifungal Agents

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

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

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

7.6 Calcium Channel Blockers

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

7.7 Antibacterials

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

7.8 Antimycobacterials

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

7.9 Anticonvulsants

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

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

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

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

7.11 Gastric Acid Suppressors/Neutralizers

Lansoprazole and omeprazole, the proton pump inhibitors (PPIs), as CYP2C19 and CYP3A4 substrates, share the same CYP3A4 system with tacrolimus for their hepatic elimination, and may potentially competitively inhibit the CYP3A4 metabolism of tacrolimus and thereby substantially increase tacrolimus whole blood concentrations, especially in transplant patients who are intermediate or poor CYP2C19 metabolizers in which the PPIs metabolic pathway shifts from 2C19 to 3A4, as compared to those patients who are efficient CYP2C19 metabolizers.

Cimetidine, a CYP2C19 and CYP3A4 inhibitor, may also inhibit the CYP3A4 metabolism of tacrolimus and thereby substantially increase tacrolimus whole blood concentrations.

Coadministration with magnesium and aluminum hydroxide antacids increase tacrolimus whole blood concentrations. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these drugs and tacrolimus are used concomitantly.

7.12 Other Drugs

Amiodarone, bromocriptine, nefazodone, metoclopramide, danazol, ethinyl estradiol and methylprednisolone may inhibit CYP3A metabolism of tacrolimus and increase tacrolimus whole blood concentrations. Monitoring of blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these drugs and tacrolimus are coadministered.

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 arteriosis, interrupted ossification of vertebral arch, vertebral and rib malformations, omphalocele, and gallbladder agenesis) and developmental variations. In pregnant rats, tacrolimus at oral doses of 3.2 mg/kg (2.6 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 the drug, taking into account the importance of drug to the mother.

8.4 Pediatric Use

The safety and efficacy of ASTAGRAF XL in pediatric kidney transplant patients < 16 years of age has not been established.

8.5 Geriatric Use

Clinical studies of ASTAGRAF XL did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, 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, frequent monitoring of renal function is recommended; tacrolimus dosage should be reduced if indicated [*see Warnings and Precautions (5.9), 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. Frequent monitoring of tacrolimus trough concentrations is warranted in patients with hepatic impairment [*see Clinical Pharmacology (12.3)*].

8.8 Race

The data from ASTAGRAF XL administration in kidney transplant patients indicate that African-American patients may require higher doses to attain comparable trough concentrations compared to Caucasian patients [*see Dosage and Administration (2.1), Clinical Pharmacology (12.3), Clinical Studies (14)*].

10 OVERDOSAGE

Postmarketing cases of overdose with tacrolimus have been reported. Some of these cases were symptomatic with adverse reactions including 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.

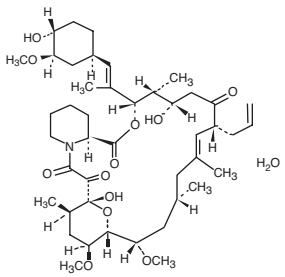
In acute oral toxicity studies, mortality was observed at or above the following doses: in orally administered adult rats, 80-fold the recommended human dose for adults; in orally administered immature rats, 18-fold the maximum adult human dose. All doses are based on body surface area conversions (mg/m^2).

11 DESCRIPTION

ASTAGRAF XL 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. The capsule shell also has a trace of printing ink, Opacode S-1-15083 Red.

Tacrolimus is the active ingredient in ASTAGRAF XL. Tacrolimus is a macrolide 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

Table 6 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 6. Pharmacokinetic Parameters of ASTAGRAF XL Once Daily in Healthy Subjects and in Kidney Transplant Patients (Under Fasted Conditions), and Statistical Comparison of PK Parameters with Prograf® Twice Daily

Population	N	ASTAGRAF XL Dose[a]	Day[b]	Pharmacokinetic Parameters of ASTAGRAF XL and ASTAGRAF XL:Prograf ratio (90% CI for ratio)[e]			
				C_{max}[c] (ng/mL)	T_{max}[d] (hr)	AUC_{24}[c] (ng•hr/mL)	C_{24}[g] (ng/mL)
Healthy Subjects	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
			Ratio (90% CI)				
			Day 1	0.67 (0.59 - 0.75)		1.02 (0.91 - 1.13)	0.81 (0.72 - 0.92)
			Day 10	0.74 (0.69 - 0.80)		0.93 (0.87-0.99)	0.87 (0.81 - 0.94)
Adult Kidney *De novo*[f]	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
			Ratio (90% CI)				
			Day 1	0.86 (0.63 - 1.19)		0.84 (0.63 - 1.12)	0.85 (0.59 - 1.17)
			Day 3	0.93 (0.71 - 1.21)		1.05 (0.82 - 1.33)	1.04 (0.79 - 1.36)
			Day 7	1.14 (0.95 - 1.38)		1.22 (1.02 - 1.46)	1.14 (0.90 - 1.44)
			Day 14	1.27 (1.03 - 1.57)		1.21 (1.02 - 1.42)	0.99 (0.82 - 1.20)
Adult Kidney (≥ 6 months post-transplant)	60	5.2 mg/day[h]	Day 14[h]	16.1 ± 5.3	2.0 [1.0 - 6.0]	222 ± 64	6.7 ± 1.9[i]

a) Healthy adult subjects (actual administered dose of ASTAGRAF XL and Prograf); Adult *de novo* kidney transplant patients (actual group mean dose of ASTAGRAF XL, corresponding doses for Prograf on Days 1, 3, 7 and 14 were 0.20, 0.18, 0.16, and 0.17 mg/kg/day, respectively)
b) Day of ASTAGRAF XL treatment and PK profiling
c) Arithmetic means ± S.D.
d) Median [range]
e) Ratio of geometric least square means
f) PK substudy of Study 2
g) Tacrolimus trough concentration before the next dose
h) Same daily dose of ASTAGRAF XL for 14 day period
i) The correlation coefficient of AUC_{24} to C_{min} r= 0.88

In *de novo* adult kidney transplant recipients, the tacrolimus systemic exposure, as assessed by dose-adjusted AUC_{24}, for ASTAGRAF XL once daily on Day 1 post-transplant was 16% lower when compared with Prograf twice daily. By Day 3 post-transplant, the dose-adjusted AUC_{24} was similar between the two formulations. On Day 14, the dose-adjusted AUC_{24} was 21% higher than Prograf, at comparable trough concentrations (C_{24}).

Due to intersubject variability in tacrolimus pharmacokinetics, individualization of dosing regimen is necessary for optimal therapy [*see Dosage and Administration (2.5)*].

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

Absorption

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 Prograf, 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

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

In a mass balance study of IV-administered radiolabeled tacrolimus to 6 healthy subjects, the mean recovery of radiolabel was 77.8 ± 12.7% with the feces accounting for 92.4 ± 1.0% of the total recovery. The elimination half-life based on radioactivity was 48.1 ± 15.9 hours whereas it was 43.5 ± 11.6 hours based on tacrolimus concentrations. The mean clearance of radiolabel was 0.029 ± 0.015 L/hr/kg and the mean clearance of tacrolimus was 0.029 ± 0.009 L/hr/kg. When administered orally (radiolabeled tacrolimus), 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 ASTAGRAF XL daily for 10 days was 37.9 ± 3.4 hours in 24 healthy subjects.

Specific Populations

Renal and Hepatic Impairment

Renal Impairment

Tacrolimus pharmacokinetics following a single administration of Prograf 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 12.0 ± 2.4 mg/dL, respectively) prior to their kidney transplant. The pharmacokinetic parameters obtained were similar for both groups. The mean clearance of tacrolimus in patients with renal dysfunction was similar to that in healthy subjects [*see Dosage and Administration (2.2), Use in Specific Populations (8.6)*].

Hepatic Impairment

Tacrolimus pharmacokinetics have been determined in six patients with mild hepatic dysfunction (mean Pugh score: 6.2) following single IV and oral administrations of Prograf. The mean clearance of tacrolimus in patients with mild hepatic dysfunction was not substantially different from that in healthy subjects. Tacrolimus pharmacokinetics were studied in 6 patients with severe hepatic dysfunction (mean Pugh score: >10). The mean clearance was substantially lower in patients with severe hepatic dysfunction, irrespective of the route of administration [*see Dosage and Administration (2.3) and Use in Specific Populations (8.7)*].

Race

African-American patients may require higher ASTAGRAF XL doses to attain similar trough concentrations as Caucasian patients [*see Dosage and Administration (2.1), Use in Specific Populations (8.8), Clinical Studies (14)*].

The pharmacokinetics of tacrolimus have been studied following single IV and oral administration of Prograf in 10 African-American, 12 Latino-American, and 12 Caucasian healthy subjects. There were no significant pharmacokinetic differences among the three ethnic groups following a 4-hour IV infusion of 0.015 mg/kg. However, after single oral administration of 5 mg, mean (±SD) tacrolimus C_{max} in African-Americans (23.6±12.1 ng/mL) was 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).

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 doses 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

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

Rifampin

In a study of 22 healthy male subjects, coadministration of a single 10 mg ASTAGRAF XL dose with rifampin (600 mg/day) for 12 days decreased mean AUC_{inf} and C_{max} of tacrolimus by 56% and 46%, respectively [*see Drug Interactions (7.8)*].

Ketoconazole

In a study of 24 healthy male subjects, coadministration of a 4 mg ASTAGRAF XL dose with ketoconazole (400 mg/day) for 9 days increased the mean AUC_{inf} and C_{max} of tacrolimus 7.5-fold and 4.6-fold, respectively [*see Drug Interactions (7.5)*].

Telaprevir

In a single dose study in 9 healthy subjects, coadministration of tacrolimus (0.5 mg single dose, as tacrolimus immediate-release) with telaprevir (750 mg three times daily for 13 days) increased the tacrolimus dose normalized C_{max} by 9.3-fold and AUC by 70-fold compared to tacrolimus alone [*see Drug Interactions (7.4)*].

Boceprevir

In a single dose study in 12 subjects, coadministration of tacrolimus (0.5 mg single dose, as tacrolimus immediate-release) with boceprevir (800 mg three times daily for 11 days) increased tacrolimus C_{max} by 9.9-fold and AUC by 17-fold compared to tacrolimus alone [*see Drug Interactions (7.4)*].

Nelfinavir

Based on a clinical study of 5 liver transplant recipients, coadministration of tacrolimus (as tacrolimus immediate-release) with nelfinavir increased blood concentrations of tacrolimus significantly and, as a result, a reduction in the tacrolimus dose by an average of 16-fold was needed to maintain mean trough tacrolimus blood concentrations of 9.7 ng/mL. It is recommended to avoid concomitant use of tacrolimus and nelfinavir unless the benefits outweigh the risks [*see Drug Interactions (7.4)*].

Magnesium-aluminum-hydroxide
In a single-dose crossover study in healthy subjects, coadministration of tacrolimus (as immediate-release) and magnesium-aluminum-hydroxide resulted in a 21% increase in the mean tacrolimus AUC and a 10% decrease in the mean tacrolimus C_{max} relative to tacrolimus administration alone [*see Drug Interactions (7.11)*].

Voriconazole (see complete prescribing information for VFEND®)
Repeat oral dose administration of voriconazole (400 mg every 12 hours for one day, then 200 mg every 12 hours for 6 days) increased tacrolimus (0.1 mg/kg single dose, as tacrolimus immediate-release formulation) C_{max} and AUC_τ in healthy subjects by an average of 2-fold (90% CI: 1.9, 2.5) and 3-fold (90% CI: 2.7, 3.8), respectively [*see Drug Interactions (7.5)*].

Posaconazole (see complete prescribing information for Noxafil®)
Repeat oral administration of posaconazole (400 mg twice daily for 7 days) increased tacrolimus (0.05 mg/kg single dose, as immediate-release formulation) C_{max} and AUC in healthy subjects by an average of 2-fold (90% CI: 2.01, 2.42) and 4.5-fold (90% CI 4.03, 5.19), respectively [*see Drug Interactions (7.5)*].

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 (C12hr) by 26% in healthy adult subjects when tacrolimus (2 doses of 0.1 mg/kg 12 hours apart, as immediate-release formulation) 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 (7.5)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were conducted in male and female rats and mice. In the 80-week mouse oral study and in the 104-week rat oral study, no relationship of tumor incidence to tacrolimus dosage was found. The highest dose used in the mouse was 3.0 mg/kg/day (0.49 times the AUC at the maximum clinical dose of 0.2 mg/kg/day) and in the rat was 5.0 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 (5.4)*].

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/m²/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.

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

Tacrolimus given orally at 1.0 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 embryolethality and adverse effects on female reproduction. Effects on female reproductive function (parturition) and embryolethal effects were indicated by a higher rate of pre-implantation loss and increased numbers of undelivered and nonviable pups. When given at 3.2 mg/kg (2.6 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

The efficacy and safety of ASTAGRAF XL in *de novo* kidney transplantation were assessed in two randomized, multicenter, active-controlled trials (Study 1 and Study 2).

Study 1 -- Induction with Basiliximab
Study 1 was a randomized, open-label trial of ASTAGRAF XL (N=214) compared to Prograf (N=212), of 12 months duration conducted primarily in the US. Patients were stratified by donor type (living or deceased) and transplant history (primary or retransplant). All patients received basiliximab induction and concomitant treatment with MMF and corticosteroids. The population was 17 to 77 years of age, the mean age was 48 years; 64% of the study population was male; 73% were Caucasian, 22% were African-American, 2% were Asian, and 3% were categorized as other races. Living donors provided 49% of the organs. The most frequent diseases leading to transplantation were balanced between the groups and included nephrosclerosis/hypertensive nephropathy, diabetic nephropathy, glomerulonephritis, and polycystic kidney disease. Premature discontinuation from treatment at the end of one year occurred in 14% of ASTAGRAF XL patients and 16% of Prograf patients, primarily due to adverse reactions.

Study 2 -- No Induction
Study 2 was a randomized, double-blind trial, (designed to remain double-blind until the last patient enrolled had completed 24 weeks on study treatment) of ASTAGRAF XL (N = 331) compared to Prograf (N = 336), of 12 months duration conducted outside the US. The patient treatment assignments remained blinded for 12 months for 96% of the patients participating in the trial. Patients with a high immunologic risk defined as a 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 recipients of donor kidneys with cold ischemia time > 30 hours, or donor kidneys from a non heart-beating donor. All patients received concomitant treatment with MMF and corticosteroids without antibody 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. Premature discontinuation from treatment at the end of one year occurred in 24% of ASTAGRAF XL patients and 19% of Prograf patients, primarily due to adverse reactions.

Tacrolimus Dosing
In Study 1, the actual tacrolimus starting dose (given any time up to Day 2 post-transplant) of ASTAGRAF XL was higher than Prograf (0.15 mg/kg versus 0.1 mg/kg). In Study 2, the actual tacrolimus doses on Day 0 (0.1 mg/kg/day pre-operative) and Day 1 (0.2 mg/kg/day post-operative) were comparable between ASTAGRAF XL and Prograf. Thereafter, to achieve comparable mean tacrolimus trough concentrations (C_{24}), higher total mean daily doses of tacrolimus were required for ASTAGRAF XL than Prograf (on average, by 15% in Study 1 and by 25% in Study 2).

In Study 1, African-American patients required higher ASTAGRAF XL doses to attain similar trough concentrations as Caucasian patients (Table 7).

Table 7. ASTAGRAF XL Doses 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

Table 8 shows the observed tacrolimus whole blood trough concentrations measured at protocol-specified time points for ASTAGRAF XL in Study 1 and Study 2. In Study 1, the protocol-specified target tacrolimus whole blood trough concentrations (C_{trough}) were 7-16 ng/mL for the first three months and 5-15 ng/mL thereafter.

Approximately 80% of ASTAGRAF XL patients maintained tacrolimus whole trough blood concentrations between 5 to 17 ng/mL during Months 1 through 2 and, then, between 4 to 12 ng/mL from Months 3 through 12. In Study 2, the protocol-specified target tacrolimus whole blood trough concentrations (C_{trough}) were 10-15 ng/mL during the first month, 5-15 ng/mL from Month 2 to Month 6, and 5-15 ng/mL thereafter. Approximately 80% of ASTAGRAF XL patients maintained tacrolimus whole trough blood concentrations between 6 to 20 ng/mL during Months 1 through 2 and, then between 6 to 14 ng/mL from Months 3 through 12.

Table 8. Observed Tacrolimus Whole Blood Trough Concentrations for ASTAGRAF XL Kidney Transplant Patients Evaluated in Studies 1 and 2

Scheduled Visit	Median (P10-P90[a]) tacrolimus whole blood trough concentrations (ng/mL)	
	Study 1	Study 2
Day 3	9.6 (4.9 - 20.2)	13.8 (6.5 - 25.5)
Day 7	9.1 (4.4 - 16.8)	10.1 (5.5 - 17.3)
Day 14	10.0 (5.7 - 16.9)	10.8 (6.7 - 17.9)
Month 1	10.5 (5.6 - 17.1)	12.0 (7.5 - 17.6)
Month 2	9.4 (6.1 - 14.2)	11.1 (6.6 - 17.3)
Month 6	7.7 (4.4 - 11.5)	9.2 (5.7 - 13.5)
Month 12	7.2 (3.8 - 10.4)	8.0 (5.1 - 13.8)

a) 10th to 90th Percentile: range of C_{trough} that excludes lowest 10% and highest 10% of C_{trough}

MMF Dosing
In Study 1, patients in each group started MMF at 1 gram twice daily. The MMF dose was reduced to less than 2 grams per day by Month 12 in 56% of patients in the ASTAGRAF XL group (Table 9). Approximately 57% of the MMF dose reductions were because of adverse reactions in the ASTAGRAF XL group [*see Adverse Reactions (6.1)*].

In Study 2, patients in each group received MMF at 1 gram twice daily starting preoperatively. In a majority of the patients, the MMF dose was reduced to 0.5 grams twice daily starting after day 14 (Table 9).

Table 9. Distribution of ASTAGRAF XL/MMF Patients (%) Based on Time-Averaged MMF Dose[a]

Time period (Days)	Study 1 Time-averaged MMF dose[a]			Study 2 Time-averaged MMF dose[a]		
	Less than 2.0 (g/day)	2.0 (g/day)	Greater than 2.0 (g/day)	Less than 2.0 (g/day)	2.0 (g/day)	Greater than 2.0 (g/day)
1-30	30%	64%	6%	82%	17%	0%
1-90	42%	52%	7%	93%	7%	0%
1-180	52%	44%	4%	94%	6%	0%
1-365	56%	41%	3%	95%	5%	0%

a) Time-averaged MMF dose = (total MMF dose)/(duration of treatment). A time-averaged MMF dose of 2.0 grams per day means that the MMF dose was not reduced in those patients during the time period.

Efficacy Results
In Study 1, the efficacy failure rate including patients who developed biopsy-proven acute rejection (BPAR), graft failure, death, and/or lost to follow-up at 12 months, as well as the rates of the individual events, is shown in Table 10 for the intent to treat (ITT) population.

Table 10. Incidence of BPAR, Graft Loss, Death or Lost to Follow-up at 12 Months

	ASTAGRAF XL/MMF	Tacrolimus Immediate- Release/MMF
	(N=214)	(N=212)
Efficacy Failure	30 (14.0%)	32 (15.1%)
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%)
Treatment Difference of efficacy failure compared to tacrolimus immediate-release/MMF group (95% CI[a])	-1.1% (-7.8%, +5.6%)	

a) 95% confidence interval calculated using normal approximation

In Study 2, the Efficacy Failure rate including patients who developed biopsy-proven acute rejection (BPAR), graft failure, death, and/or lost to follow-up at 12 months, as well as the rates of the individual events, is shown in Table 11 for the ITT population. About 1% of randomized patients were not transplanted and were not included in the ITT analysis.

Table 11. Incidence of BPAR, Graft Loss, Death or Lost to Follow-up at 12 Months

	ASTAGRAF XL/MMF	Tacrolimus Immediate-Release/MMF
	(N=331)	(N=336)
Efficacy Failure	93 (28%)	78 (23%)
Biopsy Proven Acute Rejection	68 (21%)	54 (16%)
Graft loss	28 (9%)	24 (7%)
Death	10 (3%)	8 (2%)
Lost to follow-up	4 (1%)	7 (2%)
Treatment Difference of efficacy failure compared to tacrolimus immediate-release/ MMF group (95% CI[a])	+4.9% (-1.7%, +11.5%)	

a) 95% confidence interval calculated using normal approximation

16 HOW SUPPLIED/STORAGE AND HANDLING

ASTAGRAF XL is supplied in short, square bottles as well as in blister cartons; the statement 'ONCE DAILY' appears on its label.
ASTAGRAF XL and tacrolimus immediate-release capsules are further differentiated by different color schemes.

ASTAGRAF XL (tacrolimus extended-release capsules)

0.5 mg
Oblong capsule with a light yellow cap and orange body. Capsule is branded with red "➤647" on capsule body and "0.5 mg" on capsule cap. The capsule is supplied in 30-count short, square bottles (NDC 0469-0647-73) with brown caps and in blister cartons containing 5 blister cards of 10 capsules on each card (NDC 0469-0647-11). Both bottle and blister packaging are branded with matching brown stripes.

ASTAGRAF XL (tacrolimus extended-release capsules)
1 mg
Oblong capsule with a white cap and orange body. Capsule is branded with red " 677" on capsule body and "1 mg" on capsule cap. The capsule is supplied in 30-count short, square bottles (NDC 0469-0677-73) with blue caps and in blister cartons containing 5 blister cards of 10 capsules on each card (NDC 0469-0677-11). Both bottle and blister packaging are branded with matching blue stripes.

ASTAGRAF XL (tacrolimus extended-release capsules)
5 mg
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. The capsule is supplied in 30-count short, square bottles (NDC 0469-0687-73) with orange caps and in blister cartons containing 5 blister cards of 10 capsules on each card (NDC 0469-0687-11). Both bottle and blister packaging are branded with matching orange stripes.

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
See FDA-approved patient labeling (Medication Guide)

Administration
Advise patients to:
- Inspect your ASTAGRAF XL medicine when you 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, speak to your doctor or pharmacist as soon as possible to make sure that you have the right medicine.
- Take ASTAGRAF XL at the same time everyday 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.
- Not take ASTAGRAF XL with an alcoholic beverage [*see Dosage and Administration (2.4) and Drug Interactions (7.3)*]
- Take a missed dose of ASTAGRAF XL as soon as the patient remembers but not more than 14 hours after the scheduled time (i.e. for a missed 8AM dose, take by 10PM). Beyond the 14-hour timeframe, the patient should 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 they are at increased risk of developing lymphomas and other malignancies, particularly of the skin, due to immunosuppression. Advise patients to limit exposure to sunlight and ultraviolet (UV) light by wearing protective clothing and use a sunscreen with a high protection factor [*see Boxed Warning, Warnings and Precautions (5.2)*].

Increased Risk of Infection
Inform patients they are at increased risk of developing a variety of infections, including opportunistic infections, due to immunosuppression and to contact their physician if they develop any symptoms of infection [*see Boxed Warning, Warnings and Precautions (5.3, 5.6, 5.7)*].

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 (5.8)*].

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 (5.9)*].

Neurotoxicity
Inform patients that they are at risk of developing adverse neurologic effects including seizure, altered mental status, and tremor. Advise patients to contact their physician should they develop vision changes, delirium, or tremors [*see Warnings and Precautions (5.10)*].

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 (5.11)*].

Hypertension
Inform patients that ASTAGRAF XL can cause high blood pressure which may require treatment with anti-hypertensive therapy [*see Warnings and Precautions (5.12)*].

Drug Interactions
Instruct patients to tell their health care 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 (5.14), Drug Interactions (7)*].

Pregnant Women and Nursing Mothers
Instruct patients to tell their healthcare provider if they plan to become pregnant or breast-feed their infant [*see Use in Specific Populations (8.1, 8.3)*]

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 (5.15)*].

Rx only

Product of Japan

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

Marketed by:

Astellas Pharma US, Inc.
Northbrook, IL 60062

Date: July 2013
11K084-ADV-RM-PI

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:

1. **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).
2. **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
   - sweats or chills
   - cough or flu-like symptoms
   - muscle aches
   - warm, red, or painful areas on your skin
3. **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.
ASTAGRAF XL is not for use with medicines called cyclosporine (e.g., Neoral®, Sandimmune®, and Gengraf®).
It is not known if ASTAGRAF XL is safe and effective when used with sirolimus (Rapamune®) in people who have had kidney transplants.
It is not known if ASTAGRAF XL is safe and effective in children under 16 years of age who have had kidney transplants.

What should I tell my doctor before taking 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.
- have 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.
ASTAGRAF XL may affect the way other medicines work, and other medicines may affect how ASTAGRAF XL works.
Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine. Tell your doctor or pharmacist if there are any changes to the list of medicines that you take.

How should I take ASTAGRAF XL?

- Take ASTAGRAF XL exactly as your doctor tells you to take it.
- Your doctor will tell you how much ASTAGRAF XL to take and when to take it.
- Your doctor may change your dose of ASTAGRAF XL 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.
- Taking ASTAGRAF XL at the same time each day helps to keep enough medicine in your body to give your transplanted organ the around-the-clock medicine it needs.
- 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?

- While you take ASTAGRAF XL you should not receive any live vaccines such as:
  - flu vaccine through your nose
  - measles
  - mumps
  - rubella
  - polio by mouth
  - BCG (TB vaccine)
  - yellow fever
  - chicken pox (varicella)
  - typhoid
- Avoid exposure to sunlight and UV light such as tanning machines. Wear protective clothing and use a sunscreen.
- You should not eat grapefruit or drink grapefruit juice while taking ASTAGRAF XL.
- You should not drink an alcoholic beverage when taking ASTAGRAF XL. It can increase your chances of getting serious side effects.

What are the possible side effects of ASTAGRAF XL?
ASTAGRAF XL may cause serious side effects, including:

- **See "What the most important information I should know about ASTAGRAF XL?"**
- **medication errors.** People who take ASTAGRAF XL have sometimes been given the wrong medicine because some medicines have the same ingredient (medicine) as ASTAGRAF XL. **You should 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:
  - frequent urination
  - increased thirst or hunger
  - blurred vision
  - confusion
  - drowsiness
  - loss of appetite
  - fruity smell on your breath
  - nausea, vomiting, or stomach pain
- **kidney problems.** Your doctor may do certain tests to check your kidney function while you take ASTAGRAF XL.
- **nervous system problems.** Call your doctor right away if you get any of these symptoms while taking ASTAGRAF XL. These could be signs of a serious nervous system problem:
  - confusion
  - coma
  - muscle tremors
  - numbness and tingling
  - headache
  - seizures
  - vision changes
- **high levels of potassium in your blood.** Your doctor may do certain tests to check your potassium level while you take 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 in people receiving kidney transplant are:

- diarrhea
- constipation
- nausea
- swelling of the hands, ankles, or legs
- tremors (shaking of the body)
- low red blood cell count (anemia)

Tell your doctor if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of 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 between 68ºF to 77ºF (20°C to 25ºC).
- 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.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ASTAGRAF XL for a condition for which it was not prescribed. Do not give ASTAGRAF XL 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 ASTAGRAF XL. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about ASTAGRAF XL that is written for health professionals.
For more information, go to www.ASTAGRAFXL.com or call 1-800-727-7003.

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

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

Product of Japan
Manufactured by:
Astellas Ireland Co., Limited
Killorglin, County Kerry, Ireland

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

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