CONTROL

ENVARSUS XR® (tacrolimus extended-release tablets)

Case Study Series*

Daryl

Age: 60

Medical history:
Previously diagnosed with type 2 diabetes and hypertension, with a panel reactive antibody (PRA) of 25%, matched to receive a kidney following 8 years on hemodialysis

*This case is fictional and not based on an actual patient.

Daryl's presentation

Daryl is a 60-year-old, 6-ft-tall, 245-lb African American male admitted to receive a deceased donor kidney transplant. His donor kidney has a kidney donor profile index (KDPI) of 72 and will have had approximately 24 hours of cold ischemia time when transplanted. The transplant team initiates induction therapy just prior to transplant according to their center's protocol.

Care team's objective: Get Daryl to target tacrolimus levels as quickly as possible

KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guidelines state that the earlier therapeutic blood levels of a calcineurin inhibitor (CNI) can be achieved, the more effective the CNI will be in preventing acute rejection.[1]
• Tacrolimus concentrations on post-transplant Days 2 and 5 are associated with rejection[2,3]

Care team's plan: Start Daryl on ENVARSUS XR within 24 hours of transplantation

The care team decides to include once-daily ENVARSUS XR in Daryl's initial immunosuppressive therapy plan.

Post-transplant Day 1: Daryl is started on a triple immunosuppressive therapy of mycophenolate mofetil, corticosteroids, and ENVARSUS XR at a dose of 0.14 mg/kg/day. His urine output and creatinine levels indicate that his transplanted kidney is functioning well.

Post-transplant Day 2: Daryl's trough tacrolimus level is 3.5 ng/mL, which is below the target therapeutic range of tacrolimus (6-11 ng/mL). Daryl's creatinine level continues to decrease, he has robust urine production, and there are no signs of graft rejection. The team increases Daryl's ENVARSUS XR dose and continues to monitor his kidney function and tacrolimus levels.

Post-transplant Day 3: Daryl's trough tacrolimus level is 5.8 ng/mL, below the target therapeutic goal. Knowing that steady-state concentrations are not achieved until ~7 days after initiating or changing the ENVARSUS XR dose,[4] the transplant team discharges Daryl without further dose modification, with the plan to monitor his tacrolimus levels and kidney function in clinic.

How does a patient's trough tacrolimus level factor into your discharge planning?

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.

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

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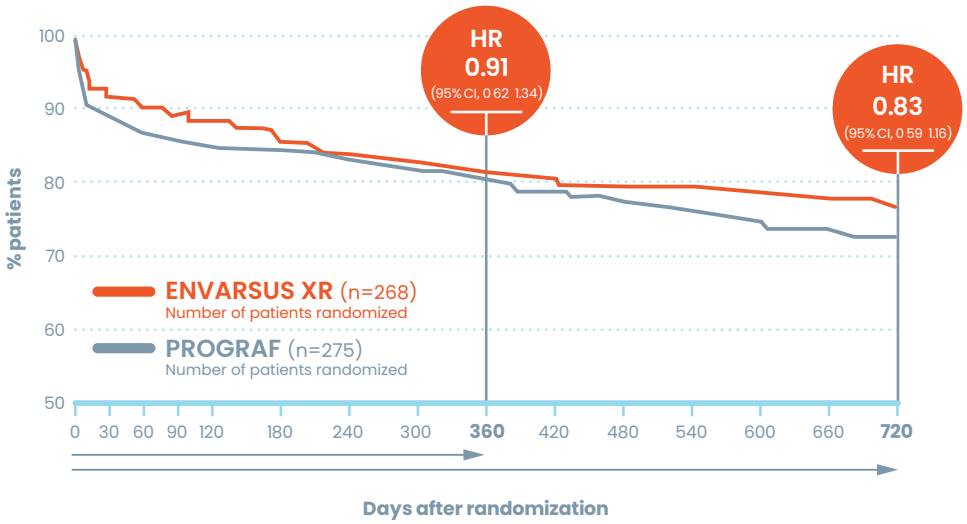
Why ENVARSUS XR was chosen for Daryl: Control from the beginning, control over time[5,6]

Patient and graft protection at 1 and 2 years

FREEDOM FROM TREATMENT FAILURE VS PROGRAF®[5,6*]



YEAR 1
9%
reduction vs PROGRAF[6]

YEAR 2
17%
reduction vs PROGRAF[6]

CI=confidence interval; HR=hazard ratio.

SIMILAR RATES OF DGF AFTER TRANSPLANT[7†]

7.1% of ENVARSUS XR patients

vs

10.9% of PROGRAF patients

DGF=delayed graft function.

TREATMENT FAILURE RATES AT 3 MONTHS[7*,‡]

10.4% of ENVARSUS XR patients

vs

14.2% of PROGRAF patients

Established safety profile

- ENVARSUS XR has been studied in 27 trials with 1657 participants[6]
- Across all safety measures, there were no significant differences between the ENVARSUS XR and PROGRAF groups in predefined potentially clinically significant laboratory measures,[§] opportunistic infections, malignancies, or composite new-onset diabetes after transplantation (NODAT) in both de novo and conversion patients[4,5‖]

*Treatment failure was a composite endpoint of biopsy-proven acute rejection (BPAR), graft failure, death, and loss to follow-up.[5,7]
†DGF was assessed via a post hoc analysis of adverse events of interest from a 12-month, Phase 3 clinical trial.[7]
‡*P* value not significant for all measures.[7]
§Not powered to demonstrate statistical significance.[8]
‖Analysis restricted to patients at risk for NODAT.[4]

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

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Could Daryl be a rapid metabolizer?

On post-transplant Day 8, Daryl's trough tacrolimus level was measured in the clinic at 6.2 ng/mL. The team suspects he is a rapid metabolizer and decides to genotype him for confirmation while increasing his ENVARSUS XR dose. A few days later in the clinic, Daryl's tacrolimus level has increased within the target range, and his genotyping results confirm he is a CYP3A5*1 carrier.

- Rapid metabolism of tacrolimus is common. Who are rapid metabolizers?
  - 45%-80% of African Americans[9,10]
  - 15%-35% of Asians[10]
  - 5%-30% of Caucasians[10,11]
  - 13%-26% of Hispanics[10,12]
- Rapid metabolizers face unique challenges post-transplant, including a higher risk for BPAR in the first 90 days ($P<0.006$)[13]
- Patients who are rapid metabolizers of tacrolimus may require higher doses to maintain target trough levels[9]

Long-term management with ENVARSUS XR

Daryl continues to be closely monitored after being discharged. He remains on ENVARSUS XR, and his transplanted kidney remains functional 2 years later.

Could ENVARSUS XR help you control tacrolimus trough levels from the time of transplant?

Key considerations when making ENVARSUS XR dose adjustments in de novo patients:

Dose once a day

For de novo patients, target trough ranges during Month 1 are 6 to 11 ng/mL and after Month 1 are 4 to 11 ng/mL. Trough levels should be monitored at least twice during the first week of treatment.[4]

Take an ENVARSUS XR–specific approach to dose adjustments

When considering how much to adjust the ENVARSUS XR dose, remember that:

- The total daily dose for ENVARSUS XR is given only once a day, not divided into 2 doses[4]
- 20% lower dose achieves comparable exposure (AUC) and trough levels[4,9]

Keep the steady-state time frame in mind

When making dose adjustments, remember that tacrolimus steady-state concentrations are achieved ~7 days after initiating or changing the ENVARSUS XR dose.[4]

IMPORTANT SAFETY INFORMATION (cont)

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.

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INDICATIONS AND USAGE

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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.

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

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WARNINGS AND PRECAUTIONS (cont)

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.

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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References: 1. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant.* 2009;9(suppl 3):S1-S155. **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.** ENVARSUS XR [package insert]. Cary, NC: Veloxis Pharmaceuticals, Inc.; 4/2024. **5.** 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. **6.** Data on file. Veloxis Pharmaceuticals, Inc.; 2020. **7.** 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. **8.** 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. **9.** 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. **10.** Staatz CE, 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. **11.** 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. **12.** 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. **13.** 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.

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