Know what awaits your patients after kidney transplant

For all patients, even the 1 in 3 who may be rapid metabolizers of tacrolimus, once-daily ENVARSUS XR delivers consistent control.[1-4]

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.

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See full Prescribing Information, including Boxed Warning, in pocket.

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

Rapid metabolism of tacrolimus is common[4-7]

Who are rapid metabolizers?

45%–80%
African American[4,5]

15%–35%
Asian[5]

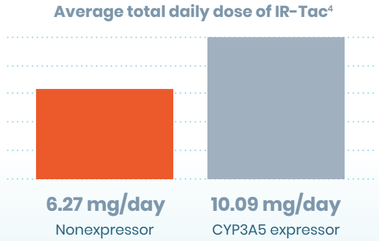
5%–30%
Caucasian[5,6]

13%–26%
Hispanic[5,7]

For 1 in 3 patients, reaching target trough levels may require higher doses[1]

Rapid metabolizers need more tacrolimus[8,9]

- Rapid metabolizers are expressors of the CYP3A5*1 gene variant[8]
- 1.5 to 2 times higher doses were needed to achieve the same target trough[9]
- Despite a 60% higher IR-Tac dose, median trough levels were below target in African American patients[8]



CYP=cytochrome P450; IR-Tac=immediate-release tacrolimus.

After transplant, rapid metabolizers of tacrolimus face unique risks

COMPLICATIONS

Rapid metabolizers are at risk for[10]
- Significantly more for-cause biopsies
- Greater CNI nephrotoxicity
- More BK nephropathy

HIGHER PEAKS

Compared with nonexpressors of CYP3A5*1, rapid metabolizers experience a **34% increase in C_{max} of tacrolimus[4]**

REJECTION

Rapid metabolizers are at higher risk for BPAR in the first 90 days after transplant ($P<0.006$)[11]

BK=BK virus; BPAR=biopsy-proven acute rejection; C_{max}=peak plasma concentration; CNI=calcineurin inhibitor.

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Everyday control with ENVARSUS XR

Navigate the challenges of immunosuppression in rapid metabolizers

OPTIMIZED EXPOSURE WITH PROVEN CONTROL[1,2]

24hr extended release

50% greater bioavailability vs Prograf® or Astagraf XL®

CONSISTENT TAC LEVELS ACROSS PATIENT TYPES*

30% reduction in peak concentration[2,4]

20% lower dose vs IR tacrolimus[4]

CONVENIENT DOSING AND PATIENT SUPPORT[2]

1x daily dosing

1 to 1 support from Veloxis transplant specialists

NO PHARMACY SUBSTITUTIONS

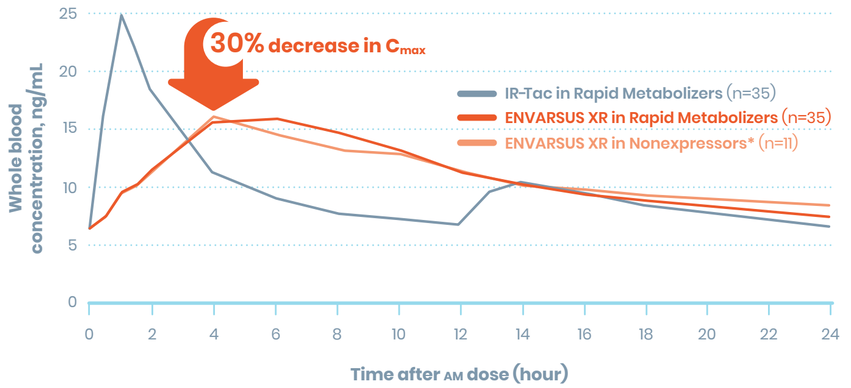
When prescribed, your patients will receive ENVARSUS XR with every refill.

*Clinical benefit of the differences in ENVARSUS XR pharmacokinetics has not been established.

Proven control, consistency, and convenience—even in rapid metabolizers[2,3,13]

Consistently achieve target levels in rapid metabolizers even at a lower dose

24-HOUR PK PROFILE OF ENVARSUS XR VS IR-TAC IN RAPID METABOLIZERS[4]



- **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 ENVARSUS XR-treated patients and 6 events in 4 patients using IR-Tac.[4]

Study Design: Phase 3b prospective, randomized, open-label, 2-sequence, crossover pharmacogenetic study to compare the steady-state PK of IR-Tac twice daily to ENVARSUS XR once daily in adult stable African American kidney transplant patients (N=46).

C_{max}=maximum concentration recorded; IR-Tac=immediate-release tacrolimus; PK=pharmacokinetics.
*Patients not expressing the CYP3A5*1 genotype.

IMPORTANT SAFETY INFORMATION

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.

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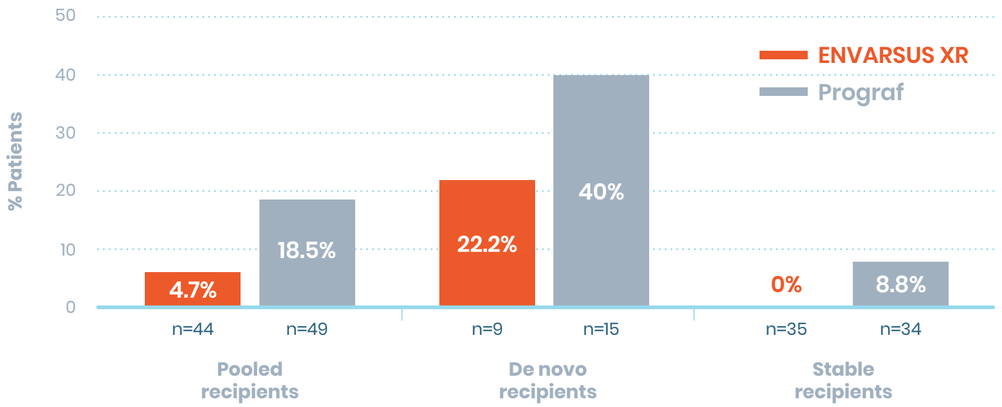
ENVARSUS XR: Optimized exposure, consistent control

Deliver consistent graft protection across treatment settings

AFRICAN AMERICAN PATIENT TREATMENT FAILURES WITH ENVARSUS XR[3]

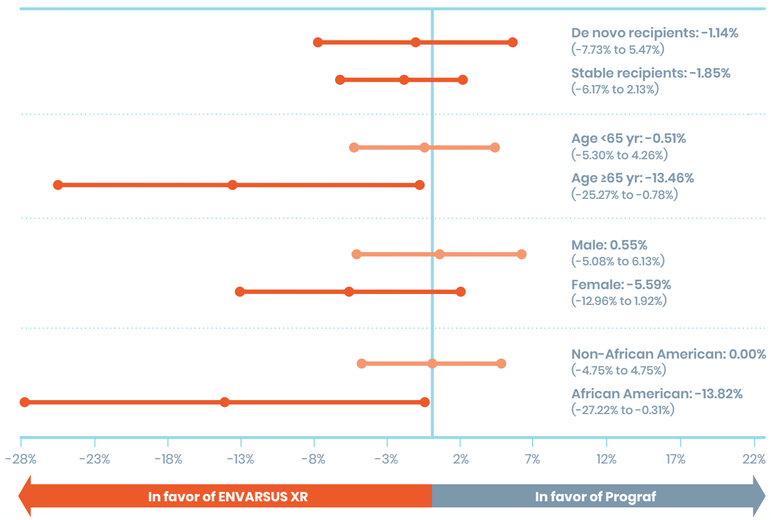


Study Design: Pooled analysis of data from 2 two-arm, parallel group, prospective, randomized, multicenter, Phase 3 clinical trials (studies 3001 and 3002). Study 3001 was an open-label trial with stable kidney transplant patients. Study 3002 was a double-blind, double-dummy trial in which de novo kidney transplant recipients were randomly assigned to ENVARSUS XR once daily or Prograf.

In both de novo and conversion African American patients, ENVARSUS XR reduced the risk for treatment failure vs Prograf[3]

Consistently protect patients from treatment failure

POOLED ANALYSIS OF TREATMENT FAILURES IN PATIENT SUBPOPULATIONS[3]



Limitations: Given that this was not a prespecified analysis, no statistical significance was derived.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont)

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.

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.

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ENVARSUS XR: Deliver consistency across safety measures

Overall SAEs in African American patients[3]

29.5% with ENVARSUS XR

VS

38.8% with Prograf

No significant safety differences between ENVARSUS XR and Prograf in de novo and conversion patients[2,14,15]*

- Predefined potentially clinically significant laboratory measures[2]
- Opportunistic infection[2]
- Malignancies[14,15]
- Composite NODAT[2†]

NODAT=new-onset diabetes after transplantation; SAE=serious adverse event.
*Clinical studies were not designed to establish comparative differences across study arms with regard to adverse reactions.
†Analysis restricted to patients at risk for NODAT.

References

1. Data on file. Veloxis Pharmaceuticals, Inc; 2020. **2.** ENVARSUS XR [package insert]. Cary, NC: Veloxis Pharmaceuticals, Inc; 2020. **3.** 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. **4.** 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. **5.** 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. **6.** 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. **7.** Claudio-Campos K, Duconge J, Cadilla CL, Ruaño G. Pharmacogenetics of drug-metabolizing enzymes in US Hispanics. *Drug Metab Pers Ther.* 2015;30(2):87-105. **8.** 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. **9.** 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. **10.** Thölking G, Fortmann C, Koch R, et al. The tacrolimus metabolism rate influences renal function after kidney transplantation. *PLoS One.* 2014;9(10):e111128. **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.** 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. **13.** 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. **14.** 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. **15.** 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.* 2012;13: 760-769.

Convenience in dosing and access

Once-daily dosing and comprehensive patient support

ENVARSUS XR has been studied to establish the optimized starting dosage for your patient—whether immediately after transplant, or when converting from a different tacrolimus.[2]

- **De novo (with antibody induction):** 0.14 mg/kg/day
- **Conversion from immediate-release tacrolimus products:** 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
- **Should be taken once daily:** Take on an empty stomach, preferably in the morning, at least 1 hour before a meal or at least 2 hours after a meal

We're committed to ensuring access to ENVARSUS XR. Whatever your patients' insurance or financial situation, we've got it covered.*

Veloxis | Transplant Support

1-844 VELOXIS (835-6947)

*Subject to eligibility requirements. See EnvarsusXR.com.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont)

Nephrotoxicity: 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.

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.

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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 coadministering ENVARSUS XR with strong CYP3A inhibitors or strong CYP3A inducers.

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 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.

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.

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.

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.

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Confidently deliver graft protection—even in rapid metabolizers

Rapid Metabolizers:	ENVARSUS XR delivers:
Require higher doses to achieve target trough[9] • 1.5 to 2 times higher doses of IR-Tac needed compared with nonexpressors	**CONTROL[12]** • Controlled, smooth release over 24 hours
Are at risk for higher peaks and negative sequelae[4,10] • 34% increase in peak blood concentration to achieve the same target trough as nonexpressors	**CONSISTENCY** Consistent exposure levels: • Avoids the high peaks with consistent exposure[3] • Delivers smooth PK results in rapid metabolizers[3,4]
Are at higher risk for inadequate immunosuppression[1] • Unable to maintain adequate immunosuppression • Require high doses of IR-Tac • Experience undesirable side effects	**CONVENIENCE** • Once-daily dosing[2] • Patient support offerings that span the treatment journey

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