BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

TRYVIO™ (aprocitentan)
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Tryvio (aprocitentan) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Individual is 18 years of age or older

2. Individual has a confirmed diagnosis of hypertension (systolic blood pressure greater than or equal to 140 mmHg) not adequately controlled on a combination of at least three other drugs used for hypertension

3. Individual has completed **ALL** the following **baseline tests** before initiation of treatment and will have continued monitoring as clinically appropriate:
    a. Serum aminotransferase levels and total bilirubin
    b. Negative pregnancy test in a woman of childbearing potential

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c. To prevent pregnancy, an individual who can become pregnant is using acceptable methods of contraception
d. Hemoglobin is greater than or equal to 10 gm/dL

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has documented failure (using maximally tolerated doses for at least 3-months), contraindication per FDA label, intolerance, or is not a candidate for use of a combination of **THREE** antihypertensive medications from the following categories:
   a. One angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)
   b. One long acting dihydropyridine calcium channel blocker
   c. One thiazide-like diuretic (chlorthalidone or indapamide)

6. Individual is not currently taking other drugs which may cause severe adverse reactions or significant drug interactions that may require discontinuation such as use with other ERA (e.g., ambrisentan, bosentan, macitentan)

7. There are **NO** FDA-label contraindications such as:
   a. Pregnancy
   b. Hypersensitivity to aprocitentan or any of its excipients or to drugs of the same class

8. Individual does not have elevated aminotransferases (>3 × ULN) or moderate to severe hepatic impairment (Child-Pugh Class B and C)

9. Individual does not kidney failure (eGFR <15 mL/min) or on dialysis

10. Individual does not have heart failure New York Heart Association stage III–IV, unstable cardiac function, or with NTproBNP ≥ 500 pg/mL

11. Individual does not have severe anemia

12. Individual does not have **ANY** of the following:
    a. Pseudo resistant hypertension due to “white coat effect”
    b. Failing to adjust/intensify drug therapy despite recognition of uncontrolled hypertension
    c. Secondary causes of hypertension such as sleep apnea, renovascular disease, hyperaldosteronism, etc.
    d. Documented non-adherence to regimen

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Tryvio (aprocitentan) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

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1. Individual has documentation of positive clinical response to therapy defined as a systolic blood pressure of less than or equal to 140 mmHg or a clinically significant reduction in blood pressure

2. Individual has been adherent with the medication

3. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use such as:
    a. Hepatotoxicity and liver failure
    b. Individual has become pregnant
    c. Clinically significant fluid retention, weight gain, worsening heart failure
    d. Significant decreases in hemoglobin and hematocrit resulting in anemia

5. Individual is not currently taking other drugs which may cause severe adverse reactions or significant drug interactions that may require discontinuation such as use with other ERA (e.g., ambrisentan, bosentan, macitentan)

6. Individual does not have elevated aminotransferases (>3 × ULN) or moderate to severe hepatic impairment (Child-Pugh Class B and C)

7. Individual does not kidney failure (eGFR <15 mL/min) or on dialysis

8. Individual does not have heart failure New York Heart Association stage III–IV, unstable cardiac function, or with NTproBNP ≥ 500 pg/mL

9. Individual does not have severe anemia

Renewal duration: 12 months

- 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:

Tryvio (aprocitentan) is an endothelin receptor antagonist (ERA) indicated for the treatment of hypertension in combination with other antihypertensive drugs, to lower blood pressure in adult patients who are not adequately controlled on other drugs.

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According to the FDA-approved package label, Tryvio (aprocitentan) is not approved for use at a 25 mg dose. The 25 mg dose has not demonstrated a meaningful improvement in blood pressure reduction as compared to the 12.5 mg dose and had an increased risk of edema/fluid retention.

Lowering blood pressure reduces the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been reported in numerous controlled clinical trials of antihypertensive drugs from a wide variety of pharmacologic classes. There are no controlled trials demonstrating reduction of risk of these events with Tryvio (aprocitentan).

Control of high BP should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve BP goals.

Aprocitentan is an ERA that inhibits the binding of endothelin (ET)-1 to ET_A and ET_B receptors. ET-1, via its receptors, mediates a variety of deleterious effects such as vasoconstriction, fibrosis, cell proliferation, and inflammation. In hypertension, ET-1 can cause endothelial dysfunction, vascular hypertrophy and remodeling, sympathetic activation, and increased aldosterone synthesis.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Resources:

Tryvio (aprocitentan) product information, revised by Idorsia Pharmaceutical Ltd 04-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 27, 2025.

Mann JFE, Flack JM. Hypertension in adults: Initial drug therapy. In: UpToDate, White WB, Law K, Forman JP (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through August 2025. Topic last updated September 12, 2025. Accessed September 30, 2025.

Brook RD, Townsend RR. Treatment of resistant hypertension. In: UpToDate, White WB, Forman JP (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through August 2025. Topic last updated September 08, 2025. Accessed September 30, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT03541174: Multi-center, Blinded, Randomized, Parallel-group, Phase 3 Study With Aprocitentan in Subjects With Resistant Hypertension (RHT). Available from: http://clinicaltrials.gov. Last update posted March 21, 2023. Last verified March 2023. Accessed October 05, 2024. Re-evaluated September 30, 2025.