Once-daily
Envarsus XR®
(tacrolimus extended-release tablets)

CONSISTENT EXPOSURE IN EACH DOSE, SUPPORT AT EVERY STEP

FROM THE OPERATING ROOM TO LONG AFTER, EACH MOMENT IN THE PATIENT JOURNEY MATTERS

See how you can help patients after kidney transplant with the consistent PK profile and robust patient support programs of ENVARSUS XR.[1]

PK=pharmacokinetic.

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

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 immunosuppressants 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.

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

What awaits your patients after transplant?

Post-kidney transplant care presents a variety of challenges—from optimizing tacrolimus exposure to managing varying metabolism across patient types.

Low tacrolimus levels on day 2 and day 5 post-transplant are early predictors of rejection[2,3]

Tacrolimus is characterized by a narrow therapeutic range—and numerous adverse outcomes are associated with levels outside of the target therapeutic range[4-6]

Complex dosing regimens can threaten adherence[7]

Rapid metabolizers* face unique risks, and need more tacrolimus than typical patients[8,9]

- Complications: CNI nephrotoxicity and BK nephropathy[10]
- Higher peaks: 34% increase in C_{max} of IR-Tac[1]
- Rejection: Higher risk for BPAR in the first 90 days after transplant (P<0.006)[11]

RAPID METABOLISM OF TACROLIMUS IS COMMON

45%–80%
African American[1,12]

15%–35%
Asian[12]

5%–30%
Caucasian[12,13]

25%-30%
Hispanic[12,13]

Encourage the transplant team to consider a tacrolimus formulation that supports a smooth and consistent PK profile from day one.[1,14]

*Rapid metabolizers are expressors of the CYP3A5*1 gene variant.[4] The definition of "rapid metabolizer" may vary by study.
BK=BK virus; C_{max}=peak plasma concentration; BPAR=biopsy-proven acute rejection; CNI=calcineurin inhibitor.

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

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.

Help patients navigate the post-transplant period with ENVARSUS XR

A ONCE-DAILY, EXTENDED-RELEASE TACROLIMUS THAT OFFERS CONSISTENCY, CONTROL, CONVENIENCE, AND CONFIDENCE[1,14-17]

CONSISTENCY
Smooth and predictable PK profile, even in rapid metabolizers[1,14]

CONTROL
Proven control over time[16,17]

CONVENIENCE
Once-daily dosing[15]

CONFIDENCE
A variety of resources and support

When evaluating tacrolimus formulations, consider one that helps deliver consistency, control, convenience, and confidence throughout the treatment journey.

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.

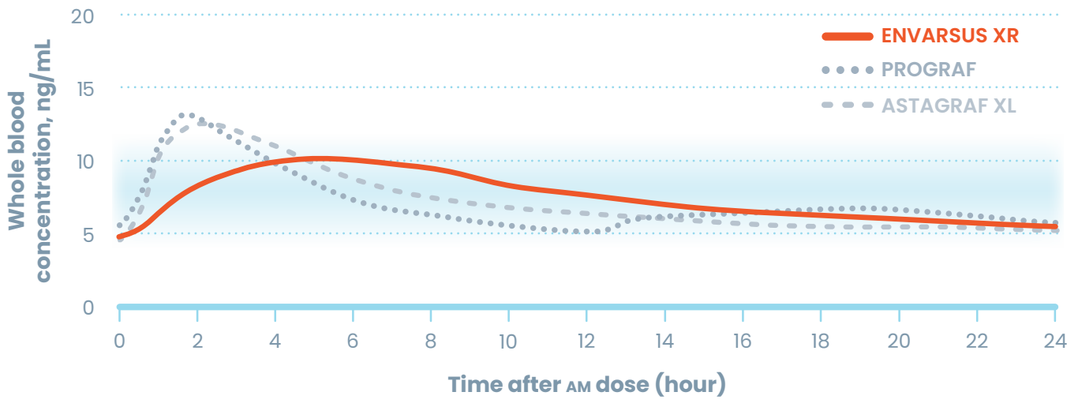
QT Prolongation: ENVARSUS XR may prolong the QT/QTc interval and cause *Torsade de pointes*. Avoid ENVARSUS XR in patients with congenital long QT syndrome. Consider obtaining electrocardiograms and monitoring electrolytes periodically during treatment in patients with congestive heart failure, bradyarrhythmias, 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, a reduction in ENVARSUS XR dosage, monitoring of tacrolimus whole blood concentrations, and monitoring for QT prolongation is recommended.

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

CONSISTENCY

ENVARSUS XR delivers consistent tacrolimus exposure with significantly lower peak vs PROGRAF® or ASTAGRAF XL®[14]

ADVANCED MELTDOSE® TECHNOLOGY DELIVERS SMOOTH TACROLIMUS LEVELS OVER 24 HOURS[14,18]



50% greater bioavailability vs PROGRAF or ASTAGRAF XL[14]

- The proprietary MeltDose® technology in ENVARSUS XR improves the release and absorption of tacrolimus over 24 hours[19]
- ENVARSUS XR avoids the peaks associated with immediate-release and other tacrolimus formulations, thereby achieving consistent tacrolimus exposure while maintaining target trough[14]
  - 30% reduction in peak concentration[1]
  - 20% lower dose vs IR-Tac[1]
  - 1 convenient, daily dose[15]

Recommend a tacrolimus formulation that smooths delivery across the day—reducing peak concentrations while achieving reliable target levels.

IR-Tac=immediate-release tacrolimus.

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

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.

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

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.

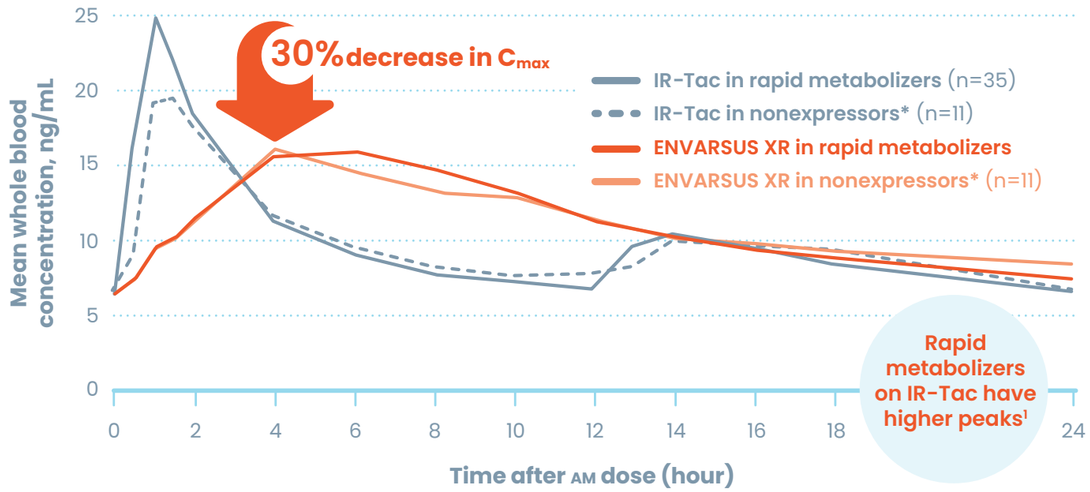
Please see Important Safety Information continued throughout and accompanying full Prescribing Information, including Boxed Warning.

CONSISTENCY

Consistent PK profile—even in rapid metabolizers[1]

ACHIEVE TARGET LEVELS CONSISTENTLY ACROSS PATIENT TYPES, EVEN AT A LOWER DOSE[1]

Eliminate the high peak associated with IR-Tac formulations and achieve target trough levels with a 20% lower dose[1]



Treatment-emergent adverse events were comparable during both the pharmacokinetic and extended-use phases of the study. During the extended-use phase, 7 patients experienced a total of 11 serious adverse events: 5 events in 3 patients treated with ENVARSUS XR and 6 events in 4 patients using IR-Tac.[1]

Consider a tacrolimus formulation designed to deliver consistent PK profiles, even in rapid metabolizers.

*Patients not expressing the CYP3A5*1 genotype.[1]

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

Study design: Phase 3b prospective, randomized, open-label, 2-sequence, 3-period, crossover pharmacogenetic study to compare the steady-state PK profile of IR-Tac twice daily with ENVARSUS XR once daily in adult stable African American kidney transplant patients (N=46). Patients were randomized to receive either IR-Tac for 7 days and then switched to ENVARSUS XR for 14 days or ENVARSUS XR for 7 days and switched to IR-Tac for 14 days. Patients continued concomitant immunosuppression per standard of care. Patients were genotyped and PK assessments were completed on study days 7, 14, and 21.[1]

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS (CONTINUED)

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.

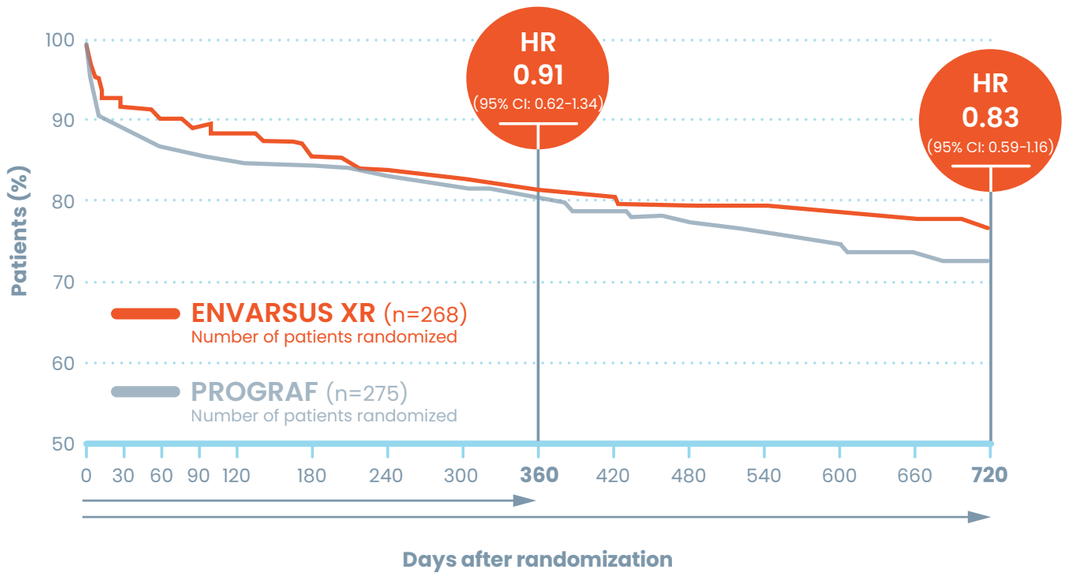
Please see Important Safety Information continued throughout and accompanying full Prescribing Information, including Boxed Warning.

CONTROL

Control from the beginning, control over time

PATIENTS REMAINING FREE FROM TREATMENT FAILURE*

Freedom from treatment failure vs PROGRAF®[16,20]



De novo study design: Phase 3, double-blind, randomized, multicenter trial to compare the efficacy and safety of ENVARSUS XR vs PROGRAF in adult de novo transplant recipients of a living or deceased donor kidney transplant (except for donation after cardiac death) (N=543). The primary efficacy endpoint was the incidence of treatment failures within 12 months after the randomization date; 507 patients completed the 24-month study period.[16,21]

YEAR 1 **9%** reduction vs PROGRAF[20]

YEAR 2 **17%** reduction vs PROGRAF[20]

ESTABLISHED SAFETY PROFILE, WITH OUTCOMES CONSISTENT WITH IR-TAC IN BOTH DE NOVO AND CONVERSION PATIENTS[15]

- Comparable performance across predefined laboratory measures[15]
- No significant difference in opportunistic infection or malignancies[16,21]
- Comparable incidence of composite NODAT[15†]

For transplant teams focused on maintaining control, ENVARSUS XR offers comparable efficacy and safety to IR-Tac across both de novo and conversion patients.

CI=confidence interval; HR=hazard ratio; NODAT=new-onset diabetes after transplant.
*Treatment failure was a composite endpoint of biopsy-proven acute rejection, graft failure, death, and lost to follow-up.[16,21]
†Analysis restricted to patients at risk for NODAT.[15]

IMPORTANT SAFETY INFORMATION (CONTINUED)

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.

CONVENIENCE CONFIDENCE

Convenience in dosing, confidence in access

Starting a patient on once-daily ENVARSUS XR is a straightforward process.[15]

RECOMMENDED ENVARSUS XR STARTING DOSES IN KIDNEY TRANSPLANT PATIENTS

De novo patients (with antibody induction)	0.14 mg/kg/day
Patients converting from IR-Tac	Administer 80% of the preconversion daily dose
Patients with severe hepatic impairment	May require a lower starting dose
African American patients	May need to be titrated to higher ENVARSUS XR dosages to attain comparable trough concentrations

ENVARSUS XR should be taken once daily on an empty stomach, preferably in the morning, at least 1 hour before a meal or at least 2 hours after a meal. If a dose is missed, take it as soon as possible within 15 hours after missing the dose; beyond the 15-hour time frame, wait until the usual scheduled time to take the next regular daily dose. Do not double the next dose.

"Once daily tacrolimus products may improve the rate of adherence compared to twice daily tacrolimus."[22*]

– 2022 ACCP/AST/ISHLT Consensus Recommendations

SUPPORT AT EVERY STEP

A dedicated **Veloxis Transplant Support** specialist is waiting to help your patients find savings, get coverage, and fill their ENVARSUS XR prescriptions. Patients can reach Veloxis Transplant Support at 1-844-VELOXIS (835-6947) for help with tasks like:

Benefit investigations | **Prior authorization assistance** | **Coordination with specialty pharmacies**

Regardless of your patient's financial situation, we may have options to help†

30-day free trial: Patients new to ENVARSUS XR may receive a onetime-per-lifetime voucher at no cost to them

$0 co-pay: Out-of-pocket savings for eligible commercially insured patients

You can be confident that ENVARSUS XR offers tools and support designed to help keep patients on track.

*Recommendation is based on a study comparing extended-release tacrolimus with IR-Tac.
†See eligibility requirements at ENVARSUSXR.com. Subject to terms and conditions.

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.

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

POST-KIDNEY TRANSPLANT CARE REQUIRES MORE THAN JUST A PRESCRIPTION

FROM A CONSISTENT PK PROFILE TO A FULL SUITE OF PATIENT SUPPORT SERVICES, YOU CAN HELP EMPOWER PATIENTS WITH ENVARSUS XR

Since 2015, 99% of US kidney transplant centers have used ENVARSUS XR for kidney transplant immunosuppression.[23] Are you ready to join them?

Talk to your Veloxis representative about how ENVARSUS XR can help support your transplant team's immunosuppression goals, or visit www.ENVARSUSXR.com/hcp to learn more.

IMPORTANT SAFETY INFORMATION (CONTINUED)

USE IN SPECIFIC POPULATIONS (CONTINUED)

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.

References: 1. 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. **2.** Undre NA, van Hooff J, Christiaans M, et al. Low systemic exposure to tacrolimus correlates with acute rejection. *Transplant Proc*. 1999;31(1-2):296-298. **3.** Borobia AM, Romero I, Jimenez C, et al. Trough tacrolimus concentrations in the first week after kidney transplantation are related to acute rejection. *Ther Drug Monit*. 2009;31(4):436-442. **4.** Hesselink DA, Bouamar R, Elens L, van Schaik RH, van Gelder T. The role of pharmacogenetics in the disposition of and response to tacrolimus in solid organ transplantation. *Clin Pharmacokinet*. 2014;53(2):123-139. **5.** Kershner RP, Fitzsimmons WE. Relationship of FK506 whole blood concentrations and efficacy and toxicity after liver and kidney transplantation. *Transplantation*. 1996;62(7):920-926. **6.** Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. *Clin Pharmacokinet*. 2004;43(10):623-653. **7.** Nevins TE, Robiner WN, Thomas W. Predictive patterns of early medication adherence in renal transplantation. *Transplantation*. 2014;98(8):878-884. **8.** Birdwell KA, Decker B, Barbarino JM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for CYP3A5 genotype and tacrolimus dosing. *Clin Pharmacol Ther*. 2015;98(1):19-24. **9.** Jacobson PA, Oetting WS, Brearley AM, et al; DeKAF investigators. Novel polymorphisms associated with tacrolimus trough concentrations: results from a multicenter kidney transplant consortium. *Transplantation*. 2011;91(3):300-308. **10.** Thölking G, Fortmann C, Koch R, et al. The tacrolimus metabolism rate influences renal function after kidney transplantation. *PLoS One*. 2014;9(10):1-8. **11.** Egeland EJ, Robertsen I, Hermann M, et al. High tacrolimus clearance is a risk factor for acute rejection in the early phase after renal transplantation. *Transplantation*. 2017;101(8):e273-e279. **12.** Staatz C, Goodman LK, Tett SE. Effect of CYP3A and ABCB1 single nucleotide polymorphisms on the pharmacokinetics and pharmacodynamics of calcineurin Inhibitors: part I. *Clin Pharmacokinet*. 2010;49(3):141-175. **13.** Kuehl P, Zhang J, Lin Y, et al. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. *Nat Genet*. 2001;27(4):383-391. **14.** Tremblay S, Nigro V, Weinberg J, Woodle ES, Alloway RR. 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. **15.** ENVARSUS XR [package insert]. Cary, NC: Veloxis Pharmaceuticals, Inc.; 4/2024. **16.** Rostaing L, Bunnapradist S, Grinyó JM, et al; Envarsus study group. 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. **17.** Bunnapradist S, Ciechanowski K, West-Thielke P, et al. Conversion from twice-daily tacrolimus to once-daily extended release tacrolimus (LCPT): the phase III randomized MELT trial. *Am J Transplant*. 2013;13(3):760-769. **18.** 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. **19.** 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 [abstract]. *Am J Transplant*. 2013;13(suppl 5):335. **20.** Data on file. Veloxis Pharmaceuticals, Inc.; 2020. **21.** Budde K, Bunnapradist S, Grinyo JM, et al; Envarsus study group. 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. **22.** Nelson J, Alvey N, Bowman L, et al. Consensus recommendations for use of maintenance immunosuppression in solid organ transplantation: endorsed by the American College of Clinical Pharmacy, American Society of Transplantation, and the International Society for Heart and Lung Transplantation. *Pharmacotherapy*. 2022;42(8):599-633. **23.** Combined Symphony Health, 867, 3PL data, 10/2024.

Veloxis® PHARMACEUTICALS an Asahi Kasei company

US-ENV-2500065 09/25

Once-daily Envarsus XR® (tacrolimus extended-release tablets)