Pharmacy Policy Bulletin: J-1398 Tryvio (aprocitentan) – Commercial and Healthcare Reform	
Number: J-1398	**Category:** Prior Authorization
Line(s) of Business: ☒ Commercial ☒ Healthcare Reform ☐ Medicare	**Benefit(s):** **Commercial:** **Prior Authorization (1.):** **1.** Miscellaneous Specialty Drugs Oral = Yes w/ Prior Authorization **Healthcare Reform:** Not Applicable
Region(s): ☒ All ☐ Delaware ☐ New York ☐ Pennsylvania ☐ West Virginia	**Additional Restriction(s):** None
Version: J-1398-001	**Original Date:** 06/05/2024
Effective Date: 10/03/2024	**Review Date:** 06/05/2024

Drugs Product(s):	• Tryvio (aprocitentan)
FDA-Approved Indication(s):	• For treatment of hypertension (HTN) in combination with other antihypertensive drugs, to lower blood pressure in adult patients who are not adequately controlled on other drugs; lowering blood pressure reduces the risk of fatal and non-fatal CV events, primarily strokes and myocardial infarctions (MI).

Background:	• Tryvio (aprocitentan) is an endothelin receptor antagonist (ERA) that inhibits the binding of endothelin w(ET)-1 to ETA and ETB receptors. In HTN, ET-1 activation of the ETA and ETB receptors can cause endothelial dysfunction, vascular hypertrophy and remodeling, and sympathetic activation. By preventing the activation of ETA and ETB receptors, Tryvio may decrease vasoconstriction, fibrosis, cell proliferation, and inflammation, thereby decreasing blood pressure.
	• Resistant HTN is defined as inadequate blood pressure control while taking three antihypertensive medications with different mechanisms of action or use of four blood pressure agents to achieve target blood pressure. Risk factors for resistant HTN include comorbid diabetes, obesity, or chronic kidney disease (CKD). The prevalence of resistant HTN is approximately 13-17% in the adult population, and resistant HTN is associated with a high risk of complications such as MI, end stage renal disease, and stroke. Pseudoresistance due to poor medication adherence or “white coat syndrome” (increased blood pressure due to patient anxiety in clinical settings) is a common cause of resistant HTN.
	• Prior to reaching resistant HTN, patients experience therapeutic failure to guideline recommended first- and second- line HTN agents:
	  ○ First-line therapies for HTN include thiazide type diuretics (e.g. hydrochlorothiazide, chlorthalidone), calcium channel blockers (CCBs) (e.g. amlodipine), angiotensin-converting enzyme (ACE) inhibitors (e.g. lisinopril, enalapril), and angiotensin receptor blockers (ARBs) (e.g. losartan, valsartan).
	  ○ Second-line therapies are often chosen based on patient specific characteristics: loop diuretics (e.g. furosemide, bumetanide) in heart

failure (HF) or moderate to severe CKD; beta blockers (BB) in HF (e.g. metoprolol succinate, carvedilol); potassium sparing diuretics (e.g. amiloride, triamterene) in patients who experience hypokalemia while on a thiazide diuretic; and alpha-1 blockers (e.g. terazosin, prazosin) in benign prostate hyperplasia. Direct vasodilators (e.g. hydralazine) were previously recommended as preferred agents in African American patients, but this recommendation has been removed.
    - Other second line therapies are not commonly used in practice, such as central alpha-2 agonists (e.g. clonidine) due to significant central nervous system effects and aliskiren due to severe renal adverse effects.
    - Guidelines recommend assessing medication adherence and achieving optimal dosing of antihypertensive medications when treating resistant hypertension.
    - After exhausting appropriate first- and second- line therapies, assessing medication adherence, and optimizing dosing, the mineralocorticoid receptor antagonists (MRAs) spironolactone and eplerenone are guideline recommended as last line agents in resistant HTN.

Class	Drug	Usual Dose Range (mg/d)
Thiazide Diurectics	Chlorthalidone	12.5 - 25
	Hydrochlorothiazide	25 - 50
	Indapamide	1.25 - 2.5
	Metolazone	2.5 - 5
ACE Inhibitors	Benazepril	10 - 40
	Captopril	12.5 - 150
	Enalapril	5 - 40
	Fosinopril	10 - 40
	Lisinopril	10 - 40
	Moexipril	7.5 - 30
	Perindopril	4 - 16
	Quinapril	10 - 80
	Ramipril	2.5 - 20
	Trandolapril	1 - 4
ARBs	Azilsartan	40 - 80
	Candesartan	8 - 32
	Eprosartan	600 - 800
	Irbesartan	150 - 300
	Losartan	50 - 100
	Olmesartan	20 - 40
	Telmisartan	20 - 80
	Valsartan	80 - 320
Mineralcorticoid Receptor Antagonists	Eplerenone	50 - 100
	Spironolactone	25 - 100

Table 1. Dosing range of select anti-hypertensive medications.

- Prescribing Considerations:
    - Tryvio has a black box warning for major birth defects if used in pregnant patients and is contraindicated in pregnancy.
    - Tryvio has Risk Evaluation and Mitigation Strategies (REMS) for embryo-fetal toxicity. Doctors prescribing and pharmacies dispensing Tryvio must be enrolled in the Tryvio REMS program.
    - Patients of child-bearing potential should use effective contraception while taking Tryvio and for one month after discontinuation. Tryvio may

	impact spermatogenesis, and it is unknown if this effect on fertility is reversible.

Approval Criteria

I. Initial Authorization

When a benefit, coverage of Tryvio may be approved when all of the following criteria are met **(A. and B.)**:

- **A.** The member is 18 years of age or older.
- **B.** The member has a diagnosis of resistant hypertension (ICD-10: I1A.0).
- **C.** The prescriber attests that the member is adherent to currently prescribed antihypertensive medications.
- **D.** The member has experienced therapeutic failure, intolerance, or contraindication to maximally tolerated doses all of the following **(1. through 4.)**:
  - **1.** Thiazide diuretic (e.g. hydrochlorothiazide, chlorthalidone)
  - **2.** ACE or ARB (e.g. lisinopril, losartan)
  - **3.** Calcium channel blocker (e.g. amlodipine)
  - **4.** Mineralocorticoid receptor antagonist (spironolactone or eplerenone)

II. Reauthorization

When a benefit, reauthorization of Tryvio may be approved when the following criterion is met **(A.)**:

- **A.** The prescriber attests that the member achieved a reduction in blood-pressure from baseline.

III. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

Limitations of Coverage

I. Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.

II. For Commercial or HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

Authorization Duration

- Commercial and HCR Plans: If approved, up to a 12-month authorization may be granted.

Automatic Approval Criteria

None.

References:

1. Tryvio [aprocitentan]. Radnor, PA: Idorsia; March 2024.
2. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018 Jun;71(6):e13-e115.
3. DRUGDEX System (Micromedex 2.0). Greenwood Village, CO: Truven Health Analytics; 2024.

4. DynaMed. Spironolactone. Available at: https://www.dynamed.com/drug-monograph/spironolactone, Accessed March 31, 2024.