ENVARSUS XR- tacrolimus tablet, extended release
Veloxis Pharmaceuticals, Inc

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 de novo kidney transplant patients in combination with other immunosuppressants (1.1)
- The prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate-release formulations in combination with other immunosuppressants (1.2)

DOSAGE AND ADMINISTRATION

- Take once daily on empty stomach at the same time of the day, preferably in the morning. (2.1)
- Avoid eating grapefruit or drinking grapefruit juice or alcohol. (2.1)
- African-American patients may need to be titrated to higher dosages to achieve the target tacrolimus concentrations. (2.4)
- Patients with severe hepatic impairment may require a lower starting dose. (2.4)
- Frequent monitoring of trough concentrations is recommended. (2.5)

Recommended ENVARSUS XR Initial Dosage		
	Initial Oral Dosage	Whole Blood Trough Concentration Range
De novo kidney transplantation with antibody induction	0.14 mg/kg/day	Month 1: 6-11 ng/mL >Month 1: 4-11 ng/mL
Conversion from tacrolimus immediate-release formulations	80% of the pre-conversion dose of tacrolimus immediate-release	Titrate to 4-11 ng/mL

DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 0.75 mg, 1 mg, 4 mg (3)

CONTRAINDICATIONS

Known hypersensitivity to tacrolimus (4)

WARNINGS AND PRECAUTIONS

- Not Interchangeable with Other Tacrolimus Products: 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): May occur due to ENVARSUS XR, drug interactions 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; monitor relevant drug interactions. (5.8)
- QT Prolongation: Consider obtaining electrocardiograms and monitoring electrolytes in patients at high risk. (5.10)
- Immunizations: Avoid live vaccines. (5.11)
- Pure Red Cell Aplasia: Consider discontinuation. (5.12)

ADVERSE REACTIONS

- De novo kidney transplant patients: Most common adverse reactions (incidence ≥15%) include: diarrhea, anemia, urinary tract infection, hypertension, tremor, constipation, diabetes mellitus, peripheral edema, hyperkalemia and headache. (6.1)
- Conversion of kidney transplant patients from immediate-release to extended-release tacrolimus: 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. (2.4, 5.9, 7.2)
- See Full Prescribing Information for clinically significant drug interactions. (7.1, 7.2)

---------- **USE IN SPECIFIC POPULATIONS** ----------
Pregnancy: Can cause fetal harm. Advise pregnant women of the potential risk to the fetus. (8.1, 8.3)
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 9/2020

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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

1.1 Prophylaxis of Organ Rejection in De Novo Kidney Transplant Patients

ENVARSUS XR is indicated for the prophylaxis of organ rejection in kidney transplant patients in combination with other immunosuppressants *[see Clinical Studies (14.1)]*.

1.2 Prophylaxis of Organ Rejection in Stable Kidney Transplant Patients Converting from Immediate-Release Formulations

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 *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- ENVARSUS XR (tacrolimus extended-release tablets) is not interchangeable or substitutable with tacrolimus extended-release capsules, tacrolimus capsules, and tacrolimus for oral suspension. Under or overexposure to tacrolimus may result in graft rejection or other serious adverse reactions *[see Warnings and Precautions (5.3)]*. ENVARSUS XR should not be used without the supervision of a physician with experience in immunosuppressive therapy.
- ENVARSUS XR should be taken on an empty stomach consistently at the same time of the day, preferably in the morning to ensure consistent and maximum possible drug exposure, at least 1 hour before a meal or at least 2 hours after a meal *[see Clinical Pharmacology (12.3)]*.
- Advise patients to swallow ENVARSUS XR tablets whole with fluid (preferably water); patients must not chew, divide, or crush the tablets.
- If a dose is missed, instruct the patient to take it as soon as possible within 15 hours after missing the dose. Beyond the 15-hour time frame, instruct the patient to wait until the usual scheduled time to take the next regular daily dose. Instruct the patient not to double the next dose.
- Patients should avoid eating grapefruit or drinking grapefruit juice or alcoholic beverage while taking ENVARSUS XR *[see Drug Interactions (7.2)]*.

2.2 Dosing in De Novo Kidney Transplant Patients

The recommended starting dose of ENVARSUS XR in de novo kidney transplant patients is 0.14 mg/kg/day. Titrate ENVARSUS XR dosage based on clinical assessments of rejection and tolerability

and to achieve whole blood trough concentration ranges (see **Table 1**).

Table 1. Recommended Tacrolimus Whole Blood Trough Concentration Ranges in Kidney Transplant Patients with Antibody Induction

Time Period Post Transplant	Target Tacrolimus Whole Blood Trough Concentration Ranges
During Month 1	6 to 11 ng/mL
> Month 1	4 to 11 ng/mL

2.3 Dosing for Conversion from Tacrolimus Immediate-Release Formulations

To convert from a tacrolimus immediate-release product to ENVARSUS XR, administer ENVARSUS XR once daily at a 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 whole blood trough concentration ranges of 4 to 11 ng/mL.

2.4 Dosing Adjustments in African-American Patients, Patients with Hepatic Impairment, Drug Interactions

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), Clinical Pharmacology (12.3)]*.

Due to reduced clearance and prolonged half-life seen in patients with severe hepatic impairment (Child-Pugh ≥10) these patients may require a lower starting dosage of ENVARSUS XR *[see Clinical Pharmacology (12.3)]*.

Dose adjustments of ENVARSUS XR may be necessary when administered concomitantly with CYP3A inducers or CYP3A inhibitors *[see Warnings and Precautions (5.9), Drug Interactions (7.2)]*.

2.5 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 *[see Drug Interactions (7)]*, 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 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 by wearing protective clothing and using a sunscreen with a high protection factor.

Post-transplant lymphoproliferative disorder (PTLD), associated with Epstein-Barr Virus (EBV), has been reported in immunosuppressed organ transplant patients. The risk of PTLD appears greatest in 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 Not Interchangeable with Other Tacrolimus Products-Medication Errors

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

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 Adverse Reactions (6.1, 6.2), 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., including but not limited to telaprevir, boceprevir, ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin) or strong CYP3A inducers (e.g., including but not limited to rifampin, rifabutin) *[see Dosage and Administration (2.3, 2.5), 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).

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 Dosage and Administration (2.5), 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

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

- Lymphoma and Other Malignancies *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Serious Infections *[see Boxed Warning,Warnings and Precautions (5.2)]*
- New Onset Diabetes after Transplant *[see Warnings and Precautions (5.4)]*
- Nephrotoxicity due to ENVARSUS XR and Drug Interactions *[see Warnings and Precautions (5.5)]*
- Neurotoxicity *[see Warnings and Precautions (5.6)]*
- Hyperkalemia *[see Warnings and Precautions (5.7)]*
- Hypertension *[see Warnings and Precautions (5.8)]*
- QT Prolongation *[see Warnings and Precautions (5.10)]*
- Pure Red Cell Aplasia *[see Warnings and Precautions (5.12)]*

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.

Study 1- Phase 3 Clinical Study in De Novo Kidney Transplant Recipients

Study 1 (NCT 01187953), was a Phase 3 randomized study in de novo kidney transplant patients that were treated with ENVARSUS XR (N=268) or tacrolimus [immediate-release] capsules (N=275) and concomitant immunosuppressants in a double-blind, randomized, multinational study *[see Clinical Studies (14.1)]*. The proportion of patients who discontinued treatment due to adverse reactions was 8.6% and 9.8% in the ENVARSUS XR and tacrolimus capsules 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 were esophagitis, polyomavirus-associated nephropathy, graft dysfunction, complications of transplanted kidney, and diabetes mellitus, each resulting in 0.7% discontinuations among ENVARSUS XR treatment patients. In Study 1, de novo kidney transplant patients who received a starting dose of 0.17 mg/kg/day, which is higher than the recommended ENVARSUS XR starting dose of 0.14 mg/kg/day, exceeded the recommended target tacrolimus trough concentrations as high as 57 ng/mL during the first 1 to 2 weeks post-transplant *[see Dosage and Administration (2.2)]*.

Infections

The overall incidence of infections, serious infections, and infections with identified etiology reported in de novo kidney transplant recipients treated with ENVARSUS XR or tacrolimus [immediate-release] capsules in Study 1 are shown in **Table 2**.

Table 2 Percentage of Patients with Infections Through 1 Year Post-Kidney Transplant in Study 1 [a]

	ENVARSUS XR ± steroids, IL-2 receptor antagonist induction therapy, MMF/MPS or AZA **N=268**	**Tacrolimus [immediate-release] capsules ± steroids, IL-2 receptor antagonist induction therapy, MMF/MPS or AZA** **N=275**
All infections	70%	65%
Urinary Tract Infections	29%	27%
Respiratory Infections	28%	24%
Bacterial Infections	13%	18%
Cytomegalovirus Infections	11%	9%
Fungal Infections	9%	8%
Gastrointestinal Infections	6%	4%
BK virus [b]	6%	9%
Serious Infections	26%	24%

MMF/MPS- Mycophenolate mofetil/mycophenolate sodium; AZA-azathioprine

[a] Study 1 was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus [immediate-release] capsules for the adverse reactions reported in this table.
[b] BK virus-associated nephropathy (BKVAN) occurred in 1.5% (4/268) and 0.7% (2/275) in the ENVARSUS XR and tacrolimus capsules treatment groups, respectively.

New Onset Diabetes After Transplantation

New onset diabetes after transplantation (NODAT) was defined by the composite occurrence of fasting plasma glucose values ≥126 mg/dL, 2-hour post-prandial plasma glucose of at least 200 mg/dL (in oral glucose tolerance test) on two 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 Study 1 through one year post-transplant is summarized in **Table 3** below *[see Warnings and Precautions (5.4)]*.

Table 3. Percentage of Patients with NODAT Through 1 Year Post-Kidney Transplant in Study 1 [a]

	ENVARSUS XR ± steroids, IL-2 receptor antagonist induction therapy, MMF/MPS or AZA	**Tacrolimus [immediate-release] capsules ± steroids, IL-2 receptor antagonist induction therapy, MMF/MPS or AZA**

	(N=88)	AZA (N=74)
Composite NODAT [b]	21%	15%
HbA_{1c} ≥6.5%	13%	8%
Fasting Plasma Glucose Values ≥126 mg/dL on 2 consecutive occurrences	8%	11%
Oral hypoglycemic use	7%	5%
Insulin use ≥31 days	1%	4%

MMF/MPS- Mycophenolate mofetil/mycophenolate sodium; AZA-azathioprine

[a] Study 1 was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus [immediate-release] capsules 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 ≥10% of ENVARSUS XR-treated patients compared to tacrolimus [immediate-release] capsules through one year of treatment in Study 1 is shown by treatment group in **Table 4** .

Table 4. Adverse Reactions (≥ 10%) in Kidney Transplant Patients Through 1 Year Post-Transplant in Study 1[a]

Adverse Reaction	ENVARSUS XR N=268	Tacrolimus [immediate-release] capsules N=275
Diarrhea	31%	34%
Anemia	26%	29%
Urinary Tract Infection	25%	25%
Hypertension	23%	23%
Tremor	19%	17%
Constipation	18%	25%
Diabetes Mellitus	16%	14%
Peripheral Edema	16%	21%
Hyperkalemia	15%	11%
Headache	15%	10%
Hypophosphatemia	13%	15%
Leukopenia	13%	14%
Nausea	13%	15%
Insomnia	13%	11%
Increased Blood Creatinine	12%	14%
Hypomagnesemia	12%	12%
Hypokalemia	12%	12%
Hyperglycemia	11%	12%

[a] Study 1 was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus [immediate-release] capsules for the adverse reactions reported in this table.

Study 2- Phase 2 Clinical Study in De Novo Kidney Transplant Recipients

Study 2 (NCT00765661) was an open-label Phase 2 study conducted in de novo kidney transplant patients randomized to once daily ENVARSUS XR (N=32) or twice daily tacrolimus [immediate-release] capsules (N=31). The study was conducted in the US and patients received an organ from a deceased or living donor. Pharmacokinetics were evaluated during the first 2 weeks with an additional 50-week treatment and follow-up to evaluate safety and efficacy *[see Clinical Studies (14.1)]*.

The starting dosage was 0.14 mg/kg/day (given once daily) for ENVARSUS XR and 0.2 mg/kg/day (given twice daily) for tacrolimus [immediate-release] capsules. On Day 2 predose, the proportion of patients in the ENVARSUS XR group with tacrolimus trough concentration that were within, above, and below 6 to 11 ng/mL was 53%, 11%, and 37%, respectively. The starting dose of 0.14 mg/kg/day in Study 2 formed the basis of dosing recommendations in de novo kidney transplant patients.

There were no deaths or graft failures in Study 2. Two patients in each arm discontinued due to adverse events. The most common adverse reactions included infections and cardiovascular events, and were

generally similar to those reported in Study 1.

Study 3- Phase 3 Clinical Studies in Stable Kidney Transplant Recipients Converted from Tacrolimus Capsules

In Study 3 (NCT00817206) stable kidney transplant patients were treated with ENVARSUS XR (N=162) or tacrolimus [immediate-release] capsules (N=162) and concomitant immunosuppressants in an open-label, randomized, multinational study *[see Clinical Studies (14.2)]*. The proportion of patients who discontinued treatment due to adverse reactions was 7.4% and 1.2% in the ENVARSUS XR and tacrolimus capsules 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 capsules are shown in **Table 5.**

Table 5. Percentage of Stable Patients with Infections Through 1 Year Post-Treatment in Study 3 [a]

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

MMF/MPS- Mycophenolate mofetil/mycophenolate sodium; AZA-azathioprine

[a] The stable kidney transplant study was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus capsules 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 capsules treatment groups, respectively.

New Onset Diabetes After Transplantation

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 HbA1c ≥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 6** below *[see Warnings and Precautions (5.4)]*.

Table 6. Percentage of Stable Patients with NODAT Through 1 Year Post- Treatment in Study 3 [a]

	ENVARSUS XR ± steroids, MMF/MPS or AZA (N=90)	**Tacrolimus [immediate-release] capsules ± 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%

MMF/MPS- Mycophenolate mofetil/mycophenolate sodium; AZA-azathioprine
[a] The stable kidney transplant study was not designed to support comparative claims of ENVARSUS XR compared to tacrolimus capsules for the adverse reactions reported in this table.
[b] Analyses restricted to patients at risk for NODAT.

Common Adverse Reactions

In Study 3, the most common (≥10%) adverse reactions observed with Envarsus XR were diarrhea (14%), and blood creatinine increased (12%).

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. The following reactions have been included due to either their seriousness, frequency of reporting or strength of causal connection to ENVARSUS XR:

- Blood and Lymphatic System Disorders: Agranulocytosis, decreased blood fibrinogen, disseminated intravascular coagulation, hemolytic anemia, hemolytic uremic syndrome, leukopenia, febrile neutropenia, pancytopenia, prolonged activated partial thromboplastin time, pure red cell aplasia *[see Warnings and Precautions (5.12)]*, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, thrombotic microangiopathy
- 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, optic neuropathy, photophobia, optic atrophy
- Gastrointestinal Disorders: Abdominal pain, 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, hepatitis (acute and chronic)
- 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
- 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 embolism, pulmonary hypertension, respiratory distress, respiratory failure
- Skin and Subcutaneous Tissue Disorders: Hyperpigmentation, photosensitivity, pruritus, rash

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 with MPA, because cyclosporine interrupts the enterohepatic recirculation of MPA while tacrolimus does not. Monitor for MPA associated adverse reactions and reduce the dose of concomitantly administered MPA products as needed.

7.2 Effects of Other Drugs/Substances on ENVARSUS XR

Table 7. Effects of Other Drugs/Substances on ENVARSUS XR[a, d]

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, 5.9, 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 (2.5) and Clinical Pharmacology (12.3)]*
Strong CYP3A Inhibitors[c,], such as: Protease inhibitors (e.g., nelfinavir, telaprevir, boceprevir, ritonavir or ritonavir containing products, azole antifungals (e.g., voriconazole, posaconazole, itraconazole, ketoconazole), antibiotics (e.g., clarithromycin, troleandomycin, chloramphenicol), nefazodone, cobicistat	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 (2.5) and Clinical Pharmacology (12.3)]*
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, isavuconazole), imatinib, nilotinib, letermovir	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)]*	Monitor tacrolimus whole blood trough concentrations and reduce ENVARSUS XR dose if needed *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*
Other drugs, such as: Magnesium and aluminum hydroxide antacids Metoclopramide	May increase tacrolimus whole blood trough concentrations and increase the risk of serious adverse reactions (e.g., neurotoxicity, QT prolongation) *[see Warnings and Precautions (5.6 and 5.10)]*	Monitor tacrolimus whole blood trough concentrations and reduce ENVARSUS XR dose if needed *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*
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 (2.5)]*

[a] ENVARSUS XR dosage adjustment recommendation based on observed effect of coadministered drug on tacrolimus exposures *[see Clinical Pharmacology (12.3)]*, literature reports of altered tacrolimus exposures, or the other drug's known CYP3A inhibitor/inducer status

[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 immediate-release tacrolimus along with supporting *in vitro* CYP3A inhibitor/inducer data, or based on drug-drug interaction studies with midazolam (sensitive CYP3A probe substrate)

[d] A drug interaction study with voriconazole was conducted for ENVARSUS XR *[see Clinical Pharmacology (12.3)]*. No other drug-drug interaction studies were conducted with ENVARSUS XR.

Direct Acting Antiviral (DAA) Therapy

The pharmacokinetics of tacrolimus may be impacted by changes in liver function during DAA therapy, related to clearance of HCV virus. Close monitoring and potential dose adjustment of tacrolimus is warranted to ensure continued efficacy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

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

Administration of oral tacrolimus to pregnant rabbits and rats throughout the period of organogenesis was associated with maternal toxicity/lethality, and an increased incidence of abortion, malformation and embryofetal death at clinically relevant doses (0.7 to 3.7 times the recommended clinical dose [0.14 mg/kg/day], on a mg/m² basis). Administration of oral tacrolimus to pregnant rats after organogenesis and throughout lactation produced maternal toxicity, effects on parturition, reduced pup viability and reduced pup weight at clinically relevant doses (1.2 to 3.7 times the recommended clinical dose, on a mg/m² basis). Administration of oral tacrolimus to rats prior to mating, and throughout gestation and lactation produced maternal toxicity/lethality, marked effects on parturition, embryofetal loss, malformations, and reduced pup viability at clinically relevant doses (1.2 to 3.7 times the recommended clinical dose, on a mg/m² basis).

Interventricular septal defects, hydronephrosis, craniofacial malformations and skeletal effects were observed in offspring that died *[see Animal Data]*.

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

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk

Risks during pregnancy are increased in organ transplant recipients.

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

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

Maternal Adverse Reactions

ENVARSUS XR may increase hyperglycemia in pregnant women with diabetes (including gestational diabetes). Monitor maternal blood glucose levels regularly *[see Warnings and Precautions (5.4)]*.

ENVARSUS XR may exacerbate hypertension in pregnant women and increase pre-eclampsia. Monitor and control blood pressure *[see Warnings and Precautions (5.7, 5.8)]*.

Fetal/Neonatal Adverse Reactions

Renal dysfunction, transient neonatal hyperkalemia and low birth weight have been reported at the time of delivery in infants of mothers taking ENVARSUS XR.

Labor or Delivery

There is an increased risk for premature delivery (<37 weeks) following transplantation and maternal exposure to ENVARSUS XR.

Data

Human Data

There are no adequate and well controlled studies on the effects of tacrolimus in human pregnancy.

Safety data from the TPRI and postmarketing surveillance suggest infants exposed to tacrolimus in utero have an increased risk for miscarriage, pre-term delivery (<37 weeks), low birth weight (<2500 g), birth defects/congenital anomalies and fetal distress.

TPRI reported 450 and 241 total pregnancies in kidney and liver transplant recipients exposed to tacrolimus, respectively. The TPRI pregnancy outcomes are summarized in **Table 8.** In the table below, the number of recipients exposed to tacrolimus concomitantly with mycophenolic acid (MPA) products during the preconception and first trimester periods is high (27% and 29% for renal and liver transplant recipients, respectively). Because MPA products may also cause birth defects, the birth defect rate may be confounded and this should be taken into consideration when reviewing the data, particularly for birth defects. Birth defects observed include cardiac malformations, craniofacial malformations, renal/urogenital disorders, skeletal abnormalities, neurological abnormalities and multiple malformations.

Table 8. TPRI Reported Pregnancy Outcomes in Transplant Recipients with Exposure to Tacrolimus

	Kidney	**Liver**
Pregnancy Outcomes*	**462**	**253**
Miscarriage	24.5%	25%
Live births	**331**	**180**
Pre-term delivery (< 37 weeks)	49%	42%
Low birth weight (< 2500 g)	42%	30%
Birth defects	8%†	5%

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

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

Animal Data

Administration of oral tacrolimus to pregnant rabbits throughout organogenesis produced maternal toxicity and abortion at 0.32 mg/kg (0.7 times the recommended clinical dose based on body surface area). At 1 mg/kg (2.3 times the recommended clinical dose) embryofetal lethality and fetal malformations (ventricular hypoplasia, interventricular septal defect, bulbous aortic arch, stenosis of ductus arteriosus, omphalocele, gallbladder agenesis, skeletal anomalies) were observed. Administration of 3.2 mg/kg oral tacrolimus (3.7 times the recommended clinical dose) to pregnant rats throughout organogenesis produced maternal toxicity/lethality, embryofetal lethality and decreased fetal body weight in the offspring of C-sectioned dams; and decreased pup viability and interventricular septal defect in offspring of dams that delivered.

In a peri/postnatal development study, oral administration of tacrolimus to pregnant rats during late gestation (after organogenesis) and throughout lactation produced maternal toxicity, effects of parturition, and reduced pup viability at 3.2 mg/kg (3.7 times the recommended clinical dose); among these pups that died early, an increased incidence of kidney hydronephrosis was observed. Reduced pup weight was observed at 1mg/kg (1.2 times the recommended clinical dose).

Administration of oral tacrolimus to rats prior to mating, and throughout gestation and lactation produced maternal toxicity/lethality, embryofetal loss and reduced pup viability at 3.2 mg/kg (3.7 times the recommended clinical dose). Interventricular septal defects, hydronephrosis, craniofacial malformations and skeletal effects were observed in offspring that died. Effects on parturition (incomplete delivery of nonviable pups) were observed at 1 mg/kg (1.2 times the recommended clinical dose) *[see Nonclinical Toxicology (13.1)]*.

8.2 Lactation

Risk Summary

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

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for ENVARSUS XR and any potential adverse effects on the breastfed child from ENVARSUS XR or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

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

Infertility

Based on findings in animals, male and female fertility may be compromised by treatment with ENVARSUS XR *[see Nonclinical Toxicology (13.1)]*.

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 Studies 1, 2 and 3, there were 37 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) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

The mean clearance of tacrolimus was substantially lower in patients with severe hepatic impairment (mean Child-Pugh score: >10) compared to healthy subjects with normal hepatic function *[see Clinical Pharmacology (12.3)]*. With greater tacrolimus whole blood trough concentrations in patients with severe hepatic impairment, there is a greater risk of adverse reactions and dosage reduction is recommended *[see Dosage and Administration (2.4)]*. 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. The pharmacokinetics of ENVARSUS XR were evaluated in a study of 46 stable African-American kidney transplant recipients converted from tacrolimus immediate-release to ENVARSUS XR and indicated that an 80% conversion factor is appropriate for African-American patients *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

African-American and Hispanic kidney transplant patients are at an increased risk for new onset diabetes after transplant. Monitor blood glucose concentrations and treat appropriately *[see Warnings and Precautions (5.4)]*.

10 OVERDOSAGE

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

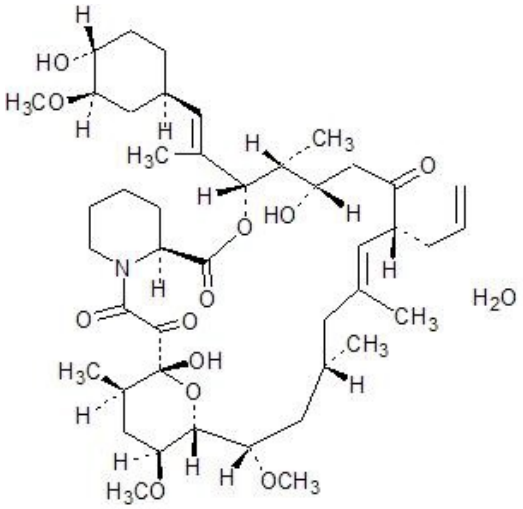
- nervous system disorders (tremor, headache, confusional state, balance disorders, encephalopathy, lethargy and somnolence)
- gastrointestinal disturbances (nausea, vomiting, and diarrhea)
- abnormal renal function (increased blood urea nitrogen and elevated serum creatinine)
- urticaria
- hypertension
- 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 recommending its use. General supportive measures and treatment of specific symptoms should be followed in all cases of overdosage.

11 DESCRIPTION

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

The chemical structure of tacrolimus is:



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

ENVARSUS XR 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

Tacrolimus inhibits the expression and/or production of several cytokines that include interleukin (IL)-1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, gamma interferon, tumor necrosis factor-alpha, and granulocyte macrophage colony stimulating factor. Tacrolimus also inhibits IL-2 receptor expression and nitric oxide release, induces apoptosis and production of transforming growth factor-beta that can lead to immunosuppressive activity. The net result is the inhibition of T-lymphocyte activation and proliferation as well as T-helper-cell-dependent B-cell response (i.e., immunosuppression).

12.3 Pharmacokinetics

Table 9 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 9. Pharmacokinetic Parameters of ENVARSUS XR by Study Day in Healthy Subjects and Kidney Transplant Patients Under Fasted Conditions

Population	ENVARSUS XR Dose	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[a] (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[a] *De novo*[e] (n=21)	11.8 mg [f] 10 mg 9.5 mg	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[a] *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[a] (≥ 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 [j]
Adult African-American Kidney[k] (≥ 6 months post-transplant) (n=46)	7.8 mg	Day 7[i]	18.4 ± 7.2	5.0 [1 - 16]	272 ± 97	7.8 ± 2.9 [j]

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. *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
k) Conversion to ENVARSUS XR at a mean dose of 80% of the total daily dose of tacrolimus immediate-release resulted in equivalent exposure with a 30% reduction in C_{max}.

In de novo adult kidney transplant patients, the administration of ENVARSUS XR once daily at a starting dose of 0.14 mg/kg/day results in a tacrolimus systemic exposure (AUC_{24}) on Day 1 post-transplant that is up to 10% lower than that of tacrolimus immediate-release capsules twice daily administered at a starting dose of 0.1 mg/kg/day, while similar tacrolimus trough concentrations (C_{24}) are achieved. As steady state is achieved (typically within 7 days of stable ENVARSUS XR dosing), the AUC_{24} of ENVARSUS XR is approximately 15% higher than that of tacrolimus immediate-release capsules, at comparable trough concentrations (C_{24}).

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 de novo kidney transplant patients, the median time to achieve maximum blood concentrations (C_{max}) of ENVARSUS XR was approximately 6 to 10 hours (T_{max}) on day 1 post-transplant; the median T_{max} at steady state was 4 to 6 hours. In healthy subjects, the oral bioavailability of ENVARSUS XR was approximately 50% higher as compared with both tacrolimus immediate-release and extended-release capsule 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.

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. ENVARSUS XR tablets 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 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

Patients With 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)]*.

Patients With 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 clearance was substantially lower in patients with severe hepatic impairment *[see Dosage and Administration (2.3) and Use in Specific Populations (8.7)]*.

Racial or Ethnic Groups

The pharmacokinetics of ENVARSUS XR were evaluated in a study of 46 stable African American kidney transplant recipients converted from tacrolimus immediate-release to ENVARSUS XR. Approximately 80% of the African American patients were carriers of the active, wild type CYP3A5*1 allele. Regardless of genotype status, the PK results demonstrated similar exposure, lower C_{max}, prolonged T_{max}, and increased bioavailability compared to tacrolimus immediate-release *[see Dosage and Administration (2.3) and Use in Specific Populations (8.8)]*.

Male and Female Patients

A formal trial to evaluate the effect of gender on tacrolimus pharmacokinetics has not been conducted. In a sub-group analysis from the two combined Phase 3 studies in kidney transplant recipients (Study 1 and Study 3) performed with ENVARSUS XR over one year of treatment, no gender-dependent differences in tacrolimus systemic exposures were observed.

Drug Interaction Studies

Because tacrolimus is metabolized mainly by CYP3A enzymes, drugs or substances known to inhibit these enzymes and/or are known CYP3A substrates may increase tacrolimus whole blood concentrations. Drugs known to induce CYP3A enzymes may decrease tacrolimus whole blood concentrations *[see Warnings and Precautions (5.9) and Drug Interactions (7.2)]*.

Voriconazole: Co-administration of ENVARSUS XR with voriconazole following 400 mg BID of voriconazole resulted in a tacrolimus mean AUC_{inf} increase by 2.62 fold and C_{max} by 2.03 fold.

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 3mg/kg/day (0.84 times the AUC at the recommended clinical dose of 0.14 mg/kg/day) and in the rat was 5 mg/kg/day (0.24 times the AUC at the recommended clinical dose of 0.14 mg/kg/day) *[see Boxed Warning and 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.

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

Mutagenesis

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

Impairment of Fertility

Tacrolimus subcutaneously administered to male rats at paternally toxic doses of 2 mg/kg/day (2.3 times the recommended clinical dose based on body surface area) or 3 mg/kg/day (3.4 times the recommended clinical dose based on body surface area) resulted in a dose-related decrease in sperm count. Tacrolimus administered orally at 1mg/kg (1.2 times the recommended 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- and post-implantation loss and increased numbers of undelivered and nonviable pups. When administered at 3.2 mg/kg (3.7 times the recommended clinical dose based on body surface area), tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on estrus cycles, parturition, pup viability, and pup malformations.

14 CLINICAL STUDIES

14.1 Clinical Studies in De Novo Kidney Transplant Recipients

Study 1

Study 1 (NCT 01187953) was a Phase 3, 12-month, randomized, double-blind, multinational study comparing once daily ENVARSUS XR (N=268) to twice daily tacrolimus [immediate-release] capsules (N=275) in patients who received a de novo kidney transplant. Patients received the first dose of the study drug anytime within 48 hours of graft reperfusion. All patients received only IL-2 receptor antagonist induction therapy and concomitant treatment with mycophenolate mofetil (MMF) and corticosteroids. Approximately 97% of all patients received antibody induction therapy with basiliximab and 91% of all patients received corticosteroids and MMF.

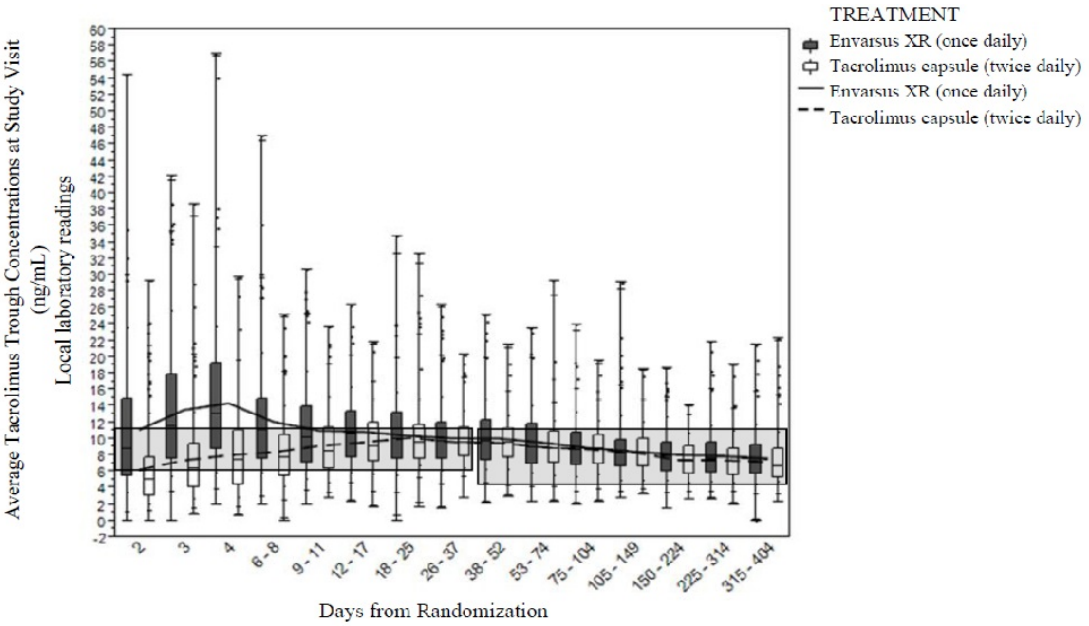
The mean age of the study population was 46 years; 65% were male; 77% were Caucasian, 5% were African-American, 4% were Asian and 14% were categorized as other races. Living donors provided 49% of the organs and 51% of patients received a kidney transplant from a deceased donor. Patients with clinically relevant ECG abnormalities (including QTc prolongation and reversible ischemia) and clinically symptomatic congestive heart failure or patients with documented left ventricular ejection fraction of less than 45% were excluded. Patients with a panel reactive antibody (PRA) >30%, who received a kidney from a non-heart-beating donor or with cold ischemia time >30 hours were also excluded. Premature discontinuation from treatment at the end of one year occurred in 22% of ENVARSUS XR patients and 19% of tacrolimus [immediate-release] capsules patients.

Tacrolimus Therapy

In Study 1, de novo kidney transplant patients were dosed initially at a starting dosage of 0.17 mg/kg given once daily for ENVARSUS XR (approximately 1.2-fold higher than the recommended starting dosage) and 0.1 mg/kg/day (given twice daily) for tacrolimus [immediate-release] capsule, with doses then modified to maintain tacrolimus trough concentrations between 6-11 ng/mL for the first 30 days and then between 4-11 ng/L for the remainder of the study. In the first week of dosing, the tacrolimus doses administered were, on average, ~40% higher in the ENVARSUS XR group compared to the tacrolimus capsule group and were similar in both treatment groups from Day 10 to Week 3. Thereafter, tacrolimus doses were, on average, 10% to 20% lower for ENVARSUS XR than in the tacrolimus capsule group.

Tacrolimus whole blood trough concentrations were monitored on Days 2, 3, 4, 7, 10, 14, 21, 30, 45, 60, 90, 120, 180, 270, and 360. On Day 2 predose, the proportion of patients in the ENVARSUS XR group with tacrolimus trough concentration that were within, above and below the target tacrolimus trough concentration range of 6 to 11 ng/mL was 33%, 39%, and 28%, respectively, compared to 27%, 12%, and 61%, in the tacrolimus [immediate release] capsule group. The average tacrolimus trough concentrations (per local laboratory reading) for the ENVARSUS XR group were above the target range during the first week post-transplant, and higher than in the tacrolimus capsule group during the first 2 weeks post-transplant (see Figure 1). Thereafter, the mean tacrolimus trough concentrations were similar between the treatment groups.

Figure 1. Study 1 Tacrolimus Trough Concentrations by Treatment Group and Visits



Legend: central box represents the 25th to 75th percentile along with the median line (50th percentile); whiskers show the entire range of trough concentrations from minimum to maximum values; line graph connects the mean trough concentration values; shaded gray regions depict the protocol specified target tacrolimus trough concentration ranges

Concomitant Immunosuppressive Drugs

In Study 1, the concomitant use of mycophenolate products was comparable between the ENVARSUS XR and tacrolimus [immediate-release] capsule treatment groups. Patients in both groups started MMF at an average dose of 1 gram twice daily. The MMF daily dose was reduced to less than 2 grams over the course of the study; the mean MMF equivalent total daily dose was approximately 1.5 grams at Month 12 in both treatment groups. Likewise, the average doses of corticosteroids were comparable between the two treatment groups throughout the 12-month study period. Majority (96% ENVARSUS XR and 99% tacrolimus [immediate-release] capsules) of the patients received two 20 mg doses of basiliximab for antibody induction.

Efficacy Results

The efficacy failure rates 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, are shown by treatment group in **Table 10** for the intent-to-treat population.

Table 10. Incidence of BPAR, Graft Loss, Death or Lost to Follow-up at 12 Months in De Novo Kidney Transplant Patients in Study 1

	ENVARSUS XR, MMF, steroids, and IL-2 receptor antagonist induction therapy N=268	**Tacrolimus [Immediate-Release] capsules, MMF, steroids, and IL-2 receptor antagonist induction therapy N=275**
Overall Treatment Difference of efficacy failure compared to tacrolimus immediate-release (95% CI)[a]	-1.0% (-7.6%, 5.6%)	
Treatment Failure	50 (18.7%)	54 (19.6%)
Biopsy Proven Acute Rejection	36 (13.4%)	37 (13.5%)
Graft Failure	9 (3.4%)	11 (4.0%)
Death	8 (3.0%)	8 (2.9%)
Lost to Follow-up	4 (1.5%)	5 (1.8%)

[a] 95% CI was calculated using normal approximation.

Glomerular Filtration Rates

Renal function was assessed as change from Day 30 (baseline) by eGFR calculated using the MDRD7 equation. Baseline eGFR values were 53.8 ml/min/1.73 m^2 and 54.4 ml/min/1.73 m^2, and 12 month eGFR values were 58.6 ml/min/1.73 m^2 and 59.8 ml/min/1.73 m^2 in the ENVARSUS XR and the tacrolimus [immediate-release] capsule groups, respectively, maintaining the small difference of approximately

1ml/min/1.73 m^2 between the treatment groups.

Study 2

Study 2 (NCT 00765661) was an open-label Phase 2 study conducted in de novo kidney transplant patients randomized to once daily ENVARSUS XR (N=32) or twice daily tacrolimus [immediate-release] capsule(N=31). The study was conducted in the US and patients received an organ from a deceased or living donor. Pharmacokinetics were evaluated during the first 2 weeks with an additional 50-week treatment and follow-up to evaluate safety and efficacy.

Study 2 did not have any exclusion criteria based on cardiac disease or ECG findings but patients who received a kidney from a non-heart-beating donor or with cold ischemia time ≥ 36 hours were excluded. Patients were randomized within 12 hours after transplantation and received the first dose of the study drug within 48 hours of graft reperfusion. Induction treatment and concomitant immunosuppressive therapy were allowed per center-specific practices.

The mean age of study population was 47 years (range 23-69); 68% were male; 75% were Caucasian, 21% were African- American, 5% were Asian. Two patients in each group withdrew early from the study due to adverse events.

Tacrolimus Therapy

In Study 2, *de novo* kidney transplant patients received a starting dosage of 0.14 mg/kg/day (given once daily) for ENVARSUS XR and 0.20 mg/kg/day (given twice daily) for tacrolimus [immediate-release] capsule. On Day 2 predose, the proportion of patients in the ENVARSUS XR group with tacrolimus trough concentration that were within, above, and below 6 to 11 ng/mL was 53%, 11%, and 37%, respectively. In Study 1, the proportion of de novo kidney transplant patients receiving a starting dose of 0.1 mg/kg/day of tacrolimus capsules that were within, above, and below 6 to 11 ng/mL on Day 2 predose was 27%, 12%, and 61%, respectively.

Concomitant Immunosuppressive Drugs

In Study 2, concomitant therapy with mycophenolate products or azathioprine, corticosteroids, and antibody induction was permitted but not required. The mean daily MMF, prednisone, and antibody induction doses were similar between the ENVARSUS XR and tacrolimus capsules treatment groups.

Efficacy

There were no deaths or graft failures in Study 2. Acute rejection rates at 12 months were 3.1% (1/32) in the ENVARSUS XR group and 6.5% (2/31) in the tacrolimus capsules group and 2 patients (one in each group) were lost to follow-up.

14.2 Conversion Study from Tacrolimus Capsules in Stable Kidney Transplant Recipients

Study 3

The conversion study, Study 3 (NCT00817206), was a Phase 3 randomized, open-label, multinational study evaluating once daily ENVARSUS XR when used to replace tacrolimus [immediate-release] capsules 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] capsules 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 capsules to once daily ENVARSUS XR (N=163) or 2) continue tacrolimus capsules 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 capsule patients.

Tacrolimus Therapy

In Study 3, stable kidney transplant patients converted to ENVARSUS XR at an average daily dose that was 80% of their tacrolimus [immediate-release] capsules 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 capsules 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 capsules continuation group; the baseline values were 7.8 ± 2.3, and 8.0 ± 2.3, respectively.

MMF Therapy

In Study 3, the average daily mycophenolate equivalent doses were comparable between the ENVARSUS XR and tacrolimus capsules 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 11** for the modified intent-to-treat population.

Table 11. Incidence of BPAR, Graft Loss, Death or Lost to Follow-up at 12 Months in Stable Kidney Transplant Patients in Study 3

	ENVARSUS XR ± Steroids ± MMF, MPS, or AZA N=162	**Tacrolimus [Immediate-Release] Capsules ± Steroids ± MMF, MPS, or AZA N=162**
Treatment Failure	4 (2.5%)	4 (2.5%)
Overall Treatment Difference of efficacy failure compared to tacrolimus immediate-release (95% CI)[a]	0% (-4.2%, 4.2%)	
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 m^2 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 capsules treatment groups, respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

ENVARSUS XR is supplied in round HDPE bottles with twist-off caps (see **Table 12**); the statement 'ONCE-DAILY' appears on its labels.

Table 12. Strengths of ENVARSUS XR

Strength	Description	NDC
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.	30-count (NDC 68992-3075-3) 100-count (NDC 68992-3075-1)
1 mg	Oval, white to off-white uncoated extended-release tablet, debossed with "1" on one side and "TCS" on the other side.	30-count (NDC 68992-3010-3) 100-count (NDC 68992-3010-1)
4 mg	Oval, white to off-white uncoated extended-release tablet, debossed with "4" on one side and "TCS" on the other side.	30-count (NDC 68992-3040-3) 100-count (NDC 68992-3040-1)

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

17 PATIENT COUNSELING INFORMATION

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

17.1 Administration

Advise patients 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. at least 1 hour before or at least 2 hours after a meal 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 alcoholic beverages, grapefruit, and grapefruit juice while on ENVARSUS XR *[see Dosage and Administration (2.1) and Drug Interactions (7.2)]*.
- Take a missed dose as soon as possible but not more than 15 hours after the scheduled time (i.e., for a missed 8 AM dose, take it no later than 10 PM). 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)]*.

17.2 Development of Lymphoma and Other Malignancies

Inform patients that they are at an increased risk of developing lymphomas and other malignancies, particularly of the skin, due to immunosuppression. Advise patients to limit exposure to sunlight and ultraviolet (UV) light by wearing protective clothing and use a sunscreen with a high protection factor *[see Boxed Warning and Warnings and Precautions (5.1)]*.

17.3 Increased Risk of Infection

Inform patients that they are at an increased risk of developing a variety of infections, including opportunistic infections, due to immunosuppression and to contact their physician if they develop any symptoms of infection such as fever, sweats or chills, cough or flu-like symptoms, muscle aches, or warm, red, painful areas on the skin *[see Boxed Warning and Warnings and Precautions (5.2)]*.

17.4 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)]*.

17.5 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)]*.

17.6 Neurotoxicity

Inform patients that they are at risk of developing adverse neurologic effects including seizure, altered mental status, and tremor. Advise patients to contact their physician should they develop vision changes, delirium, or tremors *[see Warnings and Precautions (5.6)]*.

17.7 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)]*.

17.8 Hypertension

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

17.9 Drug Interactions

Instruct patients to tell their healthcare providers when they start or stop taking any concomitant medications, including prescription and non-prescription medicines, natural or herbal remedies, dietary supplements and vitamins. Some medications could alter tacrolimus concentrations in the blood and thus may require the adjustment of the dosage of ENVARSUS XR. Advise patients to avoid grapefruit, grapefruit juice and alcoholic beverages *[see Warnings and Precautions (5.9) and Drug Interactions (7)]*.

17.10 Pregnancy, Lactation and Infertility

Inform women of childbearing potential that ENVARSUS XR can harm the fetus. Instruct male and

female patients to discuss with their healthcare provider family planning options including appropriate contraception. Also discuss with pregnant patients the risks and benefits of breastfeeding their infant *[see Use in Specific Populations (8.1, 8.2, 8.3)]*.

Encourage female transplant patients who become pregnant and male patients who have fathered a pregnancy, exposed to immunosuppressants including tacrolimus, to enroll in the voluntary Transplantation Pregnancy Registry International. To enroll or register, patients can call the toll-free number 1-877-955-6877 or https://www.transplantpregnancyregistry.org.

Based on animal studies, ENVARSUS XR may affect fertility in males and females *[see Nonclinical Toxicology (13.1)]*.

17.11 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.
Cary, North Carolina 27513
United States

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 healthcare provider about your medical condition or your treatment. If you have any questions about ENVARSUS XR, ask your healthcare provider 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
   - cough or flu-like symptoms
   - warm, red, or painful areas on your skin
   - muscle aches
   - sweats or chills

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, tacrolimus [immediate-release] capsules or tacrolimus for oral suspension. Your healthcare provider 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 healthcare provider if you:

- plan to receive any live vaccines. Ask your healthcare provider if you are not sure if your vaccine is a live vaccine.

- have or have had liver, kidney or heart problems.
- have any other medical conditions.
- are pregnant or plan to become pregnant. ENVARSUS XR may harm your unborn baby.
  - If you are able to become pregnant, you should use effective birth control before and during treatment with ENVARSUS XR. Talk to your healthcare provider about birth control methods that may be right for you.
  - Males who have female partners that are able to become pregnant should also use effective birth control before and during treatment with ENVARSUS XR. Talk to your healthcare provider before starting treatment with ENVARSUS XR about birth control methods that may be right for you.
  - There is a pregnancy registry for females who become pregnant and males who have fathered a pregnancy during treatment with ENVARSUS XR. The purpose of this registry is to collect information about your health and of your baby. To enrol in this voluntary registry, call 1-877-955-6877.
- are breastfeeding or plan to breastfeed. ENVARSUS XR passes into your breast milk. You and your healthcare provider should decide if you will breastfeed while taking ENVARSUS XR

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, natural, herbal or nutritional 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 healthcare provider tells you to take it.
- Your healthcare provider may change your dose of ENVARSUS XR if needed. **Do not** stop taking or change your dose of ENVARSUS XR without talking to your healthcare provider.
- Take ENVARSUS XR once daily with fluid (preferably water) on an empty stomach, at least 1 hour before or at least 2 hours after a meal, at the same time each day (preferably in the morning).
- Take ENVARSUS XR tablets whole. **Do not** chew, divide, crush, or dissolve ENVARSUS XR tablets before swallowing. If you cannot swallow ENVARSUS XR tablets whole, tell your healthcare provider.
- 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 missing 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 healthcare provider 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 the most important information I should know about ENVARSUS XR?"**
- **problems from medication errors such as 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 healthcare provider right away if you think you were given the wrong medicine.
  - Ask your healthcare provider or pharmacist if you are not sure what ENVARSUS XR should look like.
- **high blood sugar (diabetes)**. Your healthcare provider may do certain tests to check for diabetes while you take ENVARSUS XR. Call your healthcare provider 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**. Kidney problems are serious and common side effects of ENVARSUS XR. Your healthcare provider may do certain tests to check for kidney function while you take ENVARSUS XR.
- **nervous system problems**. Nervous system problems are a serious and common side effect of ENVARSUS XR. Call your healthcare provider right away if you get any of these symptoms while taking ENVARSUS XR. These could be signs of serious nervous system problems:
  - confusion
  - coma
  - seizures
  - numbness and tingling
  - headache
  - vision changes
  - muscle tremors
- **high levels of potassium in your blood**. Your healthcare provider may do certain tests to check your potassium level while you take ENVARSUS XR.
- **high blood pressure**. Your healthcare provider will monitor your blood pressure while you take ENVARSUS XR.
- **changes in the electrical activity of your heart (QT prolongation).**
- **severe low blood cell count (anemia)**

The most common side effects of ENVARSUS XR are 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 healthcare provider or pharmacist.

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

How should I store 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.

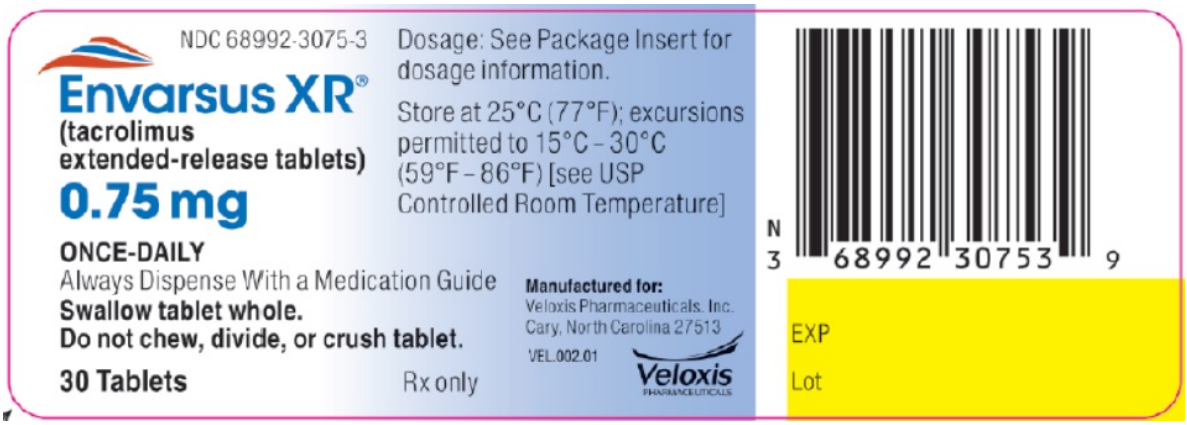
General information about the safe and effective use of ENVARSUS XR.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ENVARSUS XR for a condition for which it was not prescribed. Do not give ENVARSUS XR to other people, even if they have the same 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 healthcare provider. You can ask your pharmacist or healthcare provider 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
Manufactured for: **Veloxis Pharmaceuticals, Inc.,** Cary, North Carolina 27513, United States

This Medication Guide has been approved by the U.S. Food and Drug Administration.
Revised: December 2018

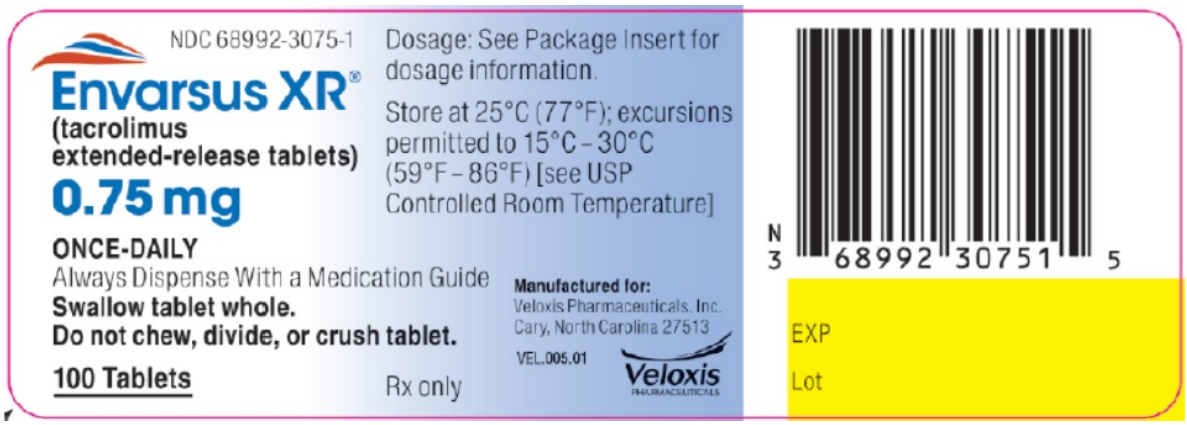
PRINCIPAL DISPLAY PANEL - Envarsus 0.75 mg 30 Count Carton Label

PRINCIPAL DISPLAY PANEL - Envarsus 0.75 mg 30 Count Bottle Label

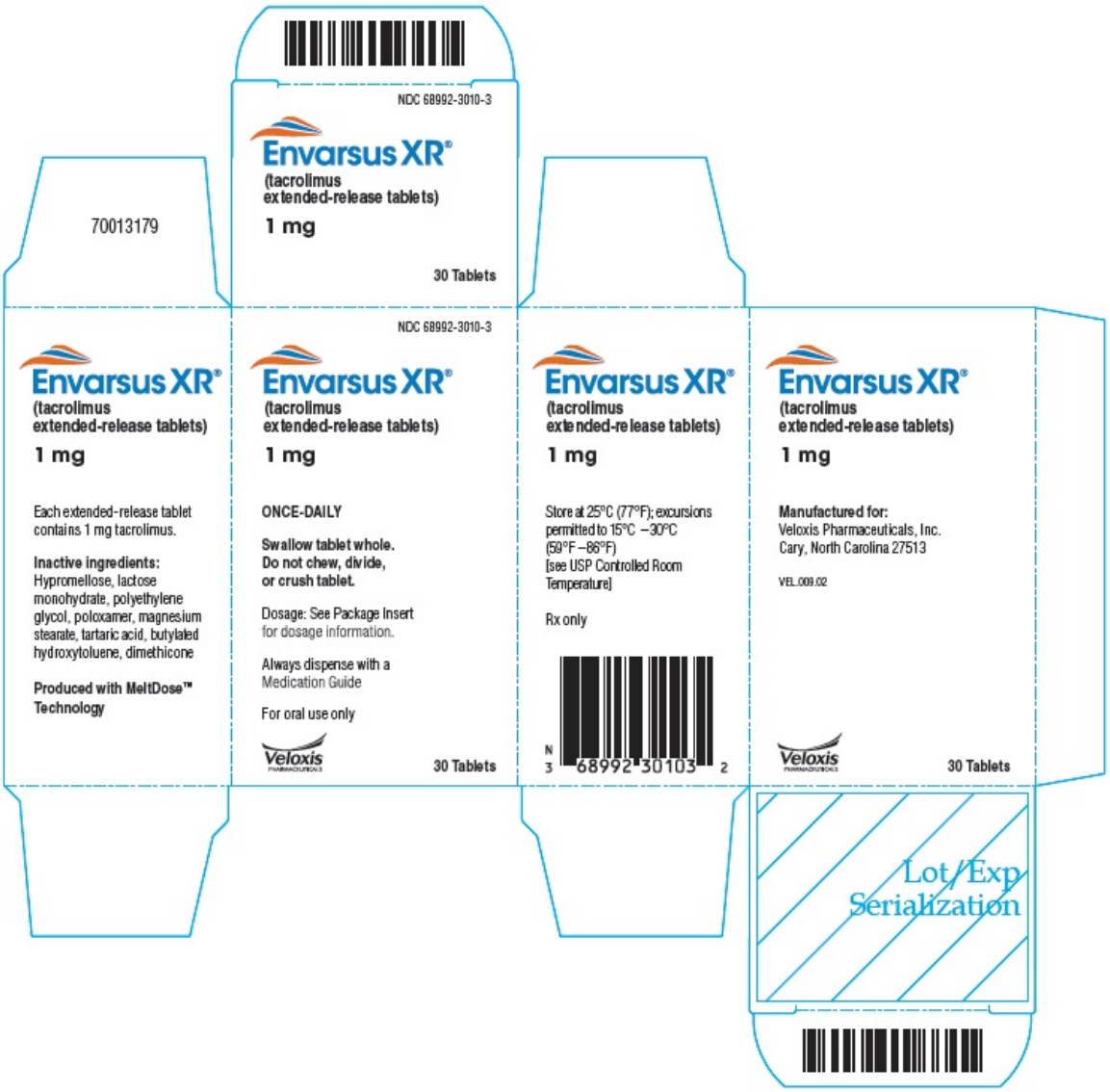


PRINCIPAL DISPLAY PANEL - Envarsus 0.75 mg 100 Count Carton Label

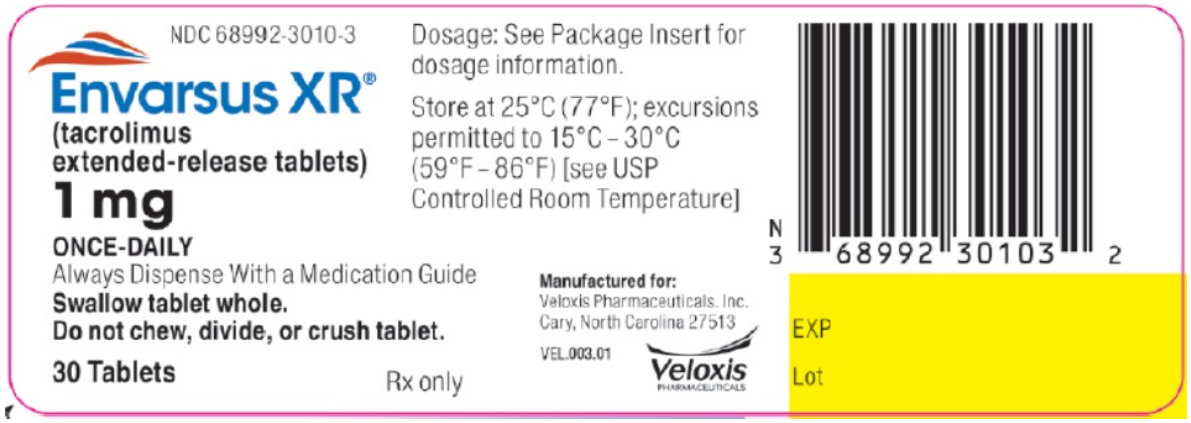
PRINCIPAL DISPLAY PANEL - Envarsus 0.75 mg 100 Count Bottle Label



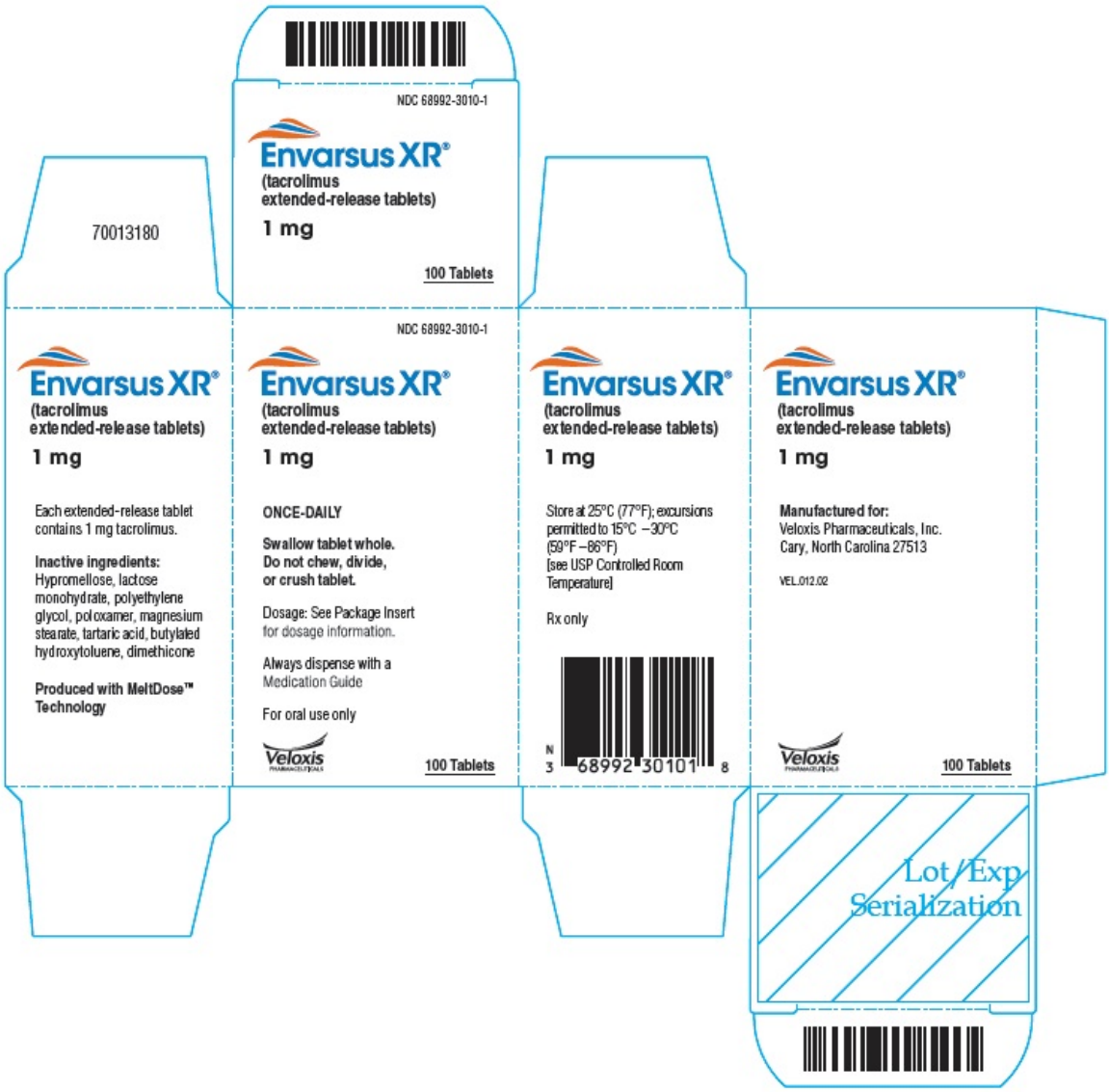
PRINCIPAL DISPLAY PANEL - Envarsus 1 mg 30 Count Carton Label



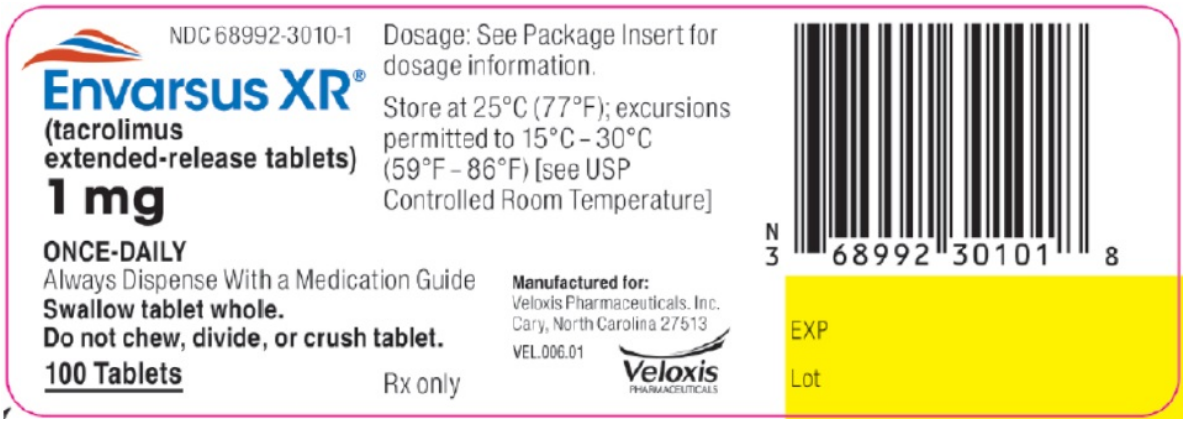
PRINCIPAL DISPLAY PANEL - Envarsus 1 mg 30 Count Bottle Label



PRINCIPAL DISPLAY PANEL - Envarsus 1 mg 100 Count Carton Label

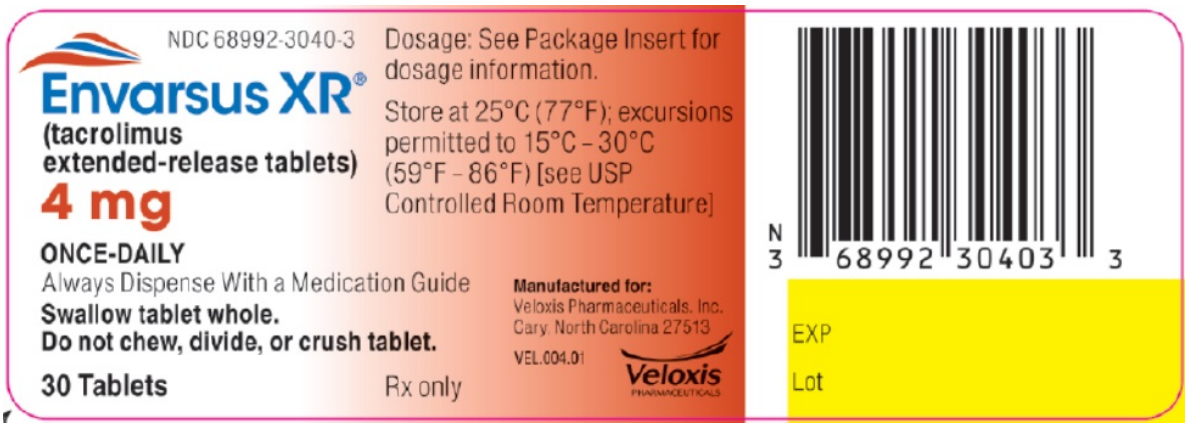


PRINCIPAL DISPLAY PANEL - Envarsus 1 mg 100 Count Bottle Label



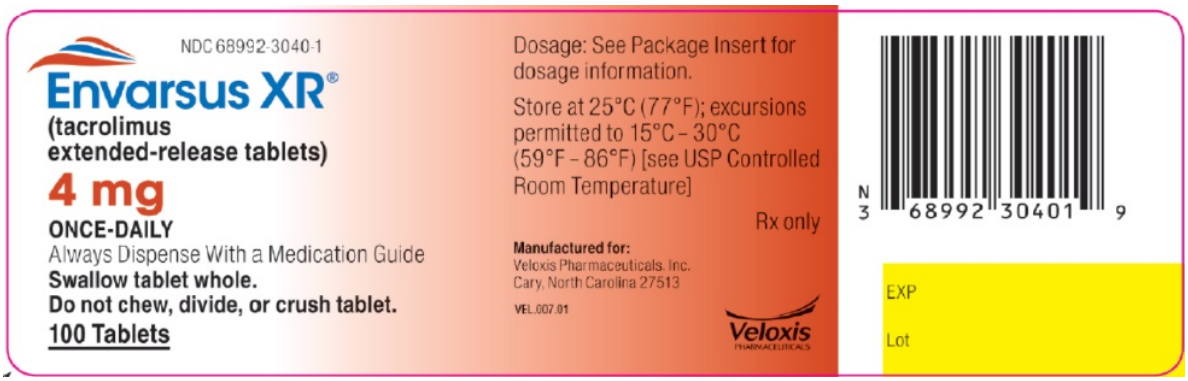
PRINCIPAL DISPLAY PANEL - Envarsus 4 mg 30 Count Carton Label

PRINCIPAL DISPLAY PANEL - Envarsus 4 mg 30 Count Bottle Label



PRINCIPAL DISPLAY PANEL - Envarsus 4 mg 100 Count Carton Label

PRINCIPAL DISPLAY PANEL - Envarsus 4 mg 100 Count Bottle Label



ENVARSUS XR

tacrolimus tablet, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68992-3075
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TACROLIMUS (UNII: WM0HAQ4WNM) (TACROLIMUS ANHYDROUS - UNII:Y5L2157C4J)	TACROLIMUS ANHYDROUS	0.75 mg

Inactive Ingredients

Ingredient Name	Strength
HYPROMELLOSES (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
POLYETHYLENE GLYCOL 6000 (UNII: 30IQX730WE)	
POLOXAMER 188 (UNII: LQA7B6G8JG)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TARTARIC ACID (UNII: W4888I119H)	
BUTYLATED HYDROXYTOLUENE (UNII: 1P9D0Z171K)	
DIMETHICONE (UNII: 92RU3N3Y1O)	

Product Characteristics

Color	WHITE (White to Off-White)	**Score**	no score
Shape	OVAL	**Size**	11mm
Flavor		**Imprint Code**	075;TCS
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68992-3075-3	1 in 1 CARTON	09/01/2015	
1		1 in 1 POUCH		
1		30 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		
2	NDC:68992-3075-1	1 in 1 CARTON	09/01/2015	
2		1 in 1 POUCH		
2		100 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA206406	09/01/2015	

ENVARSUS XR

tacrolimus tablet, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68992-3010
Route of Administration	ORAL		

Active Ingredient/Active Moiety

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

Inactive Ingredients

Ingredient Name	Strength
HYPROMELLOSES (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
POLYETHYLENE GLYCOL 6000 (UNII: 30IQX730WE)	
POLOXAMER 188 (UNII: LQA7B6G8JG)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TARTARIC ACID (UNII: W4888I119H)	
BUTYLATED HYDROXYTOLUENE (UNII: 1P9D0Z171K)	
DIMETHICONE (UNII: 92RU3N3Y1O)	

Product Characteristics

Color	WHITE (White to Off-White)	**Score**	no score
Shape	OVAL	**Size**	11mm
Flavor		**Imprint Code**	1;TCS
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68992-3010-3	1 in 1 CARTON	09/01/2015	
1		1 in 1 POUCH		
1		30 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		
2	NDC:68992-3010-1	1 in 1 CARTON	09/01/2015	
2		1 in 1 POUCH		
2		100 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA206406	09/01/2015	

ENVARSUS XR

tacrolimus tablet, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68992-3040
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TACROLIMUS (UNII: WM0HAQ4WNM) (TACROLIMUS ANHYDROUS - UNII:Y5L2157C4J)	TACROLIMUS ANHYDROUS	4 mg

Inactive Ingredients

Ingredient Name	Strength
HYPROMELLOSES (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
POLYETHYLENE GLYCOL 6000 (UNII: 30IQX730WE)	
POLOXAMER 188 (UNII: LQA7B6G8JG)	

MAGNESIUM STEARATE (UNII: 70097M6I30)	
TARTARIC ACID (UNII: W4888I119H)	
BUTYLATED HYDROXYTOLUENE (UNII: 1P9D0Z171K)	
DIMETHICONE (UNII: 92RU3N3Y1O)	

Product Characteristics

Color	WHITE (White to Off-White)	**Score**	no score
Shape	OVAL	**Size**	16mm
Flavor		**Imprint Code**	4;TCS
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68992-3040-3	1 in 1 CARTON	09/01/2015	
1		1 in 1 POUCH		
1		30 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		
2	NDC:68992-3040-1	1 in 1 CARTON	09/01/2015	
2		1 in 1 POUCH		
2		100 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA206406	09/01/2015	

Labeler - Veloxis Pharmaceuticals, Inc (028252150)

Establishment

Name	Address	ID/FEI	Business Operations
Veloxis Pharmaceuticals, Inc		028252150	MANUFACTURE(68992-3075, 68992-3010, 68992-3040)

Establishment

Name	Address	ID/FEI	Business Operations
Rottendorf Pharma GmbH		315974691	manufacture(68992-3075, 68992-3010, 68992-3040) , analysis(68992-3075, 68992-3010, 68992-3040) , label(68992-3075, 68992-3010, 68992-3040) , pack(68992-3075, 68992-3010, 68992-3040)

Establishment

Name	Address	ID/FEI	Business Operations
Carton Service, Incorporated		928861723	label(68992-3075, 68992-3010, 68992-3040) , pack(68992-3075, 68992-3010, 68992-3040)