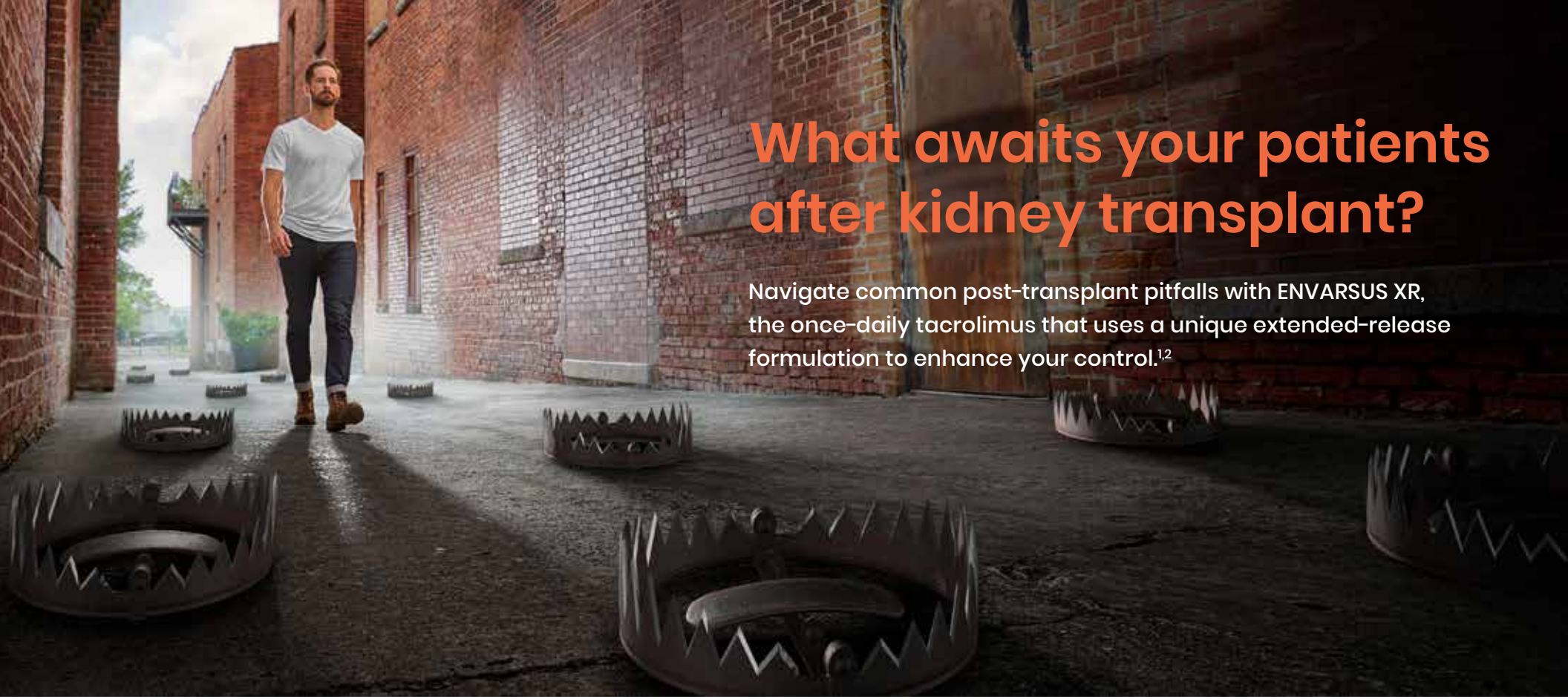


What awaits your patients after kidney transplant?

Navigate common post-transplant pitfalls with ENVARSUS XR, the once-daily tacrolimus that uses a unique extended-release formulation to enhance your control.[1,2]

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

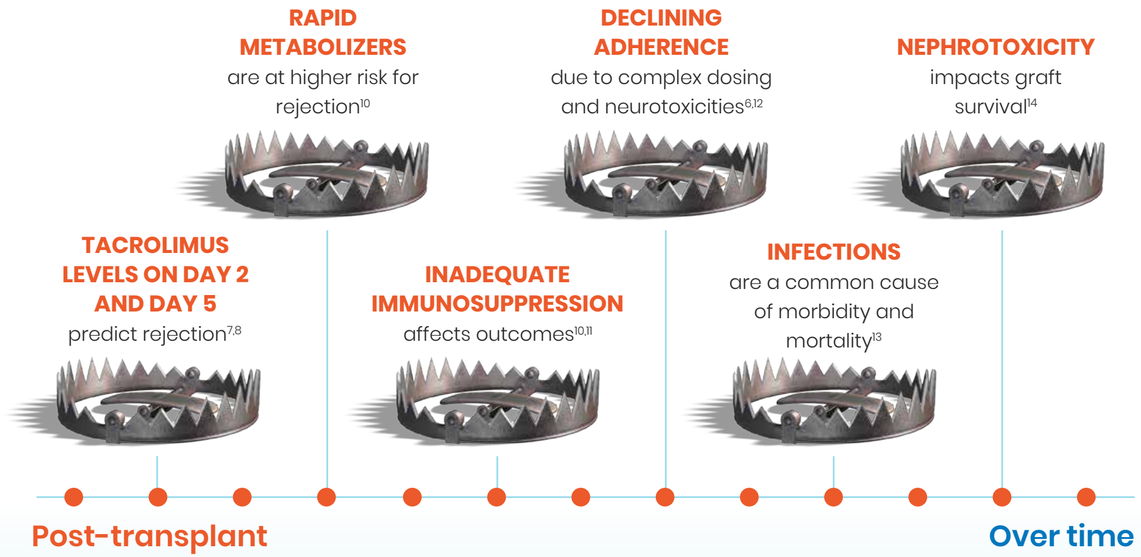
ENVARSUS XR is contraindicated in patients with known hypersensitivity to tacrolimus.

Please see Important Safety Information throughout and on pages 14 and 15.
See full Prescribing Information, including Boxed Warning, in pocket.

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

What awaits your patients after transplant?

A need for control, consistency, and convenience from immunosuppressive therapy[3-6]



ENVARSUS XR: Proven control, consistency, convenience[1,2,15]

Prepare your patients for the journey ahead with ENVARSUS XR

OPTIMIZED EXPOSURE WITH PROVEN CONTROL[16]

- **24hr** extended release
- **50%** greater bioavailability vs Prograf® or Astagraf XL®

CONSISTENT TAC LEVELS ACROSS PATIENT TYPES*

- **30%** reduction in peak concentration[1,17]
- **20%** lower dose vs IR tacrolimus[17]

CONVENIENT DOSING AND PATIENT SUPPORT[1]

- **1x** daily dosing
- **1to1** support from Veloxis transplant specialists

*Clinical benefit of the differences in ENVARSUS XR PK has not be established.

NO PHARMACY SUBSTITUTIONS

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

IR=immediate-release; PK=pharmacokinetics; Tac=tacrolimus.

INDICATIONS AND USAGE

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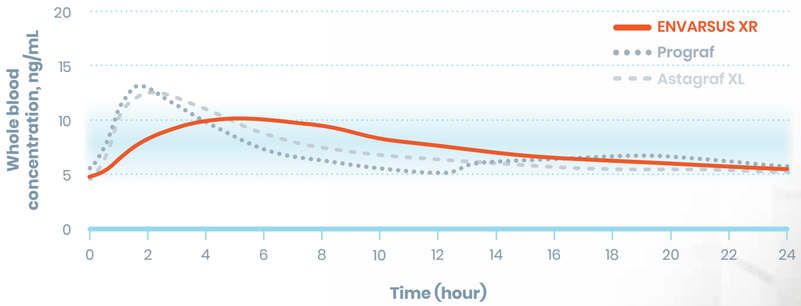
CONTROL WITH CONFIDENCE

ENVARSUS XR: Control from the beginning, control over time

Stay on target with smooth and predictable delivery

ENVARSUS XR ACHIEVED TARGET EXPOSURE WITH A SIGNIFICANTLY LOWER PEAK VS PROGRAF OR ASTAGRAF XL[16]*



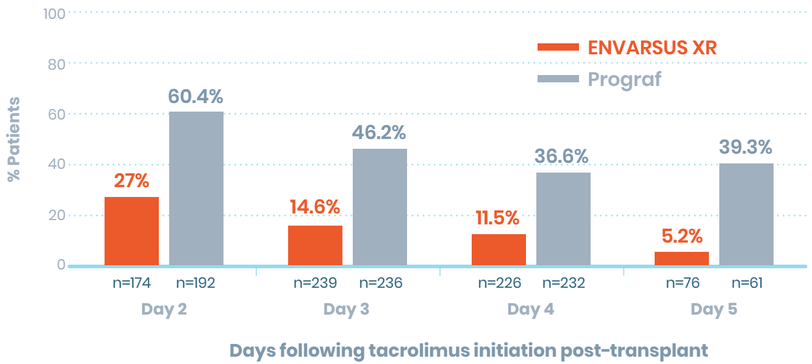
Study Design: Open-label, randomized, 2-sequence, 3-period crossover trial of adult stable kidney transplant patients (N=32). The primary objective of the study was to evaluate the PK profile of ENVARSUS XR vs Prograf and Astagraf XL.

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

*Normalized to mean whole blood concentrations of tacrolimus based on conversion factors of 1 (Prograf); 1.08 (Astagraf XL); 0.7 (ENVARSUS XR).

Rapidly achieve exposure in de novo patients

SIGNIFICANTLY FEWER PATIENTS HAD TROUGH LEVELS BELOW 6 ng/mL FROM DAY 2 TO DAY 5[1,18]



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. Overall, 507 patients completed the 24-month study period.[19,20]

- In an open-label Phase 2 study conducted in de novo kidney transplant patients, 53% of ENVARSUS XR patients reached target levels (6-11 ng/mL) after a single starting dose of 0.14 mg/kg[1]

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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CONTROL WITH CONFIDENCE

ENVARSUS XR: Control that keeps patients on course

Lasting efficacy in de novo patients

LONG-TERM GRAFT PROTECTION

	Year 1[1]		Year 2[20]	
	ENVARSUS XR (n=268)	Prograf (n=275)	**ENVARSUS XR (n=268)**	Prograf (n=275)
BPAR	**13.4**	13.5	**17.2**	18.2
Graft failure	**3.4**	4	**4.1**	5.5
Death	**3**	2.9	**4.1**	4.7
Lost to follow-up	**1.5**	1.8	**1.5**	2.9
Treatment failure composite*	**18.7**	19.6	**23.1**	27.3

BPAR=biopsy-proven acute rejection; DGF=delayed graft function; eGFR=estimated glomerular filtration rate.
P-value not significant for all measures.
*Treatment failure was a composite endpoint of BPAR, graft failure, death, and lost to follow-up.[20]

SIMILAR RATES OF DGF AFTER TRANSPLANT[19]

7.1% of ENVARSUS XR patients vs **10.9%** of Prograf patients

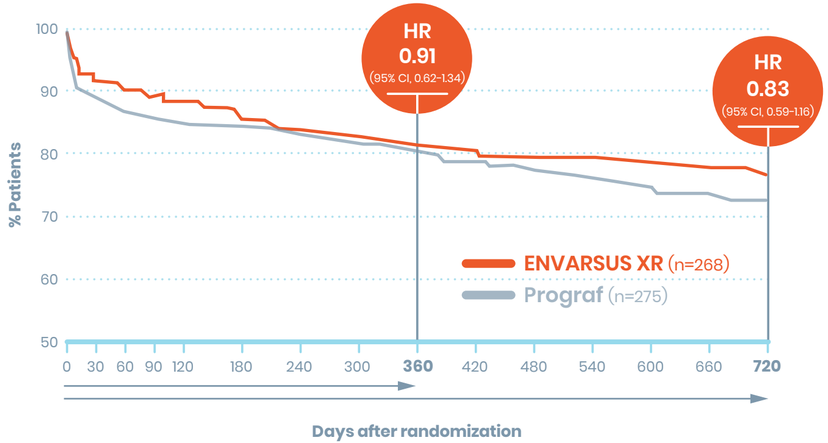
DGF=delayed graft function.

TREATMENT FAILURE RATES AT 3 MONTHS[19]

10.4% of ENVARSUS XR patients vs **14.2%** of Prograf patients

Patients remaining free from treatment failure

TIME FREE FROM TREATMENT FAILURE VS PROGRAF[18,20]



CI=confidence interval; HR=hazard ratio.

YEAR 1 **9%** → YEAR 2 **17%**

reduction vs Prograf[18] reduction vs Prograf[18]

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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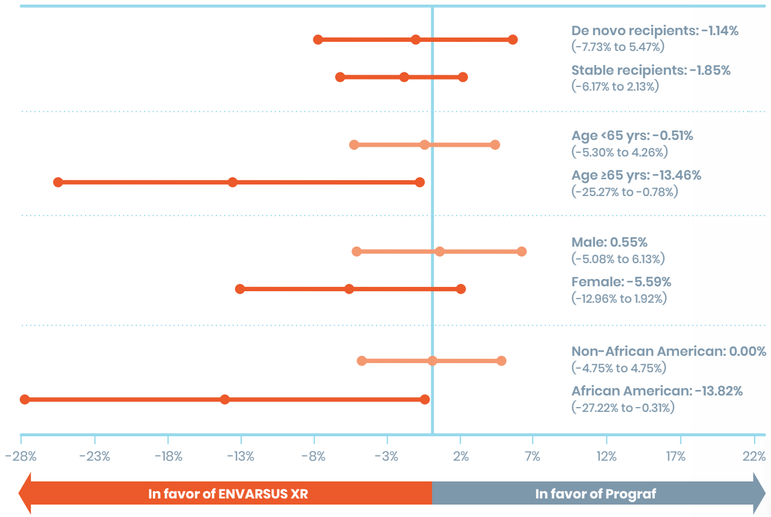
CONTROL WITH CONFIDENCE

ENVARSUS XR: Consistency across all tacrolimus patients

Pooled analysis of treatment failure across patient subpopulations

RISK FOR TREATMENT FAILURE AT 12 MONTHS[15]*



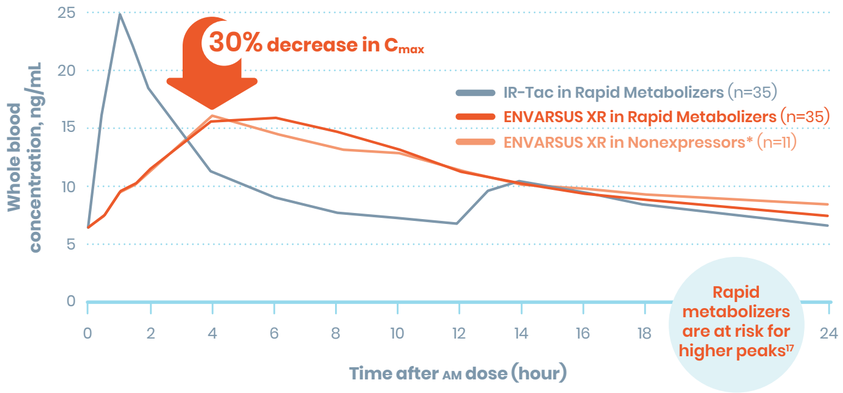
Study Design: Pooled analysis of data from 2 two-arm, parallel group, prospective, randomized, multicenter, Phase 3 clinical trials (studies 3001 and 3002). Study 3001 was an open-label trial in adult stable kidney transplant patients. Study 3002 was a double-blind, double-dummy trial in which de novo kidney transplant recipients were randomly assigned to ENVARSUS XR once daily or Prograf.[15]

*All values presented as risk reduction (95% CI).

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

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

ELIMINATE THE HIGH PEAK ASSOCIATED WITH IR-TAC FORMULATIONS AND ACHIEVE TARGET TROUGH LEVELS WITH A 20% LOWER DOSE[17]



- **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[17]

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). 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.[17]

C_{max}=maximum concentration recorded; CYP=cytochrome P450; IR-Tac=immediate-release tacrolimus.
*Patients not expressing the CYP3A5*1 genotype.[17]

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

ENVARSUS XR: Consistent safety profile

Safety signals consistent with IR-Tac

NO SIGNIFICANT SAFETY DIFFERENCES BETWEEN ENVARSUS XR AND PROGRAF IN DE NOVO AND CONVERSION PATIENTS[1]

Comparable performance across predefined laboratory measures*

No significant difference in opportunistic infection or malignancies[19]

Comparable incidence of composite NODAT†

NODAT=new-onset diabetes after transplant.
*Not powered to demonstrate statistical significance.[17]
†Analysis restricted to patients at risk for NODAT.

ENVARSUS XR HAS BEEN STUDIED IN 27 TRIALS WITH 1,657 SUBJECTS[18]

Phase 1
19 trials
516 healthy subjects

Phase 2
3 trials
147 kidney transplant patients

Phase 3
2 trials
869 kidney transplant patients

Phase 3b
3 trials
125 kidney transplant patients

Convenient once-daily dosing

Immunosuppression simplified with extended-release dosing

OVERCOMES THE LIMITATIONS OF OTHER TACROLIMUS FORMULATIONS[1,16,17]

- Once-daily dosing for all patients[1]
- Improves tacrolimus release and absorption over 24 hours[16]
- Maintains consistent whole blood concentrations above the target trough[16]
- **20% lower dose than IR-Tac achieves comparable exposure (AUC) and trough levels** in stable kidney transplant patients at ≥6 months post-transplant[1,17]

STARTING A PATIENT ON ENVARSUS XR[1]

Recommended ENVARSUS XR starting doses in kidney transplant patients	
De novo patients (with antibody induction)	0.14 mg/kg/day
Patients converting from immediate-release tacrolimus	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.

AUC=area under the curve.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont)

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.

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ENVARSUS XR: Convenient programs to help keep patients covered

Commitment to uninterrupted access

WE'RE COMMITTED TO ENSURING ACCESS TO ENVARSUS XR. WHATEVER YOUR PATIENTS' INSURANCE OR FINANCIAL SITUATION, WE'VE GOT IT COVERED.*

- **30–day free voucher:** Start your patients on ENVARSUS XR immediately, at no cost to them
- **$0 co-pay:** Out-of-pocket savings for eligible commercially insured patients

BENEFIT INVESTIGATION

- Verify coverage, identify possible restrictions, and report cost sharing by tier

PRIOR AUTHORIZATION ASSISTANCE

- Guides you through every step of a payer's process, identifying requirements, and providing templates for statements of medical necessity

COORDINATION WITH SPECIALTY PHARMACIES

- Ensures access to ENVARSUS XR before filling prescriptions

PRESCRIPTION FULFILLMENT NAVIGATION

- Identifies the most cost-effective method to fill ENVARSUS XR prescriptions

ENVARSUS XR SUPPORT THROUGH COVERMYMEDS®

- CoverMyMeds automates the PA process, making it a faster, easier way to review, complete, and track PA requests
- CoverMyMeds connects EHRs, payers, pharmacies, and providers

EHR=electronic health record; PA=prior authorization.
*Subject to eligibility requirements. See EnvarsusXR.com.

Visit EnvarsusXR.com to download the Patient Enrollment Form and get started

References: 1. ENVARSUS XR [package insert]. Cary, NC: Veloxis Pharmaceuticals, Inc.; 2020. **2.** 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. **3.** Min SI, Kim SY, Ahn SH, et al. *CYP3A5**1 allele: impacts on early acute rejection and graft function in tacrolimus-based renal transplant recipients. *Transplantation*. 2010;90(12):1394-1400. **4.** 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. **5.** Massey EK, Tielen M, Laging M, et al. Discrepancies between beliefs and behaviors: a prospective study into immunosuppressive medication adherence after kidney transplantation. *Transplantation*. 2015;99(2):375-380. **6.** Nevins TE, Robiner WN, Thomas W. Predictive patterns of early medication adherence in renal transplantation. *Transplantation*. 2014;98(8):878-884. **7.** 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. **8.** 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. **9.** 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. **10.** 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. **11.** 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. **12.** Langone A, Steinberg SM, Gedaly R, et al; STRATO investigators. Switching study of kidney transplant patients with tremor to LCP-tacro (STRATO): an open-label, multicenter, prospective phase 3b study. *Clin Transplant*. 2015;29(9):796-805. **13.** Karuthu S, Blumberg EA. Common infections in kidney transplant recipients. *Clin J Am Soc Nephrol*. 2012;7(12):2058-2070. **14.** Xia T, Zhu S, Wen Y, et al. Risk factors for calcineurin inhibitor nephrotoxicity after renal transplantation: a systematic review and meta-analysis. *Drug Des Devel Ther*. 2018;12:417-428. **15.** 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. **16.** 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. **17.** 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. **18.** Data on file. Veloxis Pharmaceuticals, Inc; 2020. **19.** 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. **20.** Rostaing L, Bunnapradist S, Grinyó SJ, 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.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont)

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.

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Once-daily
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CONTROL WITH CONFIDENCE

Important Safety Information

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WARNINGS AND PRECAUTIONS

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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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Once-daily
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CONTROL WITH CONFIDENCE

Control the course of the post-transplant treatment journey

Prepare your patients for the journey ahead with ENVARSUS XR, a unique once-daily, extended-release tacrolimus formulation.

PROVEN CONTROL

- Significantly fewer patients had trough levels below 6 ng/mL from Day 2 to Day 5 (vs Prograf)[18]
- Achieves long-term milestones in efficacy and safety[1]

DELIVERS CONSISTENCY

- Avoids the high peaks with consistent exposure[17]
- Delivers smooth pharmacokinetic results in rapid metabolizers[15,17]

OFFERS CONVENIENCE

- Once-daily dosing[1]
- Extensive support programs

INDICATIONS AND USAGE

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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.

Please see additional Important Safety Information throughout and on pages 14 and 15. See full Prescribing Information, including Boxed Warning, in pocket.

Veloxis PHARMACEUTICALS

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