Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCCAR046.0625	**CARDIOVASCULAR AGENTS** **THERAPIES FOR RESISTANT HYPERTENSION** See Table 1 for Applicable Medications
Effective Date: 8/1/2025	**Review/Revised Date**: 04/25 (snm)
Original Effective Date: 01/25	**P&T Committee Meeting Date**: 10/24, 06/25
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
For patients initiating therapy, the following criteria are required:

1. Documentation that patient has resistant hypertension, defined by blood pressure that remains above goal despite the concurrent use of maximum or maximally tolerated daily doses of three antihypertensive agents of different classes including:
    a. A calcium channel blocker (such as amlodipine, diltiazem, verapamil)
    b. An angiotensin-converting enzyme inhibitor (ACE-I) (such as lisinopril, enalapril) or angiotensin receptor blocker (ARB) (such as losartan, valsartan, candesartan)
    c. A diuretic (such as hydrochlorothiazide, chlorthalidone)
2. Documentation that patient will be using in combination with a calcium channel blocker, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and a diuretic
3. Documentation that patient has tried and had an inadequate response to, or has an intolerance or contraindication to both of the following:
    a. A mineralocorticoid receptor antagonist (such as spironolactone)
    b. One more medication indicated for hypertension from a different therapeutic class (such as a beta-blocker [such as carvedilol], a centrally

acting BP-lowering medication [such as clonidine], an alpha-blocker, hydralazine, minoxidil)

4. Confirmation of uncontrolled high blood pressure as demonstrated by systolic blood pressure greater than or equal to 140 mm Hg or diastolic blood pressure greater than or equal to 90 mm Hg taken on at least two separate occasions
5. Provider attestation that pseudo- and secondary hypertension have been ruled out (see Table 2 for examples)

For reauthorization:

1. Documentation that patient is responding to treatment as documented by sustained improvement in blood pressure, taken on at least two consecutive measurements
2. Documentation that patient will be using in combination with a calcium channel blocker, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and a diuretic

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
May be approved for patients aged eighteen (18) years and older

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a cardiologist, nephrologist, endocrinologist

COVERAGE DURATION:
Initial authorization will be approved for three months. Reauthorization will be approved for one year.

QUANTITY LIMIT:
One tablet per day

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCCAR046	CARDIOVASCULAR AGENTS THERAPIES FOR RESISTANT HYPERTENSION See Table 1 for Applicable Medications

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Aprocitentan is an endothelin receptor antagonist (ERA) that inhibits the binding of endothelin (ET)-1 to ET and ET receptors. ET-1, via its receptors (ETA and ETB), 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.

- The recommended dose is 12.5 mg tablet orally once daily.
- Aprocitentan carries a boxed warning for embryo-fetal toxicity

FDA APPROVED INDICATIONS:

Tryvio® (aprocitentan): Indicated in combination with other antihypertensive drugs, for the treatment of hypertension, to lower blood pressure in adult patients who are not adequately controlled on other drugs.

POSITION STATEMENT:

- Resistant hypertension (RH) is defined as blood pressure of a hypertensive patient that remains above goal despite the concurrent use of maximum or maximally tolerated daily doses of three antihypertensive agents of different classes (typically a long-acting calcium channel blocker, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker), and a diuretic[4]. It is more prevalent in people who are older, obese, male, African American or nonblack Hispanic[4,11]. Guidelines recommend that patients with resistant hypertension are referred to a hypertension specialist.
- When treating resistant hypertension, it is important to rule out secondary hypertension and pseudo-resistance (see Table 2 for examples)[14]. The standard blood pressure target is less than 140/90 mm Hg; however the target can be lower depending on age and comorbid conditions. The 2024 ESC guideline for the management of elevated blood pressure and hypertension recommends a target for most adults of 120-129 mm Hg / 70-79 mm Hg if tolerated to reduce CV risk.
- Although there are no other FDA-approved treatments indicated specifically for resistant hypertension, guidelines recommend adding a mineralocorticoid receptor antagonist (MRA) (specifically spironolactone however eplerenone can also be used). Spironolactone appears to be the most effective therapy at further

lowering blood pressure in patients with resistant hypertension; however, there are no outcome trials of mineralocorticoid receptor antagonists in primary hypertension. If blood pressure remains elevated, it is recommended to add-on other antihypertensives with complimentary mechanisms of action. The 2024 ESC guideline recommends the addition of a beta-blocker, then a centrally acting BP-lowering medication, an alpha-blocker, hydralazine, or a potassium sparing diuretic. These therapies are all available as low-cost generic drugs. Aprocitentan is mentioned in the 2024 ESC guideline under "New therapies with blood pressure-lowering properties that await supportive evidence from cardiovascular outcomes trials prior to guideline endorsement and routine use in hypertension"[14].

Clinical Trials:

- Approval was based on one Phase 3, randomized, blinded, multicenter, parallel-group clinical trial (*PRECISION PubMed ID #36356632)*. 730 adults with resistant hypertension and systolic blood pressure ≥ 140 mm Hg who were prescribed ≥ 3 antihypertensive medications ≥ 1 year were included. Individuals were excluded if they had severe hypertension (grade 3a), recent (previous 6 months) major CV, renal, cerebrovascular medical complications, heart failure (NYHA Stage III-IV), NT-proBNP ≥500 pg/mL, eGFR <15 mL/min/1.73 m2, alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal, severe hepatic impairment, hemoglobin <10 g/L, apparent/pseudo resistant hypertension, secondary resistant hypertension (not including obstructive sleep apnea). At baseline the mean age was 62 years (range: 24 to 84 years), 60% male, 83% White, 11% African American, 5% Asian, ~10% Hispanic, and 63% reported taking ≥4 antihypertensive medications.
- **Trial design and interventions**
    - Phase 1, screening period: ≥4 weeks, patients switched current antihypertensive agents (except beta blockers) to standardized background therapy: a calcium channel blocker (amlodipine), an angiotensin receptor antagonist (valsartan), and a diuretic (hydrochlorothiazide), at fixed doses of either 5 mg, 160 mg, or 25 mg; or 10 mg, 160 mg, or 25 mg (whichever was max tolerated)
    - Phase 2, single (patient)-blind run-in period: 4 weeks, all patients received placebo to exclude potential placebo responders
    - Phase 3: 48 weeks, active treatment period
        - *Part 1*: 4-week DB, R, PC, **Intervention**: aprocitentan 12.5 mg, aprocitentan 25 mg, or placebo in a 1:1:1 ratio
        - *Part 2*: 32-week single (patient)-blind part, **Intervention**: all patients received aprocitentan 25 mg

- *Part 3*: 12-week DB, R, and PC withdrawal part, I**ntervention**: patients re-randomized to aprocitentan 25 mg or placebo in a 1:1 ratio

- **Primary and endpoint**: Change from baseline to week 4 (part 1) in mean trough sitting office systolic blood pressure
  - **Secondary endpoints**: Change from withdrawal baseline (week 36) to week 40 (part 3) in mean trough sitting office systolic blood pressure, changes at week 4 and week 40 in mean trough sitting office diastolic blood pressure
- **Results**:
  - **Efficacy**:

Reduction in Sitting Trough BP (mm Hg) at Week 4 of DB Treatment in PRECISION Trial

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

    - Key Secondary Endpoint: In part 3, office systolic blood pressure after 4 weeks of withdrawal increased significantly with placebo compared with aprocitentan (5.8 mm Hg, 95% CI 3.7 to 7.9, p<0·0001)
    - Efficacy for the 25 mg dose was similar to the 12.5 mg dose and therefore 12.5 mg is the approved dose.
  - **Safety**:
    - Most frequently reported adverse reactions to aprocitentan 12.5 mg during Part 1 of the PRECISION study: edema/fluid retention (9.1% versus 2.1%) and anemia (3.7% versus 0%)
- Edema/fluid retention led to discontinuation of 7 patients (on the 25 mg dose); incidence was dose dependent and greater in patients with chronic kidney disease stage 3-4.

- Hemoglobin concentrations decreased to a similar degree with both aprocitentan doses (–0.8 g/dL, –0.85 g/dL, and –0.04 g/dL with aprocitentan 12.5 mg, aprocitentan 25 mg, and placebo, respectively) during part 1, stabilized during part 2 and reversed upon withdrawal during part 3.
- 11 patients required admission to hospital for heart failure (2/245 [0.8%] receiving aprocitentan 25 mg during part 1; 6/704 [0.9%] during part 2; and 2/310 [0.6%] receiving aprocitentan 25 mg and 1/303 [0.3%] receiving placebo during part 3); no cases were fatal.
- All patients had a high-risk cardiovascular medical history including diabetes, chronic kidney disease stage 3–4, and pre-existing heart failure.
- No signs of hepatotoxicity observed; however this is a risk known to the class of endothelin receptor antagonists.
- Contraindicated in patients who are pregnant or hypersensitive to aprocitentan or any of its excipients.

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Table 1

Drug	Mechanism of Action
Tryvio® (aprocitentan)	Endothelin receptor antagonist (ERA)

Table 2: Examples of Secondary Hypertension and Pseudo-resistance

Secondary Hypertension	Pseudo-resistance
• Primary aldosteronism • Renovascular hypertension • Obstructive sleep apnea • Cushing's disease • Polycythemia • Hyperparathyroidism • Hyperthyroidism • Phaeochromocytoma/paraganglioma (PPGLs) • Drug-induced hypertension • Fibromuscular dysplasia • Liddle's syndrome • Glucocorticoid-remediable aldosteronism • Excess licorice • Aortic coarctation • Acromegaly	• Poor adherence to BP-lowering medications • White-coat hypertension • Poor BP measurement method • Marked brachial artery calcification (Osler phenomenon) • Clinician inertia (inadequate doses, inappropriate combinations of BP-lowering drugs) • Munchausen syndrome