PDL DRUG REVIEW

Proprietary Name: Tryvio®
Common Name: aprocitentan
PDL Category: Cardiovascular Agents

Comparable Products	Preferred Drug List Status
ACE Inhibitors	Preferred
ARBs	Preferred
Beta-Blockers	Preferred

Pharmacology/Usage: Aprocitentan, the active ingredient of Tryvio®, is an endothelin receptor antagonist (ERA) that inhibits the binding of endothelin (ET)-1 to ET-A and ET-B receptors. ET-1, via its receptors (ET-A and ET-B) 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.

Indication: In combination with other antihypertensive drugs, is indicated for the treatment of hypertension, to lower blood pressure (BP) in adult patients who are not adequately controlled on other drugs.

There is no pregnancy category for this medication; however, the risk summary indicates that based on animal reproduction studies with other ERAs, Tryvio® can cause embryo-fetal toxicity, including birth defects and fetal death when administered to a pregnant patient and is contraindicated during pregnancy. Advise pregnant patients of the potential risk to a fetus. Refer to the information found in the box warning section regarding additional information with use in females of reproductive potential. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 12.5mg.

Recommended Dosage: Start treatment with Tryvio® in females of reproductive potential only after confirmation of a negative pregnancy test. Patients should exclude pregnancy with negative pregnancy tests monthly during treatment and one month after discontinuation of treatment with Tryvio®.

Take 12.5mg PO QD, with or without food. Swallow tablets whole. If a dose is missed, skip the missed dose and take the next dose at the regular time. Do not take two doses on the same day.

Tryvio® is not recommended in patients with kidney failure (eGFR <15ml/min) or on dialysis; however, dose adjustments are not required in patients with mild to severe renal impairment (eGFR ≥15ml/min). Dose adjustments are not required in patients with mild hepatic impairment; however, use is not recommended in patients with moderate and severe hepatic impairment.

Drug Interactions: There are no drug interactions listed with this product.

Box Warning: Tryvio® has a box warning regarding embryo-fetal toxicity, as it can cause major birth defects if used by pregnant patients. In patients who can become pregnant, obtain a negative pregnancy test prior to initiation of treatment, and counsel patients to take monthly pregnancy tests during treatment and one month after discontinuation of Tryvio®. To prevent pregnancy, patients who can become pregnant should use acceptable methods of contraception prior to the start of treatment, during treatment, and for

one month after stopping Tryvio®. Because of the risk of birth defects, Tryvio® is only available through a restricted program called the Tryvio® Risk Evaluation and Mitigation Strategy (REMS).

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Tryvio®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included edema/fluid retention (7%) and anemia (3.7%). During the initial 4-week double-blind, placebo-controlled treatment period, 0.8% of patients taking Tryvio® experienced an adverse reaction of hypersensitivity compared to no reports in patients treated with placebo.

As the box warning discusses, Tryvio® can cause fetal harm when administered during pregnancy and is contraindicated for use in patients who are pregnant. Because of the risk of embryo-fetal toxicity, Tryvio® is available only through a restricted program under a REMS called the Tryvio® REMS. Important requirements of the Tryvio® REMS includes that:

- Prescribers must be certified with the Tryvio® REMS by enrolling and completing training.
- Pharmacies that dispense Tryvio® must be certified with the Tryvio® REMS.
- Further information is available at www.TRYVIOREMS.com or by calling 1-866-429-8964.

Elevations of aminotransferases and hepatotoxicity are known effects of ERAs, including Tryvio®. To reduce the risk of potential serious hepatotoxicity, measure serum aminotransferase levels and total bilirubin prior to the start of treatment and repeat during treatment periodically and as clinically indicated. Do not start Tryvio® in patients with elevated aminotransferases (>3 X upper limit of normal or ULN) or moderate to severe hepatic impairment. Advise patients with symptoms suggesting hepatotoxicity to immediately stop treatment with Tryvio® and seek medical attention. If sustained, unexplained, clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin >2 X ULN, or if clinical symptoms of hepatotoxicity occur, discontinue Tryvio®.

Fluid retention and peripheral edema are known effects of ERAs, including Tryvio®. Tryvio® has not been studied in patients with heart failure New York Heart Association stage III-IV, unstable cardiac function, or with NTproBNP ≥500pg/ml. 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 Tryvio®.

Decreases in hemoglobin concentration and hematocrit have occurred following the use of other ERAs and were observed in the clinical trial with Tryvio®. Hemoglobin decreases usually presented early, stabilized thereafter, and were reversible after discontinuation. Initiation of Tryvio® is not recommended in patients with severe anemia. Measure hemoglobin prior to the start of treatment and periodically during treatment as clinically indicated.

Tryvio®, like other ERAs, may have an adverse effect on spermatogenesis. Counsel men about potential effects on fertility.

Contraindications:

- In pregnancy
- In patients who are hypersensitive to aprocitentan or any of its excipients.

Manufacturer: Idorsia Pharmaceuticals

Analysis: The efficacy of Tryvio® was assessed in a multipart, phase 3 multicenter study that included adults with SBP ≥140mmHg who were prescribed at least 3 antihypertensive medications. The trial included a placebo run-in period, which was followed by 3 parts as described below. Prior to the placebo run-in period, all were switched to standard background antihypertensive therapy that consisted of an angiotensin receptor blocker (ARB), a calcium channel blocker (CCB), and a diuretic, which was continued

throughout the study. Patients with concomitant use of beta-blockers continued this treatment throughout the study.

After the 4-week placebo run-in period, patients (N=730) were randomized to aprocitentan 12.5mg, aprocitentan 25mg, or placebo all once daily during the initial 4-week double-blind treatment period (part 1). At the end of 4 weeks, all patients entered the single-blind treatment period (part 2) where they received aprocitentan 25mg QD for 32 weeks. At the end of the 32 weeks, patients were re-randomized to receive either aprocitentan 25mg or placebo, during a 12-week double-blind, withdrawal period (part 3).

Included patients had a mean age of 62 years (range 24 to 84 years), while 60% were male, 83% were white, and the mean body mass index (BMI) was 34kg/m^2. At baseline, 19% had an eGFR 30-59ml/min/1.73m^2 and 3% had an eGFR 15-29 ml/min/1.73m^2. At baseline, 24% had a urine albumin-to-creatinine ratio (UACR) of 30-300mg/g and 13% had a UACR >300mg/g. About 54% of patients had a medical history of DM, 31% ischemic heart disease, and 20% congestive heart failure. At baseline, 63% of patients reported taking 4 or more antihypertensive medications.

The primary 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 25mg aprocitentan or placebo in part 3) to week 40.

BP reductions compared to placebo based on uAOBP measurements at trough are presented in the table below, which was adapted from the prescribing information. Tryvio® 12.5mg was statistically superior to placebo in reducing SiSBP at week 4 (part 1). The treatment effect was consistent for sitting diastolic BP (SiDBP).

				Difference to placebo	
Treatment group	N	Baseline mean	Least Square Mean	Least Square Mean	p-value
SiSBP (primary endpoint)					
Tryvio® 12.5mg	243	153.2	-15.4	-3.8	0.0043[1]
Placebo	244	153.3	-11.6	-	-
SiDBP					
Tryvio® 12.5mg	243	87.9	-10.4	-4.0	-
Placebo	244	87.1	-6.4	-	-

[1]Statistically significant at the 2.5% level as prespecified in the testing strategy.

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

Tryvio® is not approved for use at a 25mg dose. The 25mg dose has not demonstrated a meaningful improvement in blood pressure reduction as compared to the 12.5mg dose and had an increased risk of edema/fluid retention.

Place in Therapy: 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 infarction. Tryvio® has a box warning regarding embryo-fetal toxicity. Because of the risk of birth defects, Tryvio® is only available through a restricted program called the Tryvio® REMS. The efficacy of Tryvio® was assessed in a multipart, phase 3 multicenter study. The primary endpoint was the change in sitting SBP (SiSBP) from baseline to week 4 during part 1, and Tryvio® 12.5mg was statistically superior to placebo in reducing SiSBP at week 4 (part 1). The treatment effect was consistent for sitting diastolic BP. Tryvio® is the first FDA approved ERA indicated to lower blood pressure when used in combination with other antihypertensive treatments for those with hypertension that is not adequately controlled on other drugs.

Summary

There is no evidence at this time to support that Tryvio® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Tryvio® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement:
- ☐ **Preferred**
- ☒ **Non-Preferred**

References

[1] Tryvio [package insert]. Radnor, PA: Idorsia Pharmaceuticals US Inc.; 2024.