CONSISTENCY

ENVARSUS XR®
(tacrolimus extended-release tablets)

Case Study Series*

Carla

Age: 52

Medical history:
Diabetic renal failure, episode of early rejection following renal transplant

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

Carla's presentation

Carla received a kidney from a deceased donor ~4 months ago and was placed on an initial immunosuppressive regimen of twice-daily immediate-release tacrolimus (IR-Tac) and mycophenolate mofetil.

Carla experienced an episode of early rejection, and in response, her care team has been adjusting her tacrolimus dosing to maintain trough levels at the high end of their target range. Carla's dose has stabilized; however, her team observed that she was on high doses of IR-Tac to maintain those trough levels.

How do you manage patients who need high IR-Tac doses to maintain optimal trough tacrolimus levels?

Care team's plan: Switch Carla to ENVARSUS XR

Carla's care team decides to maintain the desired target trough level using once-daily ENVARSUS XR.

They:

- Verify her insurance and explain how she may be eligible for patient support programs
- Educate her on ENVARSUS XR's once-daily dosing
- Advise her to review the ENVARSUS XR Medication Guide, including Important Safety Information
- Check her tacrolimus blood levels twice in the first week after switching her to ENVARSUS XR and adjust her dose to achieve target trough levels

Carla's care team continues monitoring her tacrolimus levels frequently over the next several months. She maintains target trough levels at a lower total daily dose of tacrolimus, and her transplanted kidney remains functional 1 year later.

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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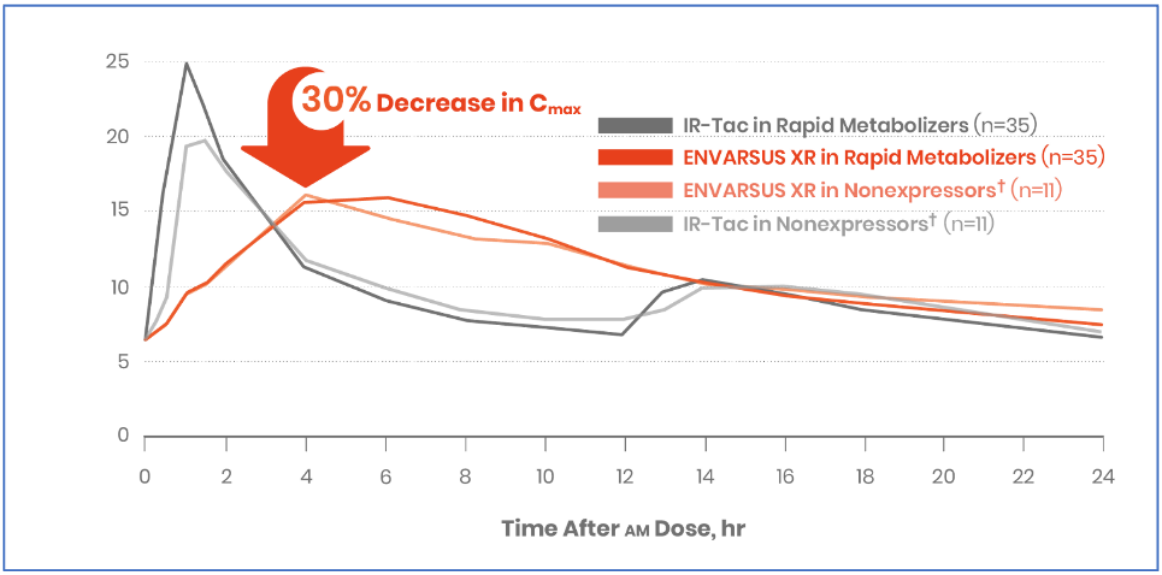
Why ENVARSUS XR was chosen for Carla

- **Comparable control with a lower total daily dose and reduced peak tacrolimus concentration.**
  - 30% reduction in peak concentration vs IR-Tac[1,2]
  - 20% lower dose achieves comparable exposure (area under the curve) and trough levels to IR-Tac[1,2]
  - 50% greater bioavailability than PROGRAF® or ASTAGRAF XL®[3]
- **Consistent safety and efficacy.** In the MELT trial, efficacy failure events and safety outcomes at 12 months were consistent between patients who switched to ENVARSUS XR and patients who remained on PROGRAF[1,4]
- **Commitment to access.** Regardless of a patient's financial situation, Veloxis may have options to help support patients switching to ENVARSUS XR



C_{max}=maximum concentration.
†Subjects not expressing the CYP3A5*1 genotype.
Clinical benefit of the differences in ENVARSUS XR pharmacokinetics has not been established.

Could switching to ENVARSUS XR help your team manage patients like Carla?

Practical tips for switching patients to ENVARSUS XR[1]:

Start at 80% of the preconversion dose

When switching from IR-Tac, start ENVARSUS XR at 80% of the total daily dose of IR-Tac.

Dose once a day

Titrate ENVARSUS XR dosage to achieve whole blood trough concentration range of 4 to 11 ng/mL.

Note that steady-state tacrolimus concentrations are achieved **approximately 7 days** after initiating or changing the ENVARSUS XR dose.

Educate your patients

It is important to educate patients switching from IR-Tac that ENVARSUS XR should be taken once daily, on an empty stomach, preferably in the morning, at least 1 hour before or 2 hours after a meal.
If a dose is missed, instruct the patient to take it **as soon as possible but no longer than 15 hours** after missing the dose.

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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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.

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

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WARNINGS AND PRECAUTIONS (cont)

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. ENVARSUS XR [package insert]. Cary, NC: Veloxis Pharmaceuticals, Inc.; 4/2024. **2.** 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. **3.** 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. **4.** Bunnapradist S, Ciechanowski K, West-Thielke P, et al. Conversion from twice-daily tacrolimus to once-daily extended-release tacrolimus (LCPT): the phase III randomization MELT trial. *Am J Transplant.* 2013;13(3):760-769.

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