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New Drug Evaluation: Tryvio™ (Aprocitentan) tablets for oral use

Date of Review: April 2025
Generic Name: aprocitentan

End Date of Literature Search: 11/08/24
Brand Name (Manufacturer): Tryvio (Idorsia)

Plain Language Summary:

- Resistant high blood pressure occurs when it remains too high despite already taking at least 3 different medicines to treat the high blood pressure; or it requires 4 or more medicines just to control the blood pressure.
- About 10% to 15% of people with high blood pressure have resistant high blood pressure. People with resistant high blood pressure often have other risk factors for heart disease such as obesity and kidney disease.
- Few medicines have shown to be effective in lowering blood pressure effectively in people with resistant high blood pressure; no medicines have shown to lower risk of heart attack or stroke in people with resistant high blood pressure.
- Aprocitentan is a new medicine approved by the US Food and Drug Administration for resistant high blood pressure. Aprocitentan was shown to modestly reduce blood pressure more than a placebo pill after 4 weeks in a study of people with resistant high blood pressure. It continued to keep blood pressure lower over 40 weeks.
- Side effects of concern include fluid build-up and a decrease in blood cell counts. Aprocitentan is not safe in pregnancy.
- Aprocitentan will be covered for individuals with resistant high blood pressure who are enrolled in the fee-for-service Oregon Health Plan after a prior authorization request by the prescriber is approved.

Research Questions:

1. What are the benefits and harms of aprocitentan in patients with resistant hypertension (RHT)?
2. Are there specific subpopulations for which aprocitentan is better tolerated or more effective?

Conclusions:

- There is low quality evidence based on one randomized controlled study that aprocitentan 12.5 mg and 25 mg once daily lowers systolic blood pressure (SBP) more than placebo (change from baseline -15.3 mmHg, -15.2 mmHg, and -11.5 mmHg, respectively) in adults with RHT on at least 3 antihypertensive medications (valsartan, amlodipine and hydrochlorothiazide) at baseline.[1] The mean difference at week 4 compared to baseline was -3.8 mmHg (95% CI -6.8 to -0.8) with aprocitentan 12.5 mg daily and -3.7 mmHg (95% CI -6.7 to -0.8) with 25 mg daily.[1] Based on the lack of additional benefit with the higher dose, only the 12.5 mg dose was approved by the Food and Drug Administration (FDA).
- There is low quality evidence based on one RCT that the blood pressure effects of aprocitentan 25 mg are sustained through 40 weeks of treatment.[1]
- There is insufficient evidence comparing aprocitentan to other medications used in RHT, including mineralocorticoid receptor antagonists.

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- There is insufficient evidence evaluating aprocitentan on clinically important cardiovascular outcomes.
- There is insufficient evidence evaluating long term safety of aprocitentan. Side effects of concern include fluid retention and anemia. Patients with advanced heart failure were excluded from the clinical trial. Aprocitentan is known to cause fetal harm and should not be used in people who are pregnant.

Recommendations:
- Implement prior authorization (PA) for aprocitentan to ensure safe and appropriate use.

Background:
Resistant hypertension (RHT) is defined as hypertension (HTN) despite the concomitant use of 3 antihypertensive drugs of different classes (including a diuretic), or controlled blood pressure with 4 or more antihypertensive drugs.[2] Pseudoresistant hypertension can occur due to inaccurate blood pressure measurements, poor adherence to medical therapy, or due to white coat hypertension. Medication nonadherence has been shown to be as high as 31% in RHT.[3] Resistant hypertension occurs in approximately 10-15% of adults with HTN.[2,3] Patients with RHT often have one or more contributing factors, such as obesity, high sodium intake, sedentary lifestyle, advanced renal disease, obstructive sleep apnea, secondary causes of hypertension, or medications that can increase blood pressure. Therefore, patients with RHT are at particularly high cardiovascular (CV) risk and are more likely to experience adverse CV events than those with controlled HTN.[4]

Standard of care for baseline treatment in RHT usually consists of an angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB), a calcium channel blocker (CCB) and a thiazide diuretic. In addition to lifestyle interventions, guidelines recommend additional medications if target blood pressure is not achieved with maximally tolerated doses of the initial 3-drug regimen (an ACE or ARB, CCB, and diuretic).[2,3] Data supported recommendations include switching the diuretic to a longer acting diuretic if available (chlorthalidone or indapamide) and adding a mineralocorticoid receptor antagonist (MRA) as the fourth line medication.[2,3] If blood pressure is still not at target, expert opinion-based recommendations include adding a beta blocker, doxazosin, clonidine, hydralazine, or minoxidil. [2,3] These are based on limited evidence and expert opinion only, and treatment decisions should be individualized.

There are very few randomized controlled trials (RCTs) evaluating fourth-line medications in RHT, and there is no evidence on clinically relevant CV outcomes in patients with RHT. Most trials are short-term, assess BP lowering efficacy only, and there is variability in patient populations and BP measuring techniques.[2,3] There is evidence that spironolactone may reduce BP in RHT when added on to first-line triple therapy compared to other antihypertensive medications; and some data suggest that doxazosin, bisoprolol, and clonidine reduce BP more than placebo in this population.[3] In one phase 3 RCT of 314 patients with RHT, spironolactone demonstrated a greater reduction in systolic blood pressure (SBP) compared with placebo (difference -8.70 mmHg; 95% confidence interval [CI] -9.72 to -7.69), doxazosin (difference -4.03 mmHg; 95% CI -5.04 to -3.02) and bisoprolol (-4.48 mmHg; 95% CI -5.50 to -3.46).[5] Data suggests that reductions in SBP of 5 and 10 mmHg are associated with approximately a 10% and 20% relative risk reduction in CV events, respectively, and a mean difference of at least 5 to 10 mmHg compared with baseline may be considered a clinically meaningful reduction.[6] However, studies have suggested that the benefits of BP control are less in RHT compared to HTN and studies on clinical outcomes are needed to better guide treatment.

Aprocitentan is an endothelin receptor antagonist (ERA) that inhibits the binding of endothelin-1 (ET-1) to its receptors, ET_a and ET_b, resulting in inhibition of potential endothelial dysfunction, vascular remodeling, sympathetic activation and aldosterone synthesis.[7] Aprocitentan has the same chemical structure as the active metabolite of macitentan, which is approved for the treatment of pulmonary arterial hypertension.[7] Other ERAs are indicated only for the treatment of pulmonary arterial hypertension, and studies of ERAs in HTN have been conflicting and resulted in high rates of adverse events, including fluid retention.[8]

Aprocitentan was FDA-approved only at the 12.5 mg dose for the treatment of RHT in combination with other antihypertensive medications in adults who are not adequately controlled on other drugs.[7]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Table 1. Pharmacology and Pharmacokinetic Properties.[7]

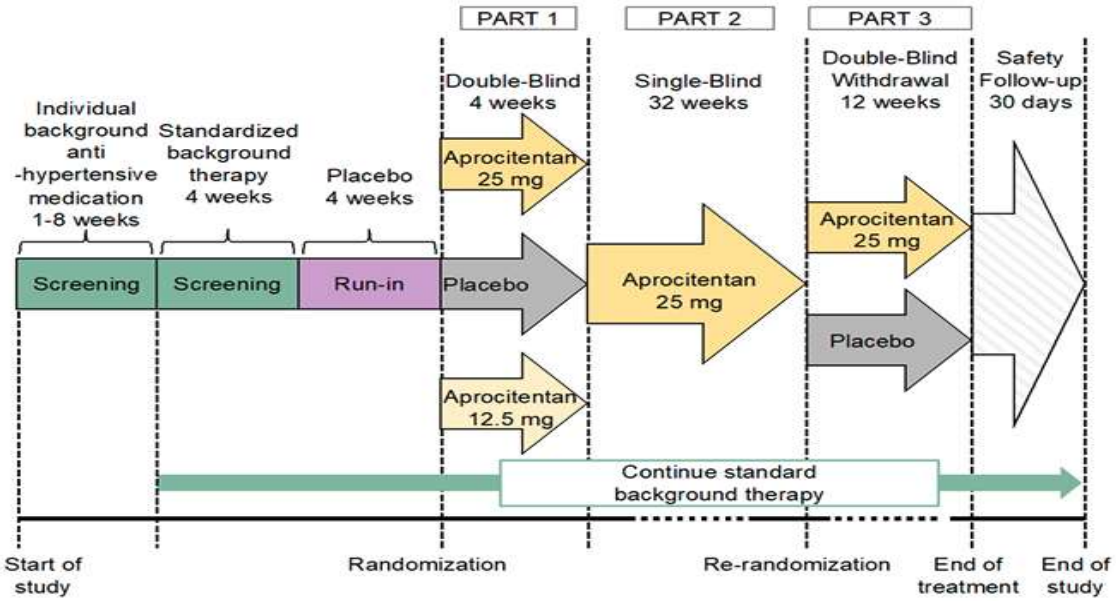
Parameter	
Mechanism of Action	Aprocitentan is an ERA that inhibits the binding of ET-1 to ET_A and ET_B receptors. In hypertension, inhibition of ET-1 decreases endothelial dysfunction, vascular hypertrophy and remodeling, sympathetic activation, and aldosterone synthesis.
Oral Bioavailability	Unknown
Distribution and Protein Binding	Vd ~20 L, Protein binding > 99%, primarily to albumin
Elimination	Urine: ~52% (0.2% as unchanged drug); feces: 25% (6.8% as unchanged drug)
Half-Life	~41 hours
Metabolism	Hepatic by UGT1A1- and UGT2B7-mediated N-glycoxidation and non-enzymatic hydrolysis

Abbreviations: ERA: endothelin receptor antagonist, ET: endothelin, L: liter, Vd: volume of distribution,

Clinical Efficacy:

Aprocitentan was FDA-approved based on one phase 3, multicenter, blinded, randomized study (PRECISION).[1,9] Eligible subjects had to have RHT, defined as a history of uncontrolled BP (SBP ≥ 140 mm Hg) despite taking at least three antihypertensive medications for at least 1 year before screening, and at least three antihypertensive drugs from different pharmacological classes for at least 4 weeks before screening.[9] All subjects switched their antihypertensive regimen to standardized background therapy, a single-pill triple combination of amlodipine, valsartan, and hydrochlorothiazide at fixed doses of either 5 mg/160 mg/25 mg or 10 mg/160 mg/25 mg. The study included an initial 4–12-week screening phase (phase 1) in which subjects switched to standardized background therapy for at least 4 weeks, a 4-week single-blind run-in period when placebo was added (phase 2), followed by a 48-week active treatment period (phase 3). [1,9] The phase 3 active treatment period consisted of a 4-week, randomized, double-blind, placebo-controlled part, in which patients were randomized to aprocitentan 12.5 mg or 25 mg once daily, or placebo (part 1). This was followed by a 32-week single-blind (patient only) part when all subjects were on aprocitentan 25 mg once daily (part 2) and a 12-week double-blind, randomized, placebo-controlled withdrawal period (part 3) in which patients were re-randomized to either placebo or aprocitentan 25 mg once daily (**Figure 1**)

Figure 1: Study Design. [Adapted by Schlaich MP, et al.][1]



At the end of the run-in period, only those demonstrating at least 80% adherence to study treatment were eligible for randomization into the active treatment period. Of the 1965 individuals screened, 730 were randomized.[1,9] The most common reason for exclusion (44.4%) was failure to meet the criteria of SBP 140 mmHg or higher after switching to the standardized background therapy. Of those randomized, 704 (96%) completed part 1, 613 (84%) completed part 2, and 577 (79%) completed part 3 of the study. [1,9]

The mean age of the study population was 62 years, 60% were men and 83% were white.[1] Seventy percent of subjects had obesity or severe obesity based on body mass index (BMI), 54% had diabetes, 20% had heart failure, and 38% had moderate to severe albuminuria. At randomization, 71% (n=516) were on the maximum dose of amlodipine and 58% (n=423) were on a beta blocker.[1] Patient characteristics were similar at baseline. The primary endpoint was the change from baseline to week 4 of the double-blind treatment period in mean trough SBP, measured by an unattended automated office blood pressure.[1] At week 4, the least square mean change in SBP was -15.3 mmHg for aprocitentan 12.5 mg (mean difference -3.8 mmHg; 95% CI -6.8 to -0.8), -15.2 mmHg for aprocitentan 25 mg (mean difference -3.7 mmHg; 95% CI -6.7 to -0.8), and -11.5 mmHg for placebo.[1] The mean differences are relatively small due to a high placebo response and are not clinically meaningful. The study was powered based on a predicted difference of 6 mmHg. The key secondary endpoint was change in SBP from withdrawal baseline (week 36) to week 40. There was a statistically significant reduction in SBP at week 40 with aprocitentan 25 mg compared to placebo (-1.5 mmHg versus 4.4 mmHg, respectively, difference from placebo -5.8 mmHg; 95%CI -8.2 to -3.4; $p<0.001$), demonstrating persistence of BP lowering effect.[1] The study was powered to detect a difference of 5 mmHg between aprocitentan 25 mg and placebo for this secondary endpoint.[1]

Aprocitentan offers another treatment option for a narrow population of RHT who have few other add-on medications available. However, there are several limitations to this study. The complex study design was intended to show sustained blood pressure effects over a long duration. However, this resulted in attrition at multiple steps in the study design and there was a lack of placebo or blinding during the 32-week part 2, which increases the risk of performance and detection bias. The two fixed doses of triple therapy were not at the maximum recommended dose for valsartan and did not include a more potent long-acting diuretic, such as chlorthalidone. Furthermore, not all subjects were on maximum dose of amlodipine. There was no clear dose response in blood pressure lowering ability with similar effect size for both doses. However, there was a dose relationship demonstrated with edema and fluid retention. Therefore, only the 12.5 mg dose was FDA-approved. The screening and run-in period requirements limit overall generalizability. Due to the complex nature of RHT and high CV risk of patients, more studies are needed directly comparing add-on medications and their impact on clinical outcomes. In the United States, the prevalence of HTN is higher among Black adults. However, only 11% of subjects in this RCT were Black or African American. Conclusions cannot be made with the small sample size; however, there was no significant treatment effect with aprocitentan compared to placebo in the Black or African American subgroup in change in ambulatory SBP at week 4 with aprocitentan 12.5 mg (-3.97 mmHg) compared to placebo (-0.74 mmHg) with a mean difference of -3.23 mmHg (95% CI -9.79 to 3.33).[1]

Clinical Safety:
In part 1, there were low rates of serious adverse events overall, and numerically higher rates in aprocitentan-treated subjects compared to placebo (3.3% with aprocitentan 12.5 mg and 25 mg versus 1.2% in placebo).[1] There were low rates of discontinuations due to adverse events in part 1 over 4 weeks (2.9% with aprocitentan 12.5 mg, 2.0% with aprocitentan 25 mg and 0.8% with placebo).[1] In the single-blind part 2, 3.8% of subjects on aprocitentan 25 mg discontinued due to adverse events. Adverse events leading to discontinuation included edema, elevated transaminases and hypersensitivity.

Adverse effects of concern with ERAs include fluid retention and anemia.[8] In part 1 of the active treatment study (4-week double blind, placebo controlled), the most common adverse events occurring with aprocitentan 12.5 mg that occurred more than placebo were edema (9.1% vs. 2.1%) and anemia (3.7% vs. 0%).[1] Fluid retention is a known risk factor of ERAs, which may be concerning in patients with advanced renal disease and heart failure. In the 4-week double blind treatment period of the study, there were more edema-related adverse events with aprocitentan 25 mg (18%) and aprocitentan 12.5 mg (9.1%) compared to placebo (2.1%).[1] The majority were mild to moderate in severity and approximately half needed diuretics. Through the entire study, 7 subjects discontinued treatment with aprocitentan 25 mg due to edema, and fluid retention was more frequent in patients with chronic kidney disease. Patients with more advanced heart failure (NYHA stage III or IV or stage II with mitral valve insufficiency or aortic stenosis) were excluded from the study, and FDA labeling recommends optimizing diuretics prior to initiating aprocitentan in subjects with heart failure. Anemia is another known adverse effect of ERAs. In the 4-week double blind treatment period, the incidence of a hemoglobin decreases greater than 2 g/dL occurred more often in subjects receiving aprocitentan 12.5 mg (7%) and 25 mg (3%) compared to placebo (1%).[1] ERAs can cause hepatotoxicity. There were no adverse events related to hepatotoxicity in part 1, but 16 subjects (2.3%) in Part 2 on aprocitentan 25 mg experienced a hepatic adverse event.

Table 2: Adverse Events occurring at ≥ 2% and ≥ 1% greater than placebo, during part 1 of Precision Study (4 weeks, double blind, randomized)[10]

	Aprocitentan 12.5 mg N=243	**Aprocitentan 25 mg N=245**	**Placebo N=242**
Peripheral edema	16 (6.6%)	35 (14.3%)	47 (19.4%)
Decreased hemoglobin	6 (2.5%)	0	0
Facial edema	4 (1.6%)	3 (1.2%)	0
Dyspnea	1 (0.4)	4 (1.6%)	0

Aprocitentan is contraindicated during pregnancy because of the known risk of teratogenicity.[7] Women of childbearing potential were only eligible for study inclusion if they had a negative pregnancy test at screening and at baseline, agreed to take pregnancy tests during the study and up to 30 days after discontinuation, and agreed to use accepted methods of birth control.[1] Due to the risk of embryo-fetal toxicity, aprocitentan is only available through a Risk Evaluation and Mitigation Strategy (REMS) program. It is recommended that patients who can become pregnant should be monitored monthly during treatment and one month after discontinuation of treatment and use acceptable contraception methods prior to initiation of treatment, during treatment, and for one month after the final dose.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Fatal and non-fatal cardiovascular events
2) All-cause mortality
3) Hospitalizations
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Change from baseline to Week 4 of double-blind treatment in mean SBP

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Schlaich, et al. (PRECISION)[1] MC, PC, PG, RCT Three-part study design including a short DB, PC part (4 weeks), long single blind active treatment (32 weeks), DB, PC withdrawal (12 weeks).	1. aprocitentan 12.5 mg once daily (APO 12.5) 2. aprocitentan 25 mg once daily (APO 25) 3. placebo one daily (PBO) On background therapy with amlodipine, valsartan, HCTZ combo pill	Demographics: Median age; 63 y (44% ≥ 65 y) Male: 60% White: 83% mean SBP: 157 mmHg 20% CHF Key Inclusion Criteria: -Age ≥ 18 y -Uncontrolled HTN despite ≥ 3 medications -SBP ≥ 140 mmHg -Not pregnant, on birth control Key Exclusion Criteria: -Pregnant or lactating -Secondary causes of HTN -SBP ≥ 180 mmHg -DBP ≥ 110 mmHg -H/o TIA, UA, or MI -Unstable CVD -eGFR < 15 ml/min -NYHA stage III or IV or II with mitral valve insufficiency and/or aortic stenosis	ITT: 1. 243 2. 243 3. 244 FAS 1. 223 2. 231 3. 224 Attrition: 1. 22.6% 2. 18.9% 3. 21.3%	Primary Endpoint: LSMC in SBP at 4 weeks APO 12.5: -15.3 mmHg APO 25: -15.2 mmHg PBO: -11.5 mmHg Mean difference: APO 12.5 vs. PBO: -3.8 (95% CI -6.8 to -0.8); p=0.0042 APO 25 vs. PBO: -3.7 (95% CI -6.7 to -0.8); p=0.0046 Secondary Endpoint: LSMC from withdrawal baseline (Week 36) in SBP at Week 40 APO 25: -1.5 mmHg PBO: +4.4 mmHg Mean difference: -5.8 (95%CI -8.2 to -3.4) P<0.001	 NA NA	Discontinuations due to AE (during 4-week DB period) 1. 6 (2.5%) 2. 5 (2.1%) 3. 2 (0.8%) P=NS Discontinuations due to AE during part 3 (withdrawal period) APO 25: 8 (2.6%) PBO: 7 (2.3%) P=NS	 NS NS	**Risk of Bias (low/high/unclear)**: Selection Bias: low; randomization via independent interactive response system; groups similar at baseline. Performance Bias: unclear; double blinded using matching placebo during first 4-week part of active treatment period only. Detection Bias: unclear; unknown if outcome assessors were blinded or if there were different methods of blood pressure measurement between sites Attrition Bias: unclear; high rates of attrition (20%) but similar between groups; analysis using FAS for primary outcome included all subjects with had a baseline BP (93% of those randomized). Reporting Bias: low; outcomes reported as prespecified. Other Bias: high; funded by Idorsia Pharmaceuticals, the manufacturer of aprocitentan. Idorsia completed data collection and contributed to study design, data analysis, data interpretation and manuscript writing.

								Applicability: Patient: Extensive screening and run-in periods limits generalizability to general population Intervention: no dose response seen in efficacy Comparator: placebo-controlled Outcomes: surrogate outcome only. No clinically meaningful outcomes were evaluated. BP was measured using an automated office blood pressure. However, it is recommended to use both office and home for diagnosis of RHT. Setting: hospitals or research centers in Europe, North America, Asia, and Australia. 32% of sites in North America.

Abbreviations [alphabetical order]: AE = adverse events; ARR = absolute risk reduction; CHF = congestive heart failure; CI = confidence interval; CVD = cardiovascular disease; DB = double blind; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FAS = full analysis set; HCTZ = hydrochlorothiazide; HTN = hypertension; ITT = intention to treat; LSMC = least square mean change; MC = multicenter; MI = myocardial infarction; mITT = modified intention to treat; mmHg = millimeters of mercury; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = nonsignificant; NYHA = New York Heart Association; PC = placebo controlled; PG = parallel group; PP = per protocol; RCT = randomized controlled trial; RHT = resistant hypertension; SBP = systolic blood pressure; TIA = transient ischemic attack; UA = unstable angina; y = years

References:

1. Schlaich MP, Bellet M, Weber MA, et al. Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial. *Lancet (London, England)*. Dec 3 2022;400(10367):1927-1937. doi:10.1016/s0140-6736(22)02034-7
2. Carey RM, Calhoun DA, Bakris GL, et al. Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association. *Hypertension (Dallas, Tex : 1979)*. Nov 2018;72(5):e53-e90. doi:10.1161/hyp.0000000000000084
3. Hiremath S, Sapir-Pichhadze R, Nakhla M, et al. Hypertension Canada's 2020 Evidence Review and Guidelines for the Management of Resistant Hypertension. *Can J Cardiol*. May 2020;36(5):625-634. doi:10.1016/j.cjca.2020.02.083
4. Pisano A, Iannone LF, Leo A, Russo E, Coppolino G, Bolignano D. Renal denervation for resistant hypertension. *Cochrane Database Syst Rev*. Nov 22 2021;11(11):Cd011499. doi:10.1002/14651858.CD011499.pub3
5. Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet (London, England)*. Nov 21 2015;386(10008):2059-2068. doi:10.1016/s0140-6736(15)00257-3
6. Kandzari DE, Mahfoud F, Weber MA, et al. Clinical Trial Design Principles and Outcomes Definitions for Device-Based Therapies for Hypertension: A Consensus Document From the Hypertension Academic Research Consortium. *Circulation*. Mar 15 2022;145(11):847-863. doi:10.1161/circulationaha.121.057687
7. Tryvio Prescribing Information. Idorsia Pharmaceuticals US Inc. Radnor, PA. 3/2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2024/217686Orig1s000Correctedltr.pdf.
8. Burnier M. Update on Endothelin Receptor Antagonists in Hypertension. *Curr Hypertens Rep*. May 19 2018;20(6):51. doi:10.1007/s11906-018-0848-0

9. Danaietash P, Verweij P, Wang JG, et al. Identifying and treating resistant hypertension in PRECISION: A randomized long-term clinical trial with aprocitentan. *J Clin Hypertens (Greenwich)*. Jul 2022;24(7):804-813. doi:10.1111/jch.14517
10. FDA Center for Drug Evaluation and Research. Aprocitentan (Tryvio) Integrated Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/217686Orig1s000TOC.cfm.

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRYVIO safely and effectively. See full prescribing information for TRYVIO.

TRYVIO™ (aprocitentan) tablets, for oral use
Initial U.S. Approval: 2024

WARNING: EMBRYO–FETAL TOXICITY
See full prescribing information for complete boxed warning.

- TRYVIO can cause major birth defects if used by pregnant patients and is contraindicated in pregnancy. (4.1, 5.1, 8.1)
- Patients who can become pregnant: Exclude pregnancy prior to initiation of treatment, monthly during treatment, and for one month after stopping TRYVIO. (2.2, 5.1, 8.3)
- Patients who can become pregnant: Use acceptable contraception prior to initiation of treatment, during treatment, and for one month after stopping TRYVIO. (2.2, 4.1, 5.1, 8.3)
- TRYVIO is only available through a restricted distribution program called the TRYVIO REMS. (5.2)

----------INDICATIONS AND USAGE----------
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. Lowering blood pressure reduces the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions. (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage of TRYVIO is 12.5 mg orally once daily, with or without food. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 12.5 mg (3)

----------CONTRAINDICATIONS----------
- Pregnancy (4.1)
- Hypersensitivity (4.2)

----------WARNINGS AND PRECAUTIONS----------
- ERAs cause hepatotoxicity and liver failure. Measure serum aminotransferase levels and total bilirubin prior to initiation of treatment and repeat periodically during treatment and as clinically indicated. (5.3)
- Fluid retention may require intervention (5.4)
- Decreases in hemoglobin (5.5)
- Decreased sperm counts (5.6)

----------ADVERSE REACTIONS----------
Most common adverse reactions (more frequent than placebo and ≥ 2% in TRYVIO-treated patients) are edema/fluid retention and anemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Idorsia Pharmaceuticals Ltd at 1-833-400-9611 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2024

Tryvio (Aprocitentan)

Goal(s):

- To ensure medication use for FDA-approved indications supported by literature.

Length of Authorization:

Up to 12 months

Requires PA:

- aprocitentan

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is there a diagnosis of resistant hypertension? NOTE: Resistant hypertension is defined as not achieving target blood pressure despite treatment with at least 3 antihypertensive medications from different classes for an adequate duration (~ 4 weeks) at maximally tolerated doses.	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
3. Is the patient on concomitant therapy with at least three other antihypertensive agents at maximally tolerated doses, including the following: a. Blocker of the renin-angiotensin system (angiotensin-converting enzyme [ACE] inhibitor or angiotensin II receptor locker [ARB]) b. Calcium channel blocker c. Thiazide or thiazide-like diuretic	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient meet ONE of the following: a. Is currently taking a mineralocorticoid receptor antagonist (MRA) (e.g. spironolactone, eplerenone), with at least three other antihypertensive medications; OR b. Has had an inadequate treatment response in blood pressure to an MRA; OR c. Has an intolerance or contraindication to an MRA	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 4/2025 (MH)
Implementation: 5/12/25