BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 1/21/16**
SECTION: DRUGS	**LAST REVIEW DATE: 1/18/18**
	LAST CRITERIA REVISION DATE: 1/18/18
	ARCHIVE DATE:

ENVARSUS XR® (tacrolimus extended-release) oral tablet

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

ENVARSUS XR® (tacrolimus extended-release) oral tablet (cont.)

Description:

Envarsus (tacrolimus) XR is a calcineurin inhibitor indicated for the prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate-release formulations, used in combination with other immunosuppressants. Tacrolimus is available as a generic immediate release formulation in 0.5 mg, 1 mg, and 5 mg capsules and is dosed twice daily. Envarsus XR is dosed once daily.

Information from the product labeling show approval of Envarsus XR was based on a single, published, open-label randomized controlled trial designed to show non-inferiority to tacrolimus IR capsules. Patients on stable doses of twice daily tacrolimus IR were randomized to either continue their current regimen or switched to Envarsus XR once daily. The two groups were found to be “non-inferior” (no difference detected) in composite efficacy failure endpoints (death, graft failure, locally read biopsy-proven acute rejection, or loss to follow up) within 12 months.

Tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin (a ubiquitous mammalian intracellular enzyme) is then formed and the phosphatase activity of calcineurin inhibited. Such inhibition prevents the dephosphorylation and translocation of various factors such as the nuclear factor of activated T-cells (NF-AT) and nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB).

Tacrolimus inhibits the expression and/or production of several cytokines that include interleukin (IL)-1 beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, gamma interferon, tumor necrosis factor-alpha, and granulocyte macrophage colony stimulating factor. Tacrolimus also inhibits IL-2 receptor expression and nitric oxide release, induces apoptosis and production of transforming growth factor-beta that can lead to immunosuppressive activity. The net result is the inhibition of T-lymphocyte activation and proliferation as well as T-helper-cell-dependent B-cell response (i.e., immunosuppression).

Envarsus XR (tacrolimus extended release)

Medication class:
Calcineurin Inhibitor, Immunosuppressant Agent

FDA-approved indication(s):
- For the prophylaxis of organ rejection in kidney transplant patients converted from tacrolimus immediate-release formulations, in combination with other immunosuppressants

Limitations of use:
- Envarsus XR tablets are not interchangeable or substitutable with other tacrolimus extended-release or immediate-release products

Recommended Dose:
- Once daily (package label does not provide any specific dose)
  - Conversion from tacrolimus IR to Envarsus XR:

ENVARSUS XR® (tacrolimus extended-release) oral tablet (cont.)

- Envarsus XR once daily dose that is 80% of the total daily dose of the tacrolimus immediate-release product, then monitor whole blood trough tacrolimus levels and titrate to achieve trough levels 4-11 ng/mL
- Monitor tacrolimus whole blood trough concentrations using a validated assay such as immunoassay or high-performance liquid chromatography with tandem mass spectrometric detection (HPLC/MS/MS). The immunosuppressive activity of tacrolimus is mainly due to the parent drug, immunoassays may react with metabolites as well as the parent drug. As a result immunoassay levels may be higher than those from HPLC/MS/MS.

Maximum dosage
- Not stated

Available Dosage Forms:
- 0.75 mg, 1 mg, and 4 mg caps

Warnings, Precautions, and other Clinical Information:
- Monitor trough tacrolimus levels periodically during therapy, after change in dose, after use of interacting drugs, after change in renal or hepatic function
- Monitor for development of infection (bacterial, viral, fungal, and protozoal, including opportunistic infection)
- Monitor glucose levels for new onset diabetes after transplant
- Consider dose reduction or discontinuation if neurotoxicity occur, especially if posterior reversible encephalopathy syndrome (PRES) occurs
- Mild to severe hyperkalemia, which may require treatment, has been reported
- Hypertension may occur and may require treatment
- Prolonged QT/QTc interval may occur, consider ECG and monitoring of electrolytes (Ca, Mg, K) in patients at risk for QT prolongation (congestive heart failure, bradyarrhythmias, or using drugs that prolong QT)
- Avoid use of live attenuate vaccines (intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines)
- Inactive vaccines may not be sufficiently immunogenic during Envarsus XR treatment
- Discontinue Envarsus XR if pure red cell aplasia (PRCA) develops
- Avoid eating grapefruit or drinking grapefruit juice
- Avoid drinking alcohol
- Absorption of tacrolimus from the GI tract is incomplete and variable
- The desired pharmacologic activity is due to the parent compound, one metabolite may have the same activity of tacrolimus
- Tacrolimus is metabolized by CYP3A4
- Strong CYP3A4 inducers may reduce tacrolimus levels
- Strong CYP3A4 inhibitors may increase tacrolimus levels
- Woman who is breast feeding an infant or child should stop breast feeding
- Envarsus XR in not indicated for use in prevention of rejection of other transplants, psoriasis, graft vs host disease, Crohn's disease, lupus nephritis, pyoderma gangrenosum, rheumatoid arthritis, or uveitis

ENVARSUS XR® (tacrolimus extended-release) oral tablet (cont.)

Criteria:

- **Criteria for initial therapy:** Envarsus XR (tacrolimus extended-release) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual is 18 years of age or older
  2. A confirmed diagnosis that use is for prophylaxis of organ rejection in kidney transplant
  3. Individual uses other immunosuppressants to prevent organ rejection in kidney transplant
  4. Individual has failure, contraindication or intolerance to the following preferred step therapy agent:
     - Immediate release Tacrolimus
  5. There are **NO** contraindications:
     - Contraindications include:
       - Known hypersensitivity to tacrolimus

  Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Envarsus XR (tacrolimus extended-release) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual's condition responded while on therapy
     - Response is defined as:
       - No rejection
  2. Individual has been adherent with the medication
  3. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
     - Contraindications as listed in the criteria for initial therapy section
     - Significant adverse effect such as:
       - Posterior reversible encephalopathy syndrome (PRES)
         - Signs and symptoms may include: rapidly evolving symptoms of seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension
       - Pure red cell aplasia (PRCA)
         - Signs and symptoms may include: fatigue, pale skin, dizziness, shortness of breath, reduced reticulocytes, low RBC but normal WBC and normal platelets
  4. There are no significant interacting drugs

  Renewal duration: 12 months

ENVARSUS XR® (tacrolimus extended-release) oral tablet (cont.)

Resources:

Envarsus XR. Package Insert. Revised by manufacturer 6/2015. Accessed 10-08-2015.

Envarsus XR. Package Insert. Revised by manufacturer 06/2016. Accessed 11-30-2016.

Envarsus XR. Package Insert. Revised by manufacturer 10/2017. Accessed 12-15-2017.

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.