Once-daily

Envarsus XR®

(tacrolimus extended-release tablets)

ENVARSUS XR MELTDOSE® LEAVE-BEHIND

STABILIZED EXPOSURE, EXTENDED RELEASE

ENVARSUS XR is a once-daily tacrolimus created with proprietary MeltDose® technology that improves the release and absorption of tacrolimus over 24 hours.[1-9]

INDICATIONS AND USAGE

ENVARSUS XR is indicated for the prophylaxis of organ rejection in de novo kidney transplant patients in combination with other immunosuppressants.

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

IMPORTANT SAFETY INFORMATION

WARNING: MALIGNANCIES AND SERIOUS INFECTIONS
Increased risk for developing serious infections and malignancies with ENVARSUS XR or other immuno-suppressants that may lead to hospitalization or death

CONTRAINDICATIONS

ENVARSUS XR is contraindicated in patients with known hypersensitivity to tacrolimus or to any of the ingredients in ENVARSUS XR.

WARNINGS AND PRECAUTIONS

Lymphoma and Other Malignancies: Immunosuppressants, including ENVARSUS XR, increase the risk of developing lymphomas and other malignancies, particularly of the skin. Post-transplant lymphoproliferative disorder (PTLD), associated with Epstein-Barr Virus (EBV), has been reported in immunosuppressed organ transplant patients.

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.

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. in some cases leading to adverse reactions. ENVARSUS XR is not interchangeable or substitutable with tacrolimus extended-release capsules, tacrolimus capsules or tacrolimus for oral suspension.

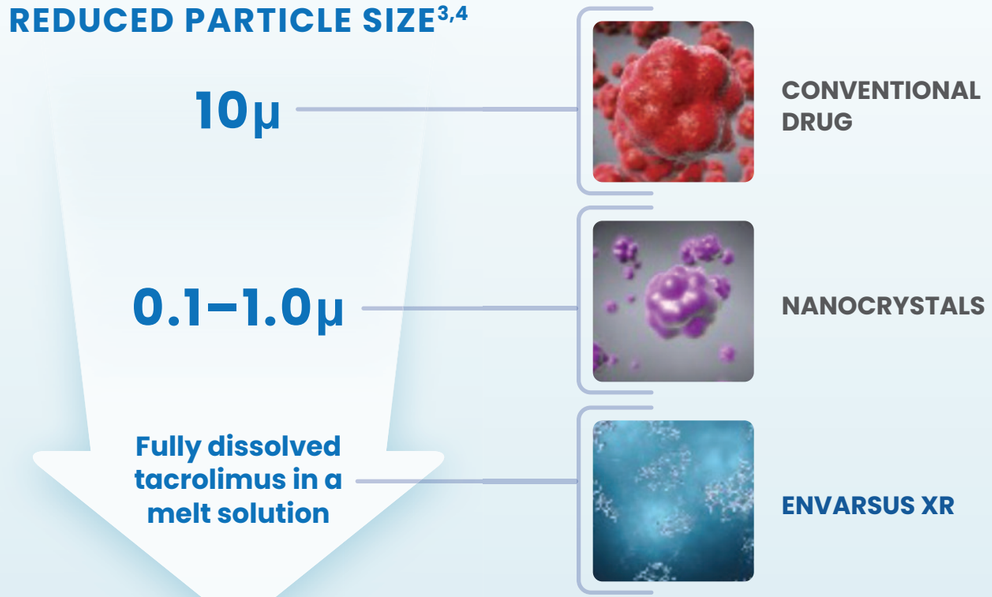
New Onset Diabetes after Transplant: ENVARSUS XR caused new onset diabetes after transplant (NODAT) in kidney transplant patients, which may be reversible in some patients. African-American and Hispanic kidney transplant patients are at an increased risk.

Nephrotoxicity due to ENVARSUS XR and Drug Interactions: ENVARSUS XR, like other calcineurin-inhibitors, can cause acute or chronic nephrotoxicity. In patients with elevated serum creatinine and tacrolimus whole blood trough concentrations greater than the recommended range, consider dosage reduction or temporary interruption of tacrolimus administration. The risk for nephrotoxicity may increase when ENVARSUS XR is concomitantly administered with CYP3A inhibitors (by increasing tacrolimus whole blood concentrations) or drugs associated with nephrotoxicity. When tacrolimus is used concurrently with CYP3A inhibitors or other known nephrotoxic drugs, monitor renal function and tacrolimus blood concentrations, and adjust dose of both tacrolimus and/or concomitant medications during concurrent use.

Please see Important Safety Information continued throughout and accompanying full Prescribing Information, including Boxed Warning, and updated Warnings and Precautions.

Discover the MeltDose® difference

With the MeltDose® technology of once-daily ENVARSUS XR, a smaller particle size allows for optimized dissolution, absorption, and oral bioavailability as compared with other conventional drugs.[3]



ENVARSUS XR stabilizes exposure with extended release over 24 hours throughout the entire GI tract[1,9]

The enhanced delivery of MeltDose® technology of ENVARSUS XR results in absorption characteristics that enable once-daily extended release and enhanced bioavailability.[1,9]

MELTDOSE® TECHNOLOGY IMPROVES THE RELEASE AND ABSORPTION OF TACROLIMUS OVER 24 HOURS[1]

These images are illustrations of scintigraphy data showing that dissolution of ENVARSUS XR takes place throughout the gut.[1] Scintigraphic images were acquired at approximately 10- to 15-minute intervals until 8 hours post-dose, then at 30-minute intervals until 16 hours post-dose, and then at 24, 36, 48, and 72 hours post-dose.[1] At 24 hours, ENVARSUS XR is present in the more distal regions of gastrointestinal tract.[1] CYP3A5 activity is greatest in the proximal gastrointestinal region and decreases downstream throughout the bowel.[10] Therefore, the delayed absorption throughout the gastrointestinal tract results in decreased presystemic metabolism.[1,10]

Study design: Single-dose, 2-way, open-label, replicate design, phase 1, pharmacoscintigraphic study performed in 8 participants.

CYP3A5=cytochrome family P450, subfamily 3A, member 5; GI=gastrointestinal.

IMPORTANT SAFETY INFORMATION (CONTINUED)
WARNINGS AND PRECAUTIONS (CONTINUED)

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.

Hyperkalemia: Mild to severe hyperkalemia, which may require treatment, has been reported with tacrolimus including ENVARSUS XR. Concomitant use of agents associated with hyperkalemia may increase the risk for hyperkalemia.

Hypertension: Hypertension is a common adverse reaction of ENVARSUS XR therapy and may require antihypertensive therapy.

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. Therefore, adjust ENVARSUS XR dose and monitor tacrolimus whole blood trough concentrations when co-administering ENVARSUS XR with strong CYP3A inhibitors or strong CYP3A inducers. A rapid, sharp rise in tacrolimus levels has been reported after co-administration with strong CYP3A4 inhibitors despite an initial reduction of tacrolimus dose. Early and frequent monitoring of tacrolimus whole blood trough levels is recommended.

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 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. When co-administering ENVARSUS XR with other substrates and/or inhibitors of CYP3A, especially those that also have the potential to prolong the QT interval, a reduction in ENVARSUS XR dosage, monitoring of tacrolimus whole blood concentrations, and monitoring for QT prolongation is recommended.

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. Inactivated vaccines noted to be safe for administration after transplantation may not be sufficiently immunogenic during treatment with ENVARSUS XR.

Pure Red Cell Aplasia: Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. If PRCA is diagnosed, consider discontinuation of ENVARSUS XR.

Cannabidiol Drug Interactions: When cannabidiol and ENVARSUS XR are co-administered, closely monitor for an increase in tacrolimus blood levels and for adverse reactions suggestive of tacrolimus toxicity. A dose reduction of ENVARSUS XR should be considered as needed when ENVARSUS XR is co-administered with cannabidiol.

Thrombotic Microangiopathy (TMA) Including Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura: Cases of thrombotic microangiopathy (TMA), including hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP), have been reported in patients treated with ENVARSUS XR. Transplant patients may have other risk factors which contribute to the risk of TMA. In patients with signs and symptoms of TMA, consider ENVARSUS XR as a risk factor. Concurrent use of ENVARSUS XR and mammalian target of rapamycin (mTOR) inhibitors may contribute to the risk of TMA.

ADVERSE REACTIONS

De Novo kidney transplant patients: Most common adverse reactions (incidence ≥15%) reported with ENVARSUS XR are diarrhea, anemia, urinary tract infection, hypertension, tremor, constipation, diabetes mellitus, peripheral edema, hyperkalemia and headache.

Conversion of kidney transplant patients from immediate-release tacrolimus: Most common adverse reactions (incidence ≥10%) reported with ENVARSUS XR include: diarrhea and blood creatinine increased.

USE IN SPECIFIC POPULATIONS

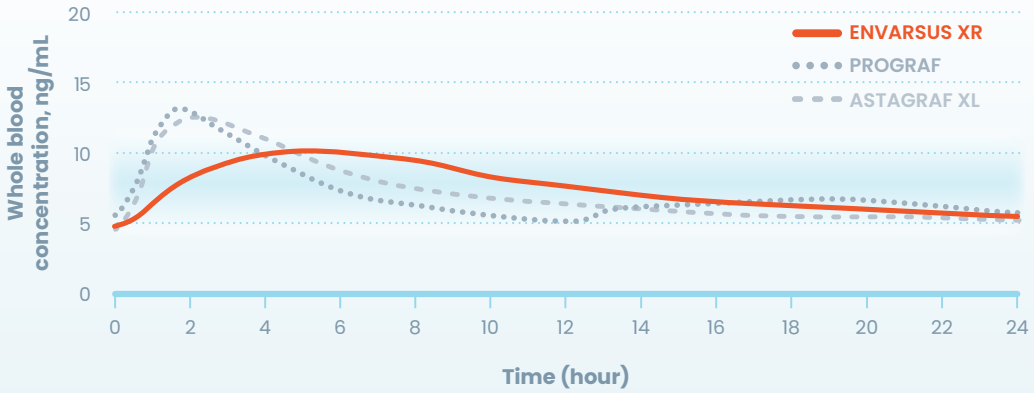
Pregnancy: Based on postmarketing surveillance, registry and animal data may cause fetal harm. Advise pregnant women of the potential risk to the fetus.

Nursing Mothers: Tacrolimus is present in human milk. Discontinue drug or nursing, taking into account the importance of drug to the mother.

Please see Important Safety Information continued throughout and accompanying full Prescribing Information, including Boxed Warning, and updated Warnings and Precautions.

ENVARSUS XR delivers target exposure with significantly lower peak vs PROGRAF® or ASTAGRAF XL®[2]

ENVARSUS XR does not cause the peaks associated with immediate-release and other tacrolimus formulations, thereby achieving consistent tacrolimus exposure while maintaining target trough.[2]



Study design: The ASTCOFF study. Open-label, randomized, 2-sequence, 3-period crossover trial of adult stable kidney transplant patients (N=32). After randomization, each patient received PROGRAF followed by either ENVARSUS XR followed by ASTAGRAF XL or ASTAGRAF XL followed by ENVARSUS XR. Twenty-four-hour PK collections were performed at the end of each 1-week period; a total of 17 or 21 time points were sampled over 24 hours. The primary objective of the study was to evaluate the PK profile of ENVARSUS XR compared with PROGRAF and ASTAGRAF XL.

Clinical benefit of the differences in ENVARSUS XR PK profile has not been established.

PK=pharmacokinetic.

ENVARSUS XR has demonstrated efficacy at 90 days,[5] 1 year,[5,9] and 2 years,[6] and an established safety profile out to 2 years.[6,9]

IMPORTANT SAFETY INFORMATION (CONTINUED)
USE IN SPECIFIC POPULATIONS (CONTINUED)

Females and Males of Reproductive Potential: 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. Based on animal studies, ENVARSUS XR may affect fertility in males and females.

Pediatric Use: The safety and efficacy of ENVARSUS XR in pediatric patients have not been established.

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.

Renal Impairment: Frequent monitoring of renal function is recommended. Lower doses may be required.

Hepatic Impairment: Frequent monitoring of tacrolimus trough concentrations is recommended. 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.

Race: African-American patients may require higher doses to attain comparable trough concentrations compared to Caucasian patients. 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.

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

Please see accompanying full Prescribing Information, including Boxed Warning, and updated Warnings and Precautions.

Visit ENVARSUSXR.com/hcp to learn more about our unique MeltDose® technology, or scan the QR code.

References: 1. Nigro V, Glicklich A, Weinberg J. Improved bioavailability of MELTDOSE once-daily formulation of tacrolimus (LCP-Tacro) with controlled agglomeration allows for consistent absorption over 24 hrs: a scintigraphic and pharmacokinetic evaluation. *Am J Transplant*. 2013;13(suppl 5):335. **2.** Tremblay S, Nigro V, Weinberg J, et al. A steady-state head-to-head pharmacokinetic comparison of all FK-506 (tacrolimus) formulations (ASTCOFF): an open-label, prospective, randomized, two-arm, three-period crossover study. *Am J Transplant*. 2017;17(2):432-442. **3.** Grinyó JM, Petruzzelli S. Once-daily LCP-tacro MeltDose tacrolimus for the prophylaxis of organ rejection in kidney and liver transplantations. *Expert Rev Clin Immunol*. 2014;10(12):1567-1579. **4.** Data on file. Veloxis Pharmaceuticals, Inc.; 2018. **5.** Budde K, Bunnapradist S, Grinyo JM, et al. Novel once-daily extended-release tacrolimus (LCPT) versus twice-daily tacrolimus in de novo kidney transplants: one-year results of phase III, double-blind, randomized trial. *Am J Transplant*. 2014;14(12):2796-2806. **6.** Rostaing L, Bunnapradist S, Grinyó JM, et al. Novel once-daily extended-release tacrolimus versus twice-daily tacrolimus in de novo kidney transplant recipients: two-year results of phase 3, double-blind, randomized trial. *Am J Kidney Dis*. 2016;67(4):648-659. **7.** Trofe-Clark J, Brennan DC, West-Thielke P, et al. Results of ASERTAA, a randomized prospective crossover pharmacogenetic study of immediate-release versus extended-release tacrolimus in African American kidney transplant recipients. *Am J Kidney Dis*. 2018;71(3):315-326. **8.** Bunnapradist S, Rostaing L, Alloway RR, et al. LCPT once-daily extended-release tacrolimus tablets versus twice-daily capsules: a pooled analysis of two phase 3 trials in important de novo and stable kidney transplant recipient subgroups. *Transpl Int*. 2016;29(5):603-611. **9.** ENVARSUS XR [package insert]. Cary, NC: Veloxis Pharmaceuticals, Inc.; 4/2024. **10.** Thörn M, Finnström N, Lundgren S, et al. Cytochromes P450 and MDR1 mRNA expression along the human gastrointestinal tract. *Br J Clin Pharmacol*. 2005;60(1):54-60.

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