**09-J5000-18**

**Original Effective Date: 07/01/25**

**Reviewed: 05/14/25**

**Revised: 00/00/00**

# Subject: Aprocitentan (Tryvio) Tablets

**THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.**



## DESCRIPTION:

Almost half of the United States adult population has hypertension, and it is a leading cause of death worldwide. Hypertension is defined as having a systolic blood pressure (SBP) of greater than or equal to 140 mm Hg and/or a diastolic blood pressure (DBP) greater than or equal to 90 mm Hg. Among the hypertension population, a subset experience resistant hypertension (RH), which is defined as a blood pressure (BP) that remains elevated despite concurrent use of three antihypertensive agents of different classes, commonly including a long-acting calcium channel blocker (CCB), a blocker of the renin-angiotensin system [e.g., angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB)], and a diuretic. Although there are no FDA-approved treatments for RH, the 2018 American Heart Association (AHA) Scientific Statement recommends mineralocorticoid receptor antagonists (MRAs) as the fourth-line treatment for RH. All agents should be administered at maximum or maximally tolerated doses and at the appropriate dosing frequency.

On March 19, 2025, the FDA approved aprocitentan (Tryvio) for the treatment of blood pressure in adult patients who are not adequately controlled on other drugs. Aprocitentan (Tryvio) is an endothelin receptor antagonist (ERA) that inhibits the binding of endothelin (ET)-1 to ETA and ETB receptors and subsequently prevents vasoconstriction, fibrosis, cell proliferation, and inflammation. In hypertension, ET-1 can cause endothelial dysfunction, vascular hypertrophy and remodeling, sympathetic activation, and increased aldosterone synthesis.

According to the prescribing information, the efficacy and safety of aprocitentan (Tryvio) was evaluated in a multipart, phase 3 multicenter study (PRECISION, NCT03541174) in adults with SBP ≥140 mmHg who were prescribed at least three antihypertensive medications. The trial included a placebo run-in period, which was followed by three parts as described below. Prior to the placebo run-in period, all patients were switched to standard background antihypertensive therapy consisting of an angiotensin

receptor blocker, a calcium channel blocker, and a diuretic, which was continued throughout the study. Patients with concomitant use of beta-blockers continued this treatment throughout the study. Following the 4-week placebo run-in period, 730 patients were randomized equally to aprocitentan at either 12.5 mg, 25 mg, or placebo once daily during the initial 4-week double-blind (DB) treatment period (part 1). At the end of 4 weeks, all patients entered the single-blind treatment period (part 2) where they received 25 mg aprocitentan once daily for 32 weeks. At the end of the 32 weeks, patients were re-randomized to receive either 25 mg aprocitentan or placebo, once daily, during a 12-week DB-withdrawal period (part 3). The primary efficacy endpoint was the change in sitting SBP (SiSBP) from baseline to Week 4 during part 1, measured at trough by unattended automated office blood pressure (uAOBP). The key secondary endpoint was the change in SiSBP measured at trough by uAOBP from Week 36 (i.e., prior to randomized withdrawal to 25 mg aprocitentan or placebo in part 3) to Week 40. Patients had a mean age of 62 years (range 24 to 84 years) and 60% were male. Patients were Caucasian (83%), African American (11%) or Asian (5%). Approximately 10% were Hispanic. The mean body mass index (BMI) was 34 kg/$m^2$ (range 18 to 64 kg/$m^2$). At baseline, 19% of patients had an eGFR 30–59 mL/min/1.73 $m^2$ and 3% had an eGFR 15– 29 mL/min/1.73 $m^2$. At baseline, 24% of patients had a urine albumin-to-creatinine ratio (UACR) of 30–300 mg/g and 13% had a UACR >300 mg/g. Approximately 54% of patients had a medical history of diabetes mellitus, 31% ischemic heart disease, and 20% congestive heart failure. At baseline, 63% of patients reported taking four or more antihypertensive medications.

BP reductions compared to placebo based on uAOBP measurements at trough are shown in Table 1. Aprocitentan (Tryvio) 12.5 mg demonstrated a statistically significant reduction in sitting systolic blood pressure (SiSBP) as compared to placebo at Week 4 (part 1). The treatment effect was consistent for sitting diastolic BP (SiDBP).

### Table 1: Reduction in sitting trough BP (mmHg) at Week 4 compared to placebo

| | | | Difference to Placebo | |
|---|---|---|---|---|
| **Treatment Group** | **Baseline Mean[a]** | **LS Mean (97.5% CL)** | **LS Mean (97.5% CL)** | **P-value** |
| **SiSBP (Primary Endpoint)** | | | | |
| 12.5 mg (N=243) | 153.2 | −15.4 (−17.5, −13.3) | −3.8 (−6.8, −0.8) | 0.0043[b] |
| Placebo (N=244) | 153.3 | −11.6 (−13.7, −9.5) | --- | --- |
| **SiDBP** | | | | |
| 12.5 mg (N=243) | 87.9 | −10.4 (−11.7, −9.1) | −4.0 (−5.8, −2.1) | --- |
| Placebo (N=244) | 87.1 | −6.4 (−7.8, −5.1) | --- | --- |

Abbreviations: BP=blood pressure; CL=confidence limits; DB=double-blind; LS mean=least squares mean; SiDBP=sitting diastolic blood pressure; SiSBP=sitting systolic blood pressure.
[a] Observed baseline value.
[b] Statistically significant at the 2.5% level as prespecified in the testing strategy.

The persistence of the BP-lowering effect of aprocitentan (Tryvio) was demonstrated in part 3 of the trial, in which patients on aprocitentan were re-randomized to placebo or 25 mg aprocitentan following a period during which all patients were treated with 25 mg. In patients re-randomized to placebo, the mean SiSBP increased, whereas in patients re-randomized to 25 mg aprocitentan the mean effect on SiSBP was maintained and was statistically significant as compared to placebo at Week 40. The

treatment effect was consistent for SiDBP. Most of the BP-lowering effect occurred within the first two weeks of treatment with aprocitentan (Tryvio). However, it is important to note that aprocitentan (Tryvio) is not approved for use at a 25 mg dose. Additionally, the 25 mg dose has not demonstrated a meaningful improvement in blood pressure reduction as compared to the 12.5 mg dose and is associated with an increased risk of edema/fluid retention.

The most common adverse reactions with aprocitentan (Tryvio) (more frequent than placebo and ≥ 2% in aprocitentan-treated patients) are edema/fluid retention and anemia.

## POSITION STATEMENT:

**Comparative Effectiveness**

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of aprocitentan (Tryvio) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Diagnosis of resistant hypertension
2. Blood pressure goal has not been achieved while on triple agent hypertension therapy with 3 different medication classes for at least 4 weeks
3. Member has tried **ALL** of the following antihypertensive classes for a minimum of 4 weeks each at a maximally tolerated dose or has a documented intolerance or contraindication:
    a. Angiotensin converting enzyme (ACE) inhibitors (e.g., enalapril, lisinopril) or angiotensin II receptor blockers (ARB) (e.g., candesartan, valsartan)
    b. Long-acting calcium channel blockers (e.g., amlodipine, diltiazem, verapamil)
    c. Diuretics (e.g., hydrochlorothiazide)
    d. Mineralocorticoid receptor antagonists (e.g., spironolactone, eplerenone)
4. Aprocitentan (Tryvio) will be used in combination with at least three antihypertensive medications from different classes at maximally tolerated doses
5. Negative pregnancy test prior to therapy initiation (only for women of reproductive potential)
6. **NONE** of the following:
    a. Elevated alanine transaminase (ALT) or aspartate aminotransferase (AST) greater than 3-times the upper limit of normal or moderate to severe hepatic impairment (Child-Pugh class B and C)
    b. Kidney failure (eGFR less than 15 mL/min/1.73m$^2$) or on dialysis
    c. Heart failure New York Heart Association stage III–IV, unstable cardiac function, or with NTproBNP greater than or equal to 500 pg/mL
    d. Severe anemia

7. Prescribed by, or in consultation with, a cardiologist or nephrologist
8. Dose will not exceed 12.5 mg by mouth once daily

**Approval duration**: 6 months

Continuation of aprocitentan (Tryvio) **meets the definition of medical necessity** for members meeting the following criteria:

1. Authorization/reauthorization for the requested agent has been previously approved by Florida Blue or another health plan in the past 2 years (if another health plan, documentation of a health plan-paid claim during the 90 days before the authorization request must be submitted), OR the member has previously met ALL indication-specific initiation criteria.
2. Member has a clinical meaningful response (i.e., reduction in BP or at goal BP)
3. Aprocitentan (Tryvio) will be used in combination with at least three antihypertensive medications from different classes at maximally tolerated doses
4. Recent negative pregnancy test (only for women of reproductive potential)
5. **NONE** of the following:
    a. Elevated alanine transaminase (ALT) or aspartate aminotransferase (AST) greater than 3-times the upper limit of normal or moderate to severe hepatic impairment (Child-Pugh class B and C)
    b. Kidney failure (eGFR less than 15 mL/min/1.73m$^2$) or on dialysis
    c. Heart failure New York Heart Association stage III–IV, unstable cardiac function, or with NTproBNP greater than or equal to 500 pg/mL
    d. Severe anemia
6. Prescribed by, or in consultation with, a cardiologist or nephrologist
7. Dose will not exceed 12.5 mg by mouth once daily

**Approval duration**: 1 year

## DOSAGE/ADMINISTRATION:

**THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.**

**FDA-approved**

- Aprocitentan (Tryvio) is an endothelin receptor antagonist 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.
- The recommended dosage of aprocitentan (Tryvio) is 12.5 mg orally once daily, with or without food.
- Advise females not to breastfeed during treatment with aprocitentan (Tryvio).

**Dose Adjustments**

- Aprocitentan (Tryvio) should not be used in patients with elevated alanine transaminase (ALT) or aspartate aminotransferase (AST) greater than 3-times the upper limit of normal or with moderate to severe hepatic impairment (Child-Pugh class B or C). No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A).
- Aprocitentan (Tryvio) should not be used in patients with kidney failure (eGFR less than 15 mL/min) or on dialysis. No dose adjustment is required in patients with mild to severe renal impairment (eGFR ≥15 mL/min).

**Drug Availability**

- Aprocitentan (Tryvio) tablets are available as 12.5 mg yellow to orange round, film-coated tablet, debossed with "AN" on one side and plain on the other side.
    - NDC 80491-8012-8, each blister contains 10 tablets
    - NDC 80491-8012-3, each bottle contains 30 tablets and has a child-resistant closure

## PRECAUTIONS:

**Boxed Warning**

- **Embryo-Fetal Toxicity**: Based on data from animal reproduction studies with endothelin receptor antagonists (ERAs), aprocitentan (Tryvio) may cause fetal harm when administered during pregnancy and is contraindicated for use in patients who are pregnant. The available human data for endothelin receptor antagonists do not establish the presence or absence of fetal harm related to the use of aprocitentan (Tryvio). Counsel patients who can become pregnant about the 3 potential risk to a fetus. Obtain a pregnancy test prior to initiation of treatment with aprocitentan (Tryvio). Advise patients who can become pregnant to use effective contraception prior to initiation of treatment with aprocitentan (Tryvio), during treatment, and for one month after the final dose of aprocitentan (Tryvio). When pregnancy is detected, discontinue aprocitentan (Tryvio) as soon as possible.

**Contraindications**

- **Pregnancy:** Use of aprocitentan (Tryvio) is contraindicated in patients who are pregnant.
- **Hypersensitivity**: Aprocitentan (Tryvio) is contraindicated in patients who are hypersensitive to aprocitentan or any of its excipients.

**Precautions/Warnings**

- **Hepatotoxicity:** Elevations of aminotransferases and hepatotoxicity are known effects of ERAs, including aprocitentan (Tryvio). Elevations in alanine transaminase (ALT) or aspartate aminotransferase (AST) of greater than 5-fold upper limit of normal (ULN) were observed rarely in patients treated with aprocitentan in the clinical trial, including cases with positive rechallenge. There were no reports of patients with ALT and/or AST >3 × ULN and total bilirubin >2 × ULN or cases of liver failure observed in aprocitentan-treated patients in the clinical trials. To reduce the risk of potential serious hepatotoxicity, measure serum aminotransferase levels and total bilirubin prior to initiation of treatment and repeat during treatment periodically and

as clinically indicated. Do not initiate aprocitentan (Tryvio) in patients with elevated aminotransferases (>3 × ULN) or moderate to severe hepatic impairment. Advise patients with symptoms suggesting hepatotoxicity (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, scleral icterus, jaundice, dark urine, fever, or itching) to immediately stop treatment with aprocitentan (Tryvio) and seek medical attention. If sustained, unexplained, clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 × ULN, or if clinical symptoms of hepatotoxicity occur, discontinue aprocitentan (Tryvio).

- **Fluid Retention:** Fluid retention and peripheral edema are known effects of ERAs, including aprocitentan (Tryvio). Edema/fluid retention was reported in 9% of aprocitentan-treated patients compared with 18% of patients receiving aprocitentan 25 mg (twice the recommended dose) and 2% on placebo in the clinical trial, requiring additional diuretic use in some patients. Older age and chronic kidney disease are risk factors for edema/fluid retention with aprocitentan (Tryvio). Aprocitentan (Tryvio) has not been studied in patients with heart failure New York Heart Association stage III–IV, unstable cardiac function, or with NTproBNP ≥500 pg/mL. Aprocitentan (Tryvio) is not recommended in these patients. Monitor for signs and symptoms of fluid retention, weight gain, and worsening heart failure. If clinically significant fluid retention develops, treat appropriately, and consider discontinuation of aprocitentan (Tryvio).
- **Hemoglobin Decrease:** Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and were observed in the clinical trial with aprocitentan (Tryvio). Hemoglobin decreases usually presented early, stabilized thereafter, and were reversible after discontinuation. A decrease in hemoglobin of >2 g/dL from baseline was observed in 7% of patients compared to 1% of placebo patients. A decrease to below 10.0 g/dL was observed in 3% of aprocitentan-treated patients compared to zero patients taking placebo. Initiation of aprocitentan (Tryvio) is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and periodically during treatment as clinically indicated.
- **Decreased Sperm Counts:** Aprocitentan (Tryvio), like other ERAs, may have an adverse effect on spermatogenesis. Counsel men about potential effects on fertility.

## BILLING/CODING INFORMATION:

The following codes may be used to describe:

### HCPCS Coding

| | |
|---|---|
| J8499 | Prescription drug, oral, non-chemotherapeutic, not otherwise specified |

### ICD-10 Diagnosis Codes That Support Medical Necessity

| | |
|---|---|
| I1A.0 | Resistant hypertension |

## REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

## PROGRAM EXCEPTIONS:

**Federal Employee Program (FEP):** Follow FEP guidelines.

**State Account Organization (SAO):** Follow SAO guidelines.

**Medicare Part D:** Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

**Medicare Advantage:** The following National Coverage Determination (NCD) was reviewed on the last guideline revised date: Self-administered Drug List (A54770). No Local Coverage Determination (LCD) was found at the time of the last guideline revised date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

## DEFINITIONS:

None

## RELATED GUIDELINES:

None

## OTHER:

None

## REFERENCES:


1. Carey RM, et al. Resistant hypertension: detection, evaluation, and management: A Scientific Statement from the American Heart Association. Hypertension. 2018;72(5):e53-e90. doi:10.1161/HYP.0000000000000084.
2. Clinical Pharmacology powered by ClinicalKey [Internet]. Tampa, FL: Elsevier.; 2025. Available at: https://www.clinicalkey.com/pharmacology/. Accessed 5/2/25.
3. DRUGDEX System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2025 May 2].
4. DynaMed [database online]. Ipswich, MA: EBSCO Information Services.; 2025. URL http://www.dynamed.com. Accessed 5/2/25.
5. Tryvio (aprocitentan) [package insert]. Radnor, PA: Idorsia Pharmaceuticals US, Inc.; April 2025.


## COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 05/14/25.

## GUIDELINE UPDATE INFORMATION:

| | |
|---|---|
| 07/01/25 | New Medical Coverage Guideline: Aprocitentan (Tryvio) for the treatment of resistant hypertension in combination with at least three antihypertensive medications from different classes at maximally tolerated doses. |