Aprocitentan (TRYVIO)
National Drug Monograph
March 2025

VA Pharmacy Benefits Management Services and VA National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information[1]

Description/Mechanism of Action

- Aprocitentan is a dual endothelin receptor antagonist (ERA) that blocks the binding of endothelin (ET)-1 to ET_A and ET_B receptors. ET-1, via the ET_A and ET_B receptors, mediates effects such as vasoconstriction, fibrosis, cell proliferation, and inflammation. In hypertension, ET-1 is associated with endothelial dysfunction, vascular hypertrophy and remodeling, sympathetic activation, and increased aldosterone synthesis. Of note, aprocitentan is the same structure as the active metabolite of macitentan, an ERA indicated for the treatment of pulmonary arterial hypertension.

Indication(s) Under Review in This Document

- Aprocitentan is the first ERA approved by FDA for the treatment of hypertension. Aprocitentan is indicated to be used in combination with other antihypertensive agents when blood pressure is inadequately controlled on other agents.

Dosage Form(s) Under Review

- Aprocitentan is available as a 12.5 mg oral tablet and is dosed orally once daily.

Clinical Evidence Summary

Efficacy Considerations

- Efficacy for FDA approval of aprocitentan was based on one industry sponsored, multipart, blinded, randomized, parallel-group phase 3 trial (PRECISION) designed to evaluate the short term and sustained effects of aprocitentan in patients with resistant hypertension. *Of note, only the 12.5 mg aprocitentan dose is approved by FDA.*

- Design and Interventions: The trial was comprised of 4 periods:

    - *Period 1* - screening period to confirm true resistant hypertension. Patients were switched from their existing hypertension medications to a standardized, fixed-dose combination tablet containing a calcium-channel blocker (CCB) (amlodipine 5 or 10 mg), an angiotensin-receptor blocker (ARB) (valsartan 160 mg), and a diuretic (hydrochlorothiazide 25 mg).

    - *Period 2* - single-blind run-in, placebo period to exclude placebo response

- ***Period 3*** **- 48-week treatment period consisting of 3 parts:**
  - part 1) 4-week, double-blind, placebo-controlled phase where patients were randomized 1:1:1 to aprocitentan 12.5 mg, 25 mg, or placebo;
  - part 2) 32-week, single-blind phase where all patients received aprocitentan 25 mg; and
  - part 3) 12-week, double blind withdrawal phase where patients were re-randomized to aprocitentan 25 mg or placebo
- *Period 4* - 30-day safety follow-up

- Key inclusion and exclusion: Eligible patients had uncontrolled hypertension despite treatment with three or more antihypertensive agents from different drug classes and SBP ≥140 mmHg at screening, the run-in period, and trial randomization. Patients were excluded if they had confirmed severe hypertension or major cardiovascular, renal, or cerebrovascular complications in past 6 months, New York Heart Association (NYHA) Class III or IV heart failure, or eGFR <15 ml/min/1.73 m^2.
- Interventions: Aprocitentan 12.5 mg, 25 mg, or placebo orally once daily
- Primary endpoint: Change in mean seated, unattended office systolic blood pressure (SBP) from baseline to week 4.
- Baseline/Disposition: A total of 730 out of 1,965 screened patients, predominantly from Europe and North America, were randomized to treatment. Patient characteristics were similar between groups (Table 1). During the active treatment period, 96% of patients completed part 1 of the trial (704 of 730); 87% of those completed part 2 (613 of 704); 94% of those completed part 3 (577 of 614).

Table 1: Selected baseline characteristics from PRECISION

Characteristic	Aprocitentan 12.5 (n=243)	Placebo (n=244)
Mean age	61 yrs	62 yrs
Male	59%	59%
Race/ethnicity		
White	84%	83%
Black or African American	12%	11%
Asian	5%	5%
eGFR 15 to <60 ml/min/1.73m^2	23%	19%
uAOBP	153/88 mmHg	153/87 mmHg
24 hr ambulatory BP	138/84 mmHg	137/83 mm Hg
On ≥4 antihypertensives*	62%	62%
Concomitant conditions		
Obesity (BMI ≥30 kg/m^2)	70%	68%
Diabetes	54%	52%
Ischemic heart disease	30%	30%
Congestive heart failure	20%	18%

BMI=body mass index; eGFR=estimated glomerular filtration rate; uAOBP=unattended automated office blood pressure

*4th agent was commonly a beta-blocker; 58% of patients continued treatment.

- Results: For the primary endpoint, aprocitentan 12.5 mg was associated with a statistically significant improvement in the office SBP of -3.8 mmHg compared to placebo at 4 weeks. Reduction in DBP was also shown (Table 2). The key secondary endpoint of persistence of BP lowering was demonstrated with aprocitentan during parts 2 and part 3 of the trial (only the 25 mg aprocitentan dose was studied).

Table 2: Selected 4-week endpoints from PRECISION

Endpoint	Aprocitentan 12.5 mg n=243	Placebo N=244
Primary Endpoint*		
Baseline SBP (mmHg)	153	153
LS mean change in SBP (mmHg)	-15.4	-11.6
Difference from placebo (mmHg)	-3.8	
Secondary Endpoint		
Baseline DBP	88	87
LS mean change in DBP	-10.4	-6.4
Difference from placebo	-4.0	

P <0.05

Safety Considerations

Safety Results from Clinical Trials: Safety data for FDA approval was obtained from the phase 3 PRECISION trial. The different phases of the trial were analyzed separately.

- **Contraindications:**
  - Pregnancy
  - Hypersensitivity

- **Warnings:**
  - ***Boxed warning - Embryofetal toxicity:*** Aprocitentan can cause major birth defects if used in pregnant women. Females who can become pregnant need to have monthly negative pregnancy tests and use effective contraception. Because of the risk of birth defects, aprocitentan is only available through a restricted program called the TRYVIO Risk Evaluation and Mitigation Strategy (REMS) (See REMS under Other Considerations).

  - ***Hepatotoxicity:*** ERAs including aprocitentan have been associated with elevated aminotransferases and hepatotoxicity. During the PRECISION trial, elevations in alanine transaminase (ALT) and aspartate aminotransferase (AST) of greater than 5 times the upper limit of normal (ULN) were reported rarely, including two cases with positive rechallenge. **Obtain baseline serum aminotransferase levels and total bilirubin prior to starting aprocitentan and monitor periodically during treatment.** Do not initiate

aprocitentan if AST or ALT is greater than 3 times ULN or in patients with moderate to severe hepatic impairment. Discontinue aprocitentan in patients with symptoms suggestive of hepatotoxicity or in the setting of elevated transaminases in conjunction with elevated bilirubin (greater than 2 times ULN).

- ***Fluid retention:*** ERAs including aprocitentan have been associated with fluid retention/edema. In PRECISION, there was a higher incidence of edema with aprocitentan 12.5 mg vs. placebo (9% vs. 2%). Edema occurred early in treatment but continued throughout the study and appeared to be dose related. **Monitor for signs and symptoms of fluid retention, weight gain, and worsening heart failure.** Aprocitentan is not recommended in patients with NYHA stage III or IV heart failure, unstable cardiac function, NTproBNP ≥500 pg/mL.

- ***Decreased hemoglobin and anemia:*** ERAs including aprocitentan have been associated with decreased hemoglobin, hematocrit, and anemia. Decreased hemoglobin occurred early in treatment, stabilized, and were reversible upon discontinuation. At week 4, the mean decrease in hemoglobin with aprocitentan 12.5 mg was 0.8 g/dL (along with 10% increase in plasma volume). Hemoglobin decreases of >2 g/dL occurred in 7% of aprocitentan vs. 1% of placebo patients. Anemia occurred in 4% of patients in the aprocitentan 12.5 mg group vs. none in the placebo group. **Obtain baseline hemoglobin prior to starting aprocitentan and monitor periodically during treatment.**

- ***Decreased sperm counts:*** ERAs including aprocitentan may have an adverse effect on spermatogenesis. It is unknown whether it is reversible. Counsel males about the potential effects on fertility.

- **Adverse reactions (Part 1, PBO-controlled, 4-weeks)**
  - **Serious adverse events:** 3.3% APRO vs. 1.2% PBO
  - **Deaths:** 1 event APRO vs. 0 events PBO
  - **Discontinuation due to adverse events:** 2.9% APRO vs. 0.8% PBO
  - **Common:** Edema/fluid retention and anemia occurred more frequently with aprocitentan vs. placebo.

- **Other adverse events of interest**
  - ***Heart failure hospitalization:*** Over the course of the PRECISION study, ten events occurred in patients taking aprocitentan (plus one event in the placebo group). All patients had cardiovascular risk factors including diabetes (n=11), chronic kidney disease stage 3 or 4 (n=6), and pre-existing heart failure (n=5). The majority of events occurred within the first three to four weeks after initiating aprocitentan.
  - ***MACE (major adverse cardiovascular events):*** MACE included cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke. FDA review of events did not raise concern with aprocitentan treatment.

Other Considerations

- **REMS:** Aprocitentan is only available through the TRYVIO REMS program due to the risk of embryo-fetal toxicity. Requirements include prescriber enrolling, training, and certification, and pharmacy certification.

- **Patients of reproductive potential**
  - *Pregnancy testing:* Females who can become pregnant should have confirmatory negative pregnancy testing prior to initiation, monthly during treatment, and one month after discontinuation of aprocitentan.
  - *Contraception:* Women who can become pregnant should use effective contraception during treatment and for one month after discontinuation.
  - *Fetal harm:* Based on animal reproduction studies with other ERAs, aprocitentan can cause embryo-fetal toxicity and fetal death when administered to a pregnant female. Use is contraindicated in pregnancy.
  - *Fertility impairment:* Adverse effects on spermatogenesis have been shown with other ERAs. Aprocitentan may impair fertility in males with reproductive potential.
  - *Lactation:* There are no human data available. Aprocitentan is excreted in rat milk and is likely present in human milk. Because of the potential for serious adverse reactions in breastfed infants, advise women not to breastfeed during treatment.

- **Geriatric use:** In the Phase 3 PRECISION study, 44% of patients were 65 years or older, and 10% were 75 years or older. Edema and fluid retention were more common in these patients compared to younger patients.
- **Renal impairment:** Aprocitentan is not recommended in patients with estimated glomerular filtration rate (eGFR) less than 15 ml/min or who are on dialysis.
- **Hepatic impairment:** Aprocitentan is not recommended for patients with moderate and severe hepatic impairment (Child-Pugh class B and C).

Other Therapeutic Options

Aprocitentan is indicated as add-on treatment when patients do not achieve the desired response with standardized treatments from three classes of medications.

Projected Place in Therapy

This section may be edited prior to final approval of document and Web posting.

- Resistant hypertension is defined as blood pressure above goal in patients who are on maximally tolerated doses of triple therapy. Triple therapy should include a diuretic (thiazide-type diuretic), calcium channel blocker, and angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (beta-blocker may be also used for patients with another compelling indication).
- The prevalence of resistant hypertension is unknown, but it has been estimated to be about 10% of patients with hypertension. In VA, it is estimated that 3,289,352 Veterans have a diagnosis of hypertension (Q2 2024 – Q1 2025).

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- Professional guidelines recommend consideration of spironolactone as a fourth line agent in patients when appropriate (or eplerenone if spironolactone is not tolerated). Before adding a fourth agent, evaluation of medication adherence should be addressed and nonpharmacologic interventions reinforced. Secondary and pseudoresistant hypertension should be considered as well.
- Aprocitentan is the first ERA approved for the treatment of resistant hypertension. It is administered as an oral tablet once daily.
- Evidence from one phase 3 study PRECISION showed that aprocitentan lowered SBP (and DBP) by about 4 mmHg more than placebo at 4 weeks.
- Persistence of BP lowering was demonstrated over a 40-week period with a higher dose of aprocitentan that was not FDA approved.
- Aprocitentan is associated with increased risk of fluid retention, edema, worsening heart failure, low hemoglobin/anemia, hepatotoxicity, and teratogenicity.
- Due to a dose dependent increased risk of fluid retention and edema along with the lack of clear advantage in efficacy over the 12.5 mg dose, FDA did not approve the higher 25 mg aprocitentan dose studied in PRECISION.
- Clinical outcomes and comparative data with other antihypertensive therapy and aprocitentan are lacking.
- A clinically important reduction in BP has been cited as 5 to 10 mmHg SBP and 3-5 mmHg DBP. A 5 mmHg reduction in SBP has been associated with a 10% relative risk reduction in MACE.
- Patients enrolled in PRECISION were older with multiple comorbidities and on multiple antihypertensives. Results are expected to be extrapolated to a Veteran population.
- Summary: Prior to initiation of therapy, there should be a multidisciplinary approach to hypertension management that includes ambulatory blood pressure monitoring and confirmation of medication adherence. Pharmacologic and lifestyle factors that can exacerbate or worsen blood pressure must be addressed (e.g., NSAIDs, alcohol consumption, obstructive sleep apnea, obesity, physical inactivity). Renal denervation therapy may also be appropriate in some patients.

Reference

1. TRYVIO (aprocitentan) oral [prescribing information online]. Idorsia Pharmaceuticals US Inc, Radnor, PA. March 2024. Accessed at: label. Accessed on February 14, 2025.
2. Center for Drug Evaluation and Research (CDER). Integrated review of aprocitentan. Food and Drug Administration (FDA). February 10, 2025.
3. Schlaich MP, Bellet M, Weber MA, et al. Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomized, parallel group, phase 3 trial. Lancet. 2022;400:1927-37.
4. VA/DoD Clinical Practice Guideline. (2020). Diagnosis and Management of Hypertension in the Primary Care Setting. Washington, DC: U.S. Government Printing Office.

5. European Society of Cardiology (ESC) 2024 Guidelines for the management of elevated blood pressure and hypertension. Eur Heart J. 2024;45:3912-4018.
6. Unger T, Borghi C, Charchar F, et al. International Society of Hypertension Global Hypertension Practice Guidelines (2020). Hypertension. 2020;75:1334-57.

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