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

ENVARSUS XR® (tacrolimus extended-release tablets), for oral use
Initial U.S. Approval: 1994

WARNING: MALIGNANCIES AND SERIOUS INFECTIONS
See full prescribing information for complete boxed warning.

Increased risk for developing serious infections and malignancies with ENVARSUS XR or other immunosuppressants that may lead to hospitalization or death (5.1, 5.2)

----------INDICATIONS AND USAGE----------
ENVARSUS XR is a calcineurin-inhibitor immunosuppressant indicated for the prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate-release formulations in combination with other immunosuppressants (1)

Limitation of use:
- Not interchangeable or substitutable with other tacrolimus products (1, 5.3)

----------DOSAGE AND ADMINISTRATION----------
- Take once daily on empty stomach, preferably in the morning (2.1)
- Avoid eating grapefruit or drinking grapefruit juice or alcohol (2.1)

Recommended ENVARSUS XR starting doses (patients with severe hepatic impairment may require a lower starting dose) (2.2)	
Conversion from tacrolimus immediate-release products	Administer 80% of the pre-conversion daily dose of tacrolimus immediate-release (2.3)

ENVARSUS XR Target Whole Blood Trough Concentrations (2.2)
4 to 11 ng/mL

- African-Americans may need to be titrated to higher dosages to achieve the target tacrolimus concentrations (2.1)
- Assess tacrolimus whole blood trough concentrations at least two times on separate days during the first week after initiation of dosing and after any dosage change, after a change in co-administration of CYP3A inducers and/or inhibitors, or after a change in renal or hepatic function (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Extended-release tablets: 0.75 mg, 1 mg, 4 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 ENVARSUS XR tablets (5.3)
- New onset diabetes after transplant: Monitor blood glucose (5.4)
- Nephrotoxicity (acute and/or chronic) due to ENVARSUS XR or concomitant nephrotoxic drugs: Monitor renal function; consider dosage reduction (5.5)
- Neurotoxicity [including risk of posterior reversible encephalopathy syndrome (PRES)]: Monitor for neurologic abnormalities; reduce dosage or discontinue ENVARSUS XR (5.6)
- Hyperkalemia: Risk may be increased with other agents associated with hyperkalemia; monitor serum potassium levels (5.7)
- Hypertension: May require antihypertensive therapy (5.8)
- QT prolongation: Consider obtaining electrocardiograms and monitoring electrolytes in patients at high risk (5.10)
- Pure red cell aplasia: Consider discontinuation (5.12)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥10%) include: diarrhea and blood creatinine increased (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Veloxis Pharmaceuticals, Inc. at 1-844-VELOXIS (1-844-835-6947) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- Risk of rejection with strong CYP3A inducers and risk of serious adverse reactions with strong CYP3A inhibitors: Adjust dose and monitor tacrolimus concentrations (2.1, 5.9, 7.2)
- See Full Prescribing Information for clinically significant drug interactions (7.1, 7.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

WARNING: MALIGNANCIES AND SERIOUS INFECTIONS

Increased risk for developing serious infections and malignancies with ENVARSUS XR or other immunosuppressants that may lead to hospitalization or death *[see Warnings and Precautions (5.1, 5.2)]*

1 INDICATIONS AND USAGE

ENVARSUS XR is indicated for the prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate-release formulations, in combination with other immunosuppressants.

Limitation of Use
ENVARSUS XR extended-release tablets are not interchangeable or substitutable with other tacrolimus extended- release or immediate-release products *[see **Warnings and Precautions (5.3)**]*.

2 DOSAGE AND ADMINISTRATION

2.1 Administration Instructions

- Take ENVARSUS XR on an empty stomach at the same time of the day, preferably in the morning (to ensure consistent and maximum possible drug exposure) *[see **Clinical Pharmacology (12.2)**]*.
- Swallow ENVARSUS XR whole with fluid (preferably water); do not chew, divide, or crush the tablets.
- If a dose is missed, take it as soon as possible within 15 hours after missing the dose; beyond the 15-hour time frame, wait until the usual scheduled time to take the next regular daily dose. Do not double the next dose.
- Avoid eating grapefruit or drinking grapefruit juice or alcoholic beverage while taking ENVARSUS XR *[see **Drug Interactions (7.2)**]*.
- African-American patients, compared to Caucasian patients, may need to be titrated to higher ENVARSUS XR dosages to attain comparable trough concentrations *[see **Use in Specific Populations (8.8)** and **Clinical Pharmacology (12.2)**]*.

2.2 Conversion from Tacrolimus Immediate-Release Formulations

To convert from a tacrolimus immediate-release product to ENVARSUS XR, administer an ENVARSUS XR once daily dose that is 80% of the total daily dose of the tacrolimus immediate-release product. Monitor tacrolimus whole blood trough concentrations and titrate ENVARSUS XR dosage to achieve target whole blood trough concentration ranges of 4 to 11 ng/mL.

2.3 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 any change in dosage, after a change in co-administration of CYP3A 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 ENVARSUS XR 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

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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

Oval, white to off-white uncoated extended-release tablets debossed with "TCS" on one side:

- 0.75 mg extended-release tablet: debossed with "0.75" on the other side.
- 1 mg extended-release tablet: debossed with "1" on the other side.
- 4 mg extended-release tablet: debossed with "4" on the other side.

4 CONTRAINDICATIONS

ENVARSUS XR is contraindicated in patients with known hypersensitivity to tacrolimus.

5 WARNINGS AND PRECAUTIONS

5.1 Lymphoma and Other Malignancies

Immunosuppressants, including ENVARSUS XR, 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 those individuals who are EBV seronegative. Monitor EBV serology during treatment.

5.2 Serious Infections

Immunosuppressants, including ENVARSUS XR, 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)**]*.

5.3 Graft Rejection and Other Serious Adverse Reactions due to Medication Errors

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

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5.4 New Onset Diabetes After Transplant

ENVARSUS XR 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)***].

5.5 Nephrotoxicity due to ENVARSUS XR and Drug Interactions

ENVARSUS XR, 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 ENVARSUS XR 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.

5.6 Neurotoxicity

ENVARSUS XR 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 ENVARSUS XR if neurotoxicity occurs.

5.7 Hyperkalemia

Mild to severe hyperkalemia, which may require treatment, has been reported with tacrolimus including ENVARSUS XR. 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.

5.8 Hypertension

Hypertension is a common adverse reaction of ENVARSUS XR therapy and may require antihypertensive therapy *[see* ***Adverse Reactions (6.1)****]*. Some antihypertensive drugs can increase the risk for hyperkalemia *[see* ***Warnings and Precautions (5.7)****]*. Calcium-channel blocking agents may increase tacrolimus blood concentrations and require dosage reduction of ENVARSUS XR *[see* ***Drug Interactions (7.2)****]*.

5.9 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 (5.6, 5.10)****]* Therefore, adjust ENVARSUS XR dose and monitor tacrolimus whole blood trough concentrations when coadministering ENVARSUS XR 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 (2.3)*** *and* ***Drug Interactions (7.2)****]*.

5.10 QT Prolongation

ENVARSUS XR may prolong the QT/QTc interval and cause Torsade de Pointes. Avoid ENVARSUS XR 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).

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When coadministering ENVARSUS XR with other substrates and/or inhibitors of CYP3A, a reduction in ENVARSUS XR dosage, monitoring of tacrolimus whole blood concentrations, and monitoring for QT prolongation is recommended *[see **Drug Interactions (7.2)**]*.

5.11 Immunizations

Whenever possible, administer the complete complement of vaccines before transplantation and treatment with ENVARSUS XR.

Avoid the use of live attenuated vaccines during treatment with ENVARSUS XR (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 ENVARSUS XR.

5.12 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 ENVARSUS XR.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

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

In an open label, randomized, multinational conversion study, stable kidney transplant patients on a tacrolimus immediate-release product and concomitant immunosuppressants were randomized to treatment with ENVARSUS XR (N=162) or to continued treatment on the tacrolimus immediate-release product (N=162) and treated for a duration of 12 months *[see **Clinical Studies (14)**]*.

The proportion of patients who discontinued treatment due to adverse reactions was 7.4% and 1.2% in the ENVARSUS XR and tacrolimus immediate-release treatment groups, respectively, through 12 months of treatment. The most common adverse reactions leading to discontinuation of study drug in the ENVARSUS XR treatment group was cardiac arrest (2 events).

Infections

The overall incidence of infections, serious infections, and infections with identified etiology reported in stable kidney transplant recipients treated with ENVARSUS XR or tacrolimus immediate-release product are shown in **Table 1**.

Table 1. Percentage of Stable Patients with Infections Through One Year Post- Treatment in the Conversion Study[a]

	ENVARSUS XR ± steroids, MMF/MPS or AZA **N=162**	**Tacrolimus immediate-release product ± steroids, MMF/MPS or AZA** **N=162**
All infections	46%	48%

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Respiratory Infections	26%	28%
Urinary Tract Infections	10%	14%
Bacterial Infections	7%	5%
Fungal Infections	4%	4%
Gastrointestinal Infections	4%	5%
BK virus [b]	2%	2%
Cytomegalovirus Infections	2%	1%
Serious Infections	8%	9%

[a] The stable kidney transplant study was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus immediate-release product for the adverse reactions reported in this table.

[b] BK virus associated nephropathy (BKVAN) occurred in 1.2% (2/162) and 0.6% (1/162) in the ENVARSUS XR and tacrolimus immediate-release treatment groups, respectively.

New Onset Diabetes After Transplantation (NODAT)

New onset diabetes after transplantation (NODAT) was defined by the composite occurrence of fasting plasma glucose values ≥126 mg/dL, 2-hour postprandial plasma glucose of at least 200 mg/dL (in oral glucose tolerance test) on 2 or more consecutive occasions post baseline, insulin requirement for ≥31 days, an oral hypoglycemic agent use ≥31 days, or HbA_{1c} ≥6.5% (at least 3 months after randomization) among kidney transplant patients with no medical history of diabetes. The incidence of NODAT for the stable kidney transplant study through one year post-transplant is summarized in **Table 2** below *[see **Warnings and Precautions (5.4)**]*.

Table 2. Percentage of Stable Patients with NODAT Through 1 Year Post- Treatment in the Conversion Study [a]

	ENVARSUS XR ± steroids , MMF/MPS or AZA (N=90)	**Tacrolimus immediate-release product ± steroids, MMF/MPS or AZA (N=95)**
Composite NODAT [b]	10%	11%
HbA_{1c} ≥6.5%	3%	7%
Fasting Plasma Glucose Values ≥126 mg/dL on 2 consecutive occurrences	8%	6%
Oral hypoglycemic use	1%	1%
Insulin Use ≥31 days	1%	0%

[a] The stable kidney transplant study was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus immediate-release product for the adverse reactions reported in this table.

[b] Analyses restricted to patients at risk for NODAT

Common Adverse Reactions

The incidence of adverse reactions that occurred in ≥5% of ENVARSUS XR-treated patients compared to tacrolimus immediate-release product through one year of treatment in the conversion study is shown by treatment group in **Table 3**.

Table 3. Adverse Reactions (≥ 5%) in Stable Kidney Transplant Patients Through 1 Year Post- Treatment in the Conversion Study[a]

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Adverse Reaction	ENVARSUS XR N=162	Tacrolimus immediate-release product N=162
Diarrhea	14%	9%
Blood Creatinine Increased	12%	9%
Urinary Tract Infection	9%	14%
Nasopharyngitis	9%	11%
Headache	9%	7%
Upper Respiratory Tract Infection	7%	9%
Peripheral Edema	7%	6%
Hypertension	4%	6%

[a]The stable kidney transplant study was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus immediate-release for the adverse reactions reported in this table.

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, decreased blood fibrinogen, disseminated intravascular coagulation, hemolytic anemia, hemolytic uremic syndrome, pancytopenia, prolonged activated partial thromboplastin time, pure red cell aplasia [*see* ***Warnings and Precaution (5.12)***], thrombocytopenic purpura, thrombotic thrombocytopenic purpura

Cardiac Disorders: Atrial fibrillation, atrial flutter, cardiac arrhythmia, cardiac arrest, electrocardiogram T wave abnormal, flushing, myocardial hypertrophy, myocardial infarction, myocardial ischaemia, pericardial effusion, QT prolongation, supraventricular extrasystoles, supraventricular tachycardia, Torsade de Pointes, deep limb venous thrombosis, ventricular fibrillation

Ear Disorders: Hearing loss including deafness

Eye Disorders: Blindness, photophobia, optic atrophy

Gastrointestinal Disorders: Colitis, dysphagia, gastrointestinal perforation, impaired gastric emptying, intestinal obstruction, mouth ulceration, peritonitis, stomach ulcer

Hepatobiliary Disorders: Bile duct stenosis, cholangitis, cirrhosis, fatty liver, hepatic cytolysis, hepatic failure, hepatic necrosis, hepatic steatosis, jaundice, hemorrhagic pancreatitis, necrotizing pancreatitis, venoocclusive liver disease

Hypersensitivity Reactions: Hypersensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria

Immune System Disorders: Graft versus host disease (acute and chronic)

Metabolism and Nutrition Disorders: Glycosuria, increased amylase, pancreatitis

Musculoskeletal and Connective Tissue Disorders: Myalgia, polyarthritis, rhabdomyolysis

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Neoplasms: Lymphoma including EBV-associated lymphoproliferative disorder, PTLD [*see* ***Warnings and Precautions (5.1)***]; leukemia

Nervous System Disorders: Carpal tunnel syndrome, cerebral infarction, coma, dysarthria, flaccid paralysis, hemiparesis, mental disorder, mutism, nerve compression, posterior reversible encephalopathy syndrome (PRES) [*see* ***Warnings and Precautions (5.6)***], progressive multifocal leukoencephalopathy (PML) sometimes fatal [*see* ***Warnings and Precautions (5.2)***], quadriplegia, speech disorder, status epilepticus, syncope

Renal and Urinary Disorder: Acute renal failure, hemorrhagic cystitis, hemolytic uremic syndrome, micturition disorder

Respiratory, Thoracic and Mediastinal Disorders: Acute respiratory distress syndrome, interstitial lung disease, lung infiltration, pulmonary hypertension, respiratory distress, respiratory failure

Skin and Subcutaneous Tissue Disorders: Hyperpigmentation, photosensitivity

7 DRUG INTERACTIONS

7.1 Mycophenolic Acid

When ENVARSUS XR is prescribed with a given dose of mycophenolic acid (MPA) product, exposure to MPA is higher with ENVARSUS XR 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/Substances on ENVARSUS XR

Table 4. Effects of Other Drugs/Substances on ENVARSUS XR[a]

Drug/Substance Class or Name	Drug Interaction Effect	Recommendations
Grapefruit or grapefruit juice[b]	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see* ***Warnings and Precautions (5.6, 5.10)****]*	Avoid grapefruit or grapefruit juice
Alcohol	May modify the rate of tacrolimus release	Avoid alcoholic beverages
Strong CYP3A Inducers[c] such as: Antimycobacterials (e.g., rifampin, rifabutin), anticonvulsants (e.g., phenytoin, carbamazepine and phenobarbital), St John's Wort	May decrease tacrolimus whole blood trough concentrations and increase the risk of rejection *[see* ***Warnings and Precautions (5.9)****]*	Increase ENVARSUS XR dose and monitor tacrolimus whole blood trough concentrations *[see* ***Dosage and Administration (2.3)*** *and* ***Clinical Pharmacology (12.2)****]*
Strong CYP3A Inhibitors[c], such as: Protease inhibitors (e.g., nelfinavir, telaprevir, boceprevir, ritonavir), azole antifungals (e.g., voriconazole, posaconazole, itraconazole, ketoconazole), antibiotics (e.g., clarithromycin, troleandomycin, chloramphenicol), nefazodone	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see* ***Warnings and Precautions (5.6, 5.9, 5.10)****]*	Reduce ENVARSUS XR dose (for voriconazole and posaconazole, give one-third of the original dose) and adjust dose based on tacrolimus whole blood trough concentrations *[see* ***Dosage and Administration (2.3)*** *and* ***Clinical Pharmacology (12.2)****]*

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Mild or Moderate CYP3A Inhibitors, such as: antibiotics (e.g., erythromycin), calcium channel blockers (e.g., verapamil, diltiazem, nifedipine, nicardipine), amiodarone, danazol, ethinyl estradiol, cimetidine, lansoprazole and omeprazole, azole antifungals (e.g., clotrimazole, fluconazole)	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see **Warnings and Precautions (5.6, 5.10)**]*	Monitor tacrolimus whole blood trough concentrations and reduce ENVARSUS XR dose if needed *[see **Dosage and Administration (2.3), Clinical Pharmacology (12.2)**]*
Other drugs, such as: Magnesium and aluminum hydroxide antacids Metoclopramide	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see **Warnings and Precautions (5.6, 5.10)**]*	Monitor tacrolimus whole blood trough concentrations and reduce ENVARSUS XR dose if needed *[see **Dosage and Administration (2.3), Clinical Pharmacology (12.2)**]*
Mild or Moderate CYP3A Inducers, such as: Methylprednisolone, prednisone	May decrease tacrolimus concentrations	Monitor tacrolimus whole blood trough concentrations and adjust ENVARSUS XR dose if needed [*see **Dosage and Administration (2.3)**]*

[a] ENVARSUS XR dosage adjustment recommendation based on observed effect of coadministered drug on tacrolimus exposures *[see **Clinical Pharmacology (12.2)**]*, literature reports of altered tacrolimus exposures, or the other drug's known CYP3A inhibitor/inducer status
[b] High dose or double strength grapefruit juice is a *strong* CYP3A inhibitor; low dose or single strength grapefruit juice is a *moderate* CYP3A inhibitor
[c] 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 0.7 times the maximum clinical dose and pregnant rats at 1.1 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. ENVARSUS XR 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 (0.7 and 2.3 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 (3.7 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 (1.2 and 3.7 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.

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8.3 Nursing Mothers

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

8.4 Pediatric Use

The safety and effectiveness of ENVARSUS XR in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of ENVARSUS XR did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In the stable kidney transplant study, there were 17 patients 65 years of age and older, and no patients were over 75 years *[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 (5.5), Clinical Pharmacology (12.2)***].

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 (12.2)***]. 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 ENVARSUS XR dosages to attain comparable trough concentrations compared to Caucasian patients [*see **Dosage and Administration (2.1), Clinical Pharmacology (12.2))***]

10 OVERDOSAGE

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

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

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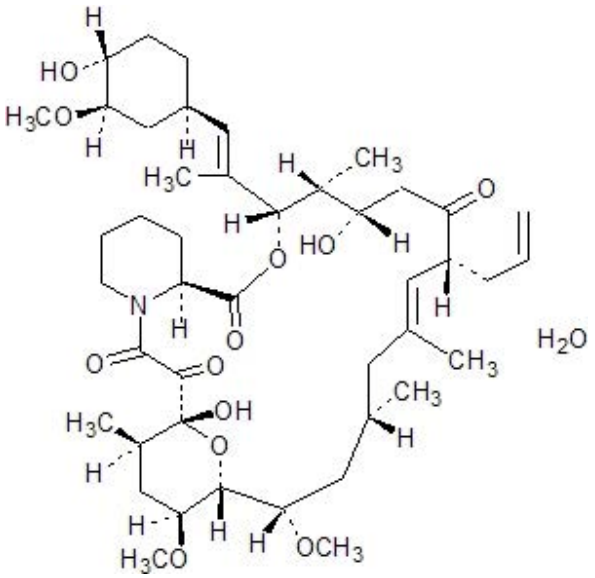
recommending its use. General supportive measures and treatment of specific symptoms should be followed in all cases of overdosage.

11 DESCRIPTION

ENVARSUS XR, a calcineurin-inhibitor immunosuppressant, is available for oral administration as extended-release tablets containing the equivalent of 0.75 mg, 1 mg, or 4 mg of anhydrous tacrolimus USP. Inactive ingredients include hypromellose USP, lactose monohydrate NF, polyethylene glycol NF, poloxamer NF, magnesium stearate NF, tartaric acid NF, butylated hydroxytoluene NF, and dimethicone NF.

Tacrolimus is the active ingredient in ENVARSUS XR. 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 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

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of T-lymphocyte activation and proliferation as well as T-helper-cell-dependent B-cell response (i.e., immunosuppression).

12.2 Pharmacokinetics

Table 5 summarizes the pharmacokinetic (PK) parameters of tacrolimus following oral administration of once-daily ENVARSUS XR in healthy subjects and in kidney transplant patients, under fasted conditions. Whole blood tacrolimus concentrations in the pharmacokinetic studies were measured using validated HPLC/MS/MS assays.

Table 5. Pharmacokinetic Parameters of ENVARSUS XR by Study Day in Healthy Subjects and Kidney Transplant Patients Under Fasted Conditions

Population	ENVARSUS XR Dose[a]	Day[b]	Pharmacokinetic Parameters of ENVARSUS XR			
			C_{max}[c] (ng/mL)	T_{max}[d] (hr)	AUC_{24}[c] (ng•hr/mL)	C_{24}[h] (ng/mL)
Healthy Subjects (n=19)	2 mg 2 mg	Day 1 Day 10	11.9 ± 3.8 8.3 ± 2.9	14.0 [6 - 28] 8.0 [1.0-12.0]	50 ± 14 140 ± 50	1.8 ± 0.6 4.6 ± 1.7
Adult Kidney *De novo*[e] (n=21)	11.8 mg [f] 10 mg 9.5mg	Day 1 Day 7 Day 14	11.8 ± 7.2 25.1 ± 16.3 27.1 ± 13.4	8.0 [4-24] 6.0 [2-12] 4.0 [1-8]	138 ± 80 335 ± 129 371 ± 104	5.2 ± 2.7 9.9 ± 4.4 11.4 ± 4.1[j]
Adult Kidney *De novo* (n=10)	15.5 mg [g] 11.4 mg 11.1 mg	Day 1 Day 14 Day 28	33.6 ± 21.8 31.1 ± 14.6 35.9± 18.7	6.0 [4-24] 4.0 [1-18] 4.0 [1-14]	377 ± 257 376 ± 140 396 ± 150	11.0 ± 6.1 9.1 ± 3.0 10.5 ± 3.2
Adult Kidney (≥ 6 months post-transplant) (n=47)	5.3 mg	Day 7[i]	13.5 ± 4.8	6.0 [1 - 16]	216 ± 63	7.0 ± 2.3

a) Healthy adult subjects (administered mg/day dose); Adult *de novo* kidney transplant patients (group average of administered mg/day dose); Adult kidney ≥ 6 months post-transplant (group average of administered mg/day dose of ENVARSUS XR, following conversion to 67% to 80% of the daily tacrolimus immediate-release capsules dose)
b) Day of ENVARSUS XR dosing and PK profiling
c) Arithmetic means ± S.D.
d) Median [range]
e) "*De novo*" refers to immunosuppression starting at the time of transplantation
f) Starting ENVARSUS XR dose = 0.14 mg/kg/day
g) Starting ENVARSUS XR dose = 0.17 mg/kg/day. In *de novo* kidney transplant patients who received ENVARSUS XR starting dose of 0.17 mg/kg/day achieved higher than recommended target tacrolimus trough concentrations, as high as 57 ng/mL during the first 1 to 2 weeks post-transplant
h) Tacrolimus trough concentration before the next dose
i) After 7 days of stable dosing with ENVARSUS XR
j) AUC_{0-24} –to- C_{24} correlation coefficient (r) at steady state was 0.80 or higher

In adult kidney transplant patients ≥ 6 months post-transplant switched to ENVARSUS® XR at 67% to 80% of the daily dose of tacrolimus immediate-release capsules, the steady state tacrolimus exposures (AUC_{24}) and tacrolimus trough concentrations (C_{24}) were comparable to the AUC_{24} and C_{24} measured prior to the switch. However, the mean C_{max} estimate was 30% lower and the median T_{max} was more prolonged (6 hours versus 2 hours) following administration of Envarsus XR as compared to that of tacrolimus immediate-release capsules.

Absorption

Absorption of tacrolimus from the gastrointestinal tract after oral administration is incomplete and variable. In healthy subjects, the oral bioavailability of ENVARSUS XR was approximately 50% higher as compared with both tacrolimus immediate-release and extended-release formulations at steady state. In healthy subjects who received single ENVARSUS XR doses ranging from 5 mg to 10 mg, the mean AUC and C_{24} of tacrolimus increased linearly and the elimination half-life did not change with increasing doses.

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Food Effects

The presence of a meal affects the absorption of tacrolimus; the rate and extent of absorption is greatest under fasted conditions. In 26 healthy subjects, administration of ENVARSUS XR following a high-fat breakfast reduced the systemic exposure (AUC) to tacrolimus by approximately 55% and the peak plasma concentration of tacrolimus (C_{max}) by 22%, with no effect on the time to reach maximum plasma concentration (T_{max}), compared to when ENVARSUS XR was administered under fasted conditions.

Chronopharmacokinetic Effect

In 26 healthy subjects, administration of ENVARSUS XR tablets in the evening resulted in a 15% lower $AUC_{0\text{-}inf}$, and a 20% lower C_{24}, as compared to morning dosing.

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 immediate-release formulation, 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 3A (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 ± 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 2 mg ENVARSUS XR once-daily for 10 days was 31.0 ± 8.1 hours (mean ± SD) in 25 healthy subjects.

Specific Populations

No dedicated pharmacokinetic studies in specific populations were conducted with ENVARSUS XR.

Renal Impairment

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

Hepatic Impairment

Tacrolimus pharmacokinetics have been determined in 6 patients with mild hepatic impairment (mean 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

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clearance was substantially lower in patients with severe hepatic impairment [*see* ***Dosage and Administration (2.2), 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:

- The mean (±SD) tacrolimus C_{max} in African-Americans (23.6±12.1 ng/mL) was lower than in Caucasians (40.2±12.6 ng/mL) and Latino-Americans (36.2±15.8 ng/mL).
- Mean $AUC_{0\text{-}inf}$ tended to be lower in African-Americans (203±115 ng·hr/mL) than Caucasians (344±186 ng·hr/mL) and Latino-Americans (274±150 ng·hr/mL).
- The mean (±SD) absolute oral bioavailability (F) in African-Americans (12±4.5%) and Latino-Americans (14±7.4%) was lower than in Caucasians (19±5.8%).
- There was no significant difference in mean terminal half-life among the three ethnic groups (range from approximately 25 to 30 hours) [*see* ***Dosage and Administration (2.1), Use in Specific Populations (8.8)***].

Gender

A formal trial to evaluate the effect of gender on tacrolimus pharmacokinetics has not been conducted. In a sub-group analysis from two combined Phase 3 studies in kidney transplant recipients performed with ENVARSUS XR over one year of treatment, no gender-dependent differences in tacrolimus systemic exposures were observed.

Drug Interaction Studies

No drug-drug interaction studies were conducted specifically with ENVARSUS XR.

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 (5.9), Drug Interactions (7.2)****]*.

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 3.0 mg/kg/day (0.84 times the AUC at the maximum clinical dose of 0.14 mg/kg/day) and in the rat was 5.0 mg/kg/day (0.24 times the AUC at the maximum clinical dose of 0.14 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^2/day. In the study, the incidence of skin tumors was minimal and the topical application of tacrolimus was not associated with skin tumor formation under ambient room lighting. However, a statistically significant elevation in the incidence of pleomorphic lymphoma in high-dose male (25/50) and female animals (27/50) and in the incidence of undifferentiated lymphoma in high-dose female animals (13/50) was noted in the mouse dermal carcinogenicity study. Lymphomas were noted in the mouse dermal carcinogenicity study at a daily dose of 3.5 mg/kg (0.1% tacrolimus ointment; 2.5-fold the human exposure in stable adult renal transplant patients converted from tacrolimus immediate-release product to ENVARSUS XR). 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.

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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 1.0 mg/kg (1.2 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 (3.7 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

Conversion Study from Tacrolimus Immediate-Release in Stable Kidney Transplant Recipients

The conversion study was a randomized, open-label, multinational study evaluating once daily ENVARSUS XR when used to replace tacrolimus immediate-release administered twice daily for maintenance immunosuppression to prevent acute allograft rejection in stable adult kidney transplant patients. Patients who received a kidney transplant 3 months to 5 years before study entry and on a stable dose of tacrolimus immediate-release of at least 2 mg per day and tacrolimus whole blood trough concentrations between 4 and 15 ng/mL were randomized to 1) switch from twice daily tacrolimus immediate-release to once daily ENVARSUS XR (N=163) or 2) continue tacrolimus immediate-release twice daily (N=163). MMF or mycophenolate sodium (MPS), or azathioprine (AZA) and/or corticosteroids were allowed as concomitant immunosuppressants during the study period according to the standard of care at the participating site.

The mean age of study population was 50 years; 67% were male; 73% were Caucasian, 22% were African-American, 2% were Asian and 3% were categorized as other races. Living donors provided 35% of the organs and 65% of patients received a kidney transplant from a deceased donor. Premature discontinuation from treatment at the end of one year occurred in 13% of ENVARSUS XR patients and 6% of tacrolimus immediate-release patients.

Study Drug: Tacrolimus

In the conversion study, stable kidney transplant patients converted to ENVARSUS XR at an average daily dose that was 80% of their tacrolimus immediate-release daily dose prior to conversion. Mean tacrolimus whole blood trough concentrations were maintained within a relatively narrow range throughout the duration of the study for both the ENVARSUS XR conversion group and the tacrolimus immediate-release continuation group. At Week 1 (after 7 days of stable dosing), the mean ± SD tacrolimus trough concentrations were 7.2 ± 3.1 ng/mL for the ENVARSUS XR conversion group and 7.7 ± 2.5 for the tacrolimus immediate-release continuation group; the baseline values were 7.8 ± 2.3, and 8.0 ± 2.3, respectively.

Study Drug: MMF

In the conversion study, the average daily mycophenolate equivalent doses were comparable between the ENVARSUS XR and tacrolimus immediate-release treatment groups.

Efficacy Results

The efficacy failure rates including patients who developed BPAR, graft failure, death, and/or lost to follow-up at 12 months, as well as the rates of the individual events, are shown by treatment group in **Table 6** for the modified intent-to-treat population.

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Table 6. Incidence of BPAR, Graft Loss, Death or Lost to Follow-up at 12 Months in Stable Kidney Transplant Patients

	ENVARSUS XR ± Steroids ± MMF, MPS, or AZA N=162	**Tacrolimus Immediate-Release ± Steroids ± MMF, MPS, or AZA N=162**
Overall Treatment Difference of efficacy failure compared to tacrolimus immediate-release (95% CI)[a]	0% (-4.2%, 4.2%)	
Treatment Failure	4 (2.5%)	4 (2.5%)
Biopsy Proven Acute Rejection	2 (1.2%)	2 (1.2%)
Graft Failure	0%	0%
Death	2 (1.2%)	1 (0.6%)
Lost to Follow-up	0%	1 (0.6%)

[a] 95% CI was calculated using an exact method that is based on the standardized statistic and inverting a 2-sided test

Glomerular Filtration Rates

The mean estimated glomerular filtration rates (eGFR), using the Modification of Diet in Renal Disease 7 (MDRD7) formula, were 61.5 ml/min/1.73 m^2 and 60.0 ml/min/1.73 m2 at baseline (Day 0) and 62.0 ml/min/1.73 m^2 and 61.4 ml/min/1.73 m^2 at 12 months in the ENVARSUS XR and tacrolimus immediate-release treatment groups, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

ENVARSUS XR is supplied in round bottles (see Table 7); the statement 'ONCE-DAILY' appears on its label.

Table 7. Strengths of ENVARSUS XR

0.75 mg	Oval, white to off-white uncoated extended-release tablet, debossed with "0.75" on one side and "TCS" on the other side. The tablets are supplied in 30-count (NDC 68992-3075-3) and 100-count (NDC 68992-3075-1) 40 ml HDPE bottles with twist off caps.
1 mg	Oval, white to off-white uncoated extended-release tablet, debossed with "1" on one side and "TCS" on the other side. The tablets are supplied in 30-count (NDC 68992-3010-3 and 100-count (NDC 68992-3010-1) 40 ml HDPE bottles with twist off caps.
4 mg	Oval, white to off-white uncoated extended-release tablet, debossed with "4" on one side and "TCS" on the other side. The tablets are supplied in 30-count 40 ml HDPE bottles (NDC 68992-3040-3) and 100-count 75 ml HDPE bottles (NDC 68992-3040-1) with twist off caps.

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].

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17 PATIENT COUNSELING INFORMATION

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

Administration

Advise patients to:

- Inspect their ENVARSUS XR medicine when they receive a new prescription and before taking it. If the appearance of the tablet 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 you have the right medicine. Other tacrolimus products cannot be substituted for ENVARSUS XR [*see* ***Warnings and Precautions (5.3)***].
- Take once-daily ENVARSUS XR at the same time every day (preferably in the morning) on an empty stomach to ensure consistent and maximum possible drug concentrations in the blood.
- Swallow tablet whole with liquid, preferably water. Do not chew, divide or crush tablet.
- Avoid alcohol, grapefruit, and grapefruit juice while on ENVARSUS XR [*see* ***Dosage and Administration (2.1), Drug Interactions (7.2)***].
- Take a missed dose as soon as possible but not more than 15 hours after the scheduled time. Beyond the 15-hour timeframe, instruct the patient to wait until the usual scheduled time the following morning to take the next regularly scheduled dose. Do not take two doses at the same time. [*see* ***Dosage and Administration (2.1)***].

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, 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, Warnings and Precautions (5.2)***].

New Onset Diabetes After Transplant

Inform patients that ENVARSUS XR 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 (5.4)***].

Nephrotoxicity

Inform patients that ENVARSUS XR 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 (5.5)***].

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 (5.6)***].

Hyperkalemia

Inform patients that ENVARSUS XR 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 (5.7)***].

Hypertension

Inform patients that ENVARSUS XR can cause high blood pressure which may require treatment with anti-hypertensive therapy [*see* ***Warnings and Precautions (5.8)***].

Drug Interactions

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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 ENVARSUS XR [*see* ***Warnings and Precautions (5.9), Drug Interactions (7)***].

Immunizations

Inform patients that ENVARSUS XR can interfere with the usual response to immunizations and that they should avoid live vaccines [*see* ***Warnings and Precautions (5.11)***].

Product of Germany

Manufactured by:
Rottendorf Pharma GmbH
59320 Ennigerloh
North Rhine-Westphalia
Germany

Manufactured for:
Veloxis Pharmaceuticals, Inc.
499 Thornall Street, 3rd floor,
Edison, New Jersey 08837
United States

Reference ID: 3804760

MEDICATION GUIDE
ENVARSUS XR® (En var' sus XR**)**
(tacrolimus extended-release tablets)

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

What is the most important information I should know about ENVARSUS XR?
ENVARSUS XR can cause serious side effects, including:

1. **Increased risk of cancer.** People who take ENVARSUS XR have an increased risk of getting some kinds of cancer, including skin and lymph gland cancer (lymphoma).
2. **Increased risk of infection.** ENVARSUS XR is a medicine that affects your immune system. ENVARSUS XR can lower the ability of your immune system to fight infections. Serious infections can happen in people receiving ENVARSUS XR that can cause death.
   Call your doctor right away if you have symptoms of an infection such as:
   - fever
   - muscle aches
   - cough or flu-like symptoms
   - sweats or chills
   - warm, red, or painful areas on your skin

What is ENVARSUS XR?

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

Who should not take ENVARSUS XR?
Do not take ENVARSUS XR if you are allergic to tacrolimus or any of the ingredients in ENVARSUS XR. See the end of this leaflet for a complete list of ingredients in ENVARSUS XR.

What should I tell my doctor before taking ENVARSUS XR?
Before you take ENVARSUS XR, 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. ENVARSUS XR may harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. ENVARSUS XR can pass into your breast milk. You and your doctor should decide if you will take ENVARSUS XR 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.
ENVARSUS XR may affect the way other medicines work, and other medicines may affect how ENVARSUS XR works.

How should I take ENVARSUS XR?

- Take ENVARSUS XR exactly as your doctor tells you to take it.
- Your doctor may change your dose of ENVARSUS XR if needed. **Do not** stop taking or change your dose of ENVARSUS XR without talking to your doctor.
- Take ENVARSUS XR once daily with fluid (preferably water) on an empty stomach at the same time each day (preferably in the morning).
- Take ENVARSUS XR tablets whole. **Do not** chew, divide or crush ENVARSUS XR tablets before swallowing. If you cannot swallow ENVARSUS XR tablets whole, tell your doctor.
- If you miss your dose of ENVARSUS XR, it should be taken as soon as possible, but no longer than 15 hours after missing your dose. If the time after you miss your dose is more than 15 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 ENVARSUS XR, call your doctor or go to the nearest hospital emergency room right away.

What should I avoid while taking ENVARSUS XR?

- 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 ENVARSUS XR.
- You should not drink alcohol while taking ENVARSUS XR.

What are the possible side effects of ENVARSUS XR?

ENVARSUS XR may cause serious side effects, including:

- **See "What is the most important information I should know about ENVARSUS XR?"**
- **graft rejection and other serious reactions.** People who take ENVARSUS XR have sometimes been given the wrong medicine because some medicines have the same ingredient (tacrolimus) as ENVARSUS XR. **Check your ENVARSUS XR 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 ENVARSUS XR should look like.
- **high blood sugar (diabetes)**. Your doctor may do certain tests to check for diabetes while you take ENVARSUS XR. 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 for kidney function while you take ENVARSUS XR.
- **nervous system problems**. Call your doctor right away if you get any of these symptoms while taking ENVARSUS XR. These could be signs of a serious nervous system problem:
  - confusion
  - coma
  - seizures
  - numbness and tingling
  - headache
  - vision changes
  - muscle tremors
- **high levels of potassium in your blood**. Your doctor may do certain tests to check your potassium level while you take ENVARSUS XR.
- **high blood pressure**. Your doctor will monitor your blood pressure while you take ENVARSUS XR.
- **changes in the electrical activity of your heart (QT prolongation).**

The most common side effects of ENVARSUS XR include, diarrhea, urinary tract infection, low red blood cell count (anemia), high blood pressure, and constipation.

These are not all the possible side effects of ENVARSUS XR. 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 ENVARSUS XR?

- Store ENVARSUS XR at room temperature between 68 ºF to 77 ºF (20 °C to 25 ºC).
- Safely throw away medicine that is out of date or no longer needed.

Keep ENVARSUS XR and all medicines out of reach of children.

General information about the safe and effective use of ENVARSUS XR.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ENVARSUS XR for a condition for which it was not prescribed. Do not give ENVARSUS XR 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 ENVARSUS XR. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about ENVARSUS XR that is written for health professionals. For more information, go to www.ENVARSUSXR.com or call 1-844-Veloxis (1-844-835-6947).

What are the ingredients in ENVARSUS XR?

Active ingredient: tacrolimus USP

Inactive ingredients: hypromellose USP, lactose monohydrate NF, polyethylene glycol NF, poloxamer NF, magnesium stearate NF, tartaric acid NF, butylated hydroxytoluene NF, and dimethicone NF

Manufactured by: **Rottendorf Pharma GmbH**, 59320 Ennigerloh, North Rhine-Westphalia, Germany Marketed by: **Veloxis Pharmaceuticals Inc.** 499 Thornall Street, 3rd floor Edison, New Jersey 08837, United States

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