PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 1/21/2016**
SECTION: DRUGS	**LAST REVIEW DATE: 2/17/2022**
	LAST CRITERIA REVISION DATE: 2/17/2022
	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.**

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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. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Nephrologist or Transplant Specialist
  2. Individual is 18 years of age or older
  3. A confirmed diagnosis that use is for prophylaxis of organ rejection in kidney transplant
  4. Individual uses other immunosuppressants to prevent organ rejection in kidney transplant
  5. Individual has failure, contraindication per FDA label, or intolerance to the following preferred agent:
     a. Immediate release tacrolimus
  6. There are no significant interacting drugs

  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 continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Nephrologist or Transplant Specialist
  2. Individual's condition responded while on therapy
     a. Response is defined as:
        i. No rejection
  3. Individual has been adherent with the medication
  4. Individual has not developed any significant adverse drug effects that may exclude continued use
     a. Significant adverse effect such as:
        i. Posterior reversible encephalopathy syndrome (PRES)
        ii. Pure red cell aplasia (PRCA)
        iii. QT prolongation
        iv. Torsades de pointes
  5. There are no significant interacting drugs

  Renewal duration: 12 months

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- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of Non-cancer Medications**
  2. **Off-Label Use of Cancer Medications**

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).

Resources:

Envarsus XR (tacrolimus extended release) tab product information, revised by Velozis Pharmaceuticals, Inc. 09-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 25, 2021.

Tacrolimus caps product information, revised by Sandoz Inc. 07-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 25, 2021.

Prograf (tacrolimus) caps product information, revised by Astellas Pharma US, Inc. 07-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 25, 2021.

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Astagraf XL (tracrolimus extended release) cap product information, revised by Astellas Pharma US, Inc. 12-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 25, 2021.

Hardinger K, Brennan DC. Kidney transplantation in adults: Maintenance immunosuppressive therapy. In: UpToDate, Legendre C, Lam AQ (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Topic last updated November 11, 2021. Accessed December 25, 2021.