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: 4/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

- **TRYVIO can cause major birth defects if used by pregnant patients *[see Contraindications (4.1), Warnings and Precautions (5.1), Use in Specific Populations (8.1)]*.**
- **In patients who can become pregnant, obtain a negative pregnancy test prior to initiation of TRYVIO and counsel patients to take monthly pregnancy tests during treatment and one month after discontinuation of TRYVIO *[see Dosage and Administration (2.2) and Use in Specific Populations (8.3)]*.**
- **To prevent pregnancy, patients who can become pregnant should use acceptable methods of contraception before the start of, during, and for one month after stopping treatment *[see Contraindications (4.1), Warnings and Precautions (5.1), Use in Specific Populations (8.3)]*.**
- **Because of the risk of birth defects, TRYVIO is only available through a restricted program called the TRYVIO Risk Evaluation and Mitigation Strategy (REMS) *[see Warning and Precautions (5.2)]*.**

1 INDICATIONS AND USAGE

TRYVIO, 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. Lowering BP reduces the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes. There are no controlled trials demonstrating reduction of risk of these events with TRYVIO.

Control of high BP should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve BP goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is BP reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher BPs, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from BP

reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower BP goal.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of TRYVIO is 12.5 mg orally once daily.

Swallow tablets whole. TRYVIO may be taken with or without food.

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.

2.2 Pregnancy Testing in Females of Reproductive Potential

Initiate 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 *[see Boxed Warning, Contraindications (4.1), Warnings and Precautions (5.1), Use in Specific Populations (8.3)]*.

3 DOSAGE FORMS AND STRENGTHS

TRYVIO (aprocitentan) tablets are available as:

- 12.5 mg: yellow to orange round, film-coated tablet, debossed with “AN” on one side and plain on the other side.

4 CONTRAINDICATIONS

4.1 Pregnancy

Use of TRYVIO is contraindicated in pregnancy. To prevent pregnancy, patients who can become pregnant should use acceptable contraception prior to initiation of treatment, during treatment, and for one month after discontinuation of treatment with TRYVIO *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.

4.2 Hypersensitivity

TRYVIO is contraindicated in patients who are hypersensitive to aprocitentan or any of its excipients *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Based on data from animal reproduction studies with endothelin receptor antagonists (ERAs), TRYVIO can cause fetal harm when administered during pregnancy and is contraindicated for use in patients who are pregnant. Exclude pregnancy and ensure use of acceptable contraceptive methods prior to initiation of treatment with TRYVIO. Counsel patients who can become pregnant about the potential risk to a fetus. Patients should monitor for pregnancy monthly during treatment and one month after discontinuation of treatment and avoid pregnancy by using acceptable contraception methods prior to initiation of treatment with TRYVIO, during treatment, and for one month after the final dose of TRYVIO. If pregnancy is detected, discontinue TRYVIO *[see Dosage and Administration (2.2), Contraindications (4.1), Warnings and Precautions (5.2), Use in Specific Populations (8.1, 8.3)]*.

5.2 TRYVIO REMS

TRYVIO is available only through a restricted program under a REMS called the TRYVIO REMS because of the risk of embryo-fetal toxicity *[see Contraindications (4.1), Warnings and Precautions (5.1), Use in Specific Populations (8.1, 8.3)]*.

Important requirements of the TRYVIO REMS include the following:

- 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 1-866-429-8964.

5.3 Hepatotoxicity

Elevations of aminotransferases and hepatotoxicity are known effects of ERAs, including TRYVIO. Elevations in alanine transaminase (ALT) or aspartate aminotransferase (AST) of greater than 5-fold upper limit of normal (ULN) were observed rarely in patients treated with aprocitentan in the clinical trial, including cases with positive rechallenge. There were no reports of patients with ALT and/or AST >3 × ULN and total bilirubin >2 × ULN or cases of liver failure observed in TRYVIO-treated patients in the clinical trials. To reduce the risk of potential serious hepatotoxicity, measure serum aminotransferase levels and total bilirubin prior to initiation of treatment and repeat during treatment periodically and as clinically indicated.

Do not initiate TRYVIO in patients with elevated aminotransferases (>3 × ULN) or moderate to severe hepatic impairment.

Advise patients with symptoms suggesting hepatotoxicity (nausea, vomiting, right upper quadrant pain, fatigue, anorexia, scleral icterus, jaundice, dark urine, fever, or itching) 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 × ULN, or if clinical symptoms of hepatotoxicity occur, discontinue TRYVIO.

5.4 Fluid Retention

Fluid retention and peripheral edema are known effects of ERAs, including TRYVIO *[see Adverse Reactions (6.1)]*. Edema/fluid retention was reported in 9% of TRYVIO-treated patients compared with 18% of patients receiving aprocitentan 25 mg (twice the recommended dose) and 2% on placebo in the clinical trial, requiring additional diuretic use in some patients. Older age and chronic kidney disease are risk factors for edema/fluid retention with TRYVIO. TRYVIO has not been studied in patients with heart failure New York Heart Association stage III–IV, unstable cardiac function, or with NTproBNP ≥500 pg/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.

5.5 Hemoglobin Decrease

Decreases in hemoglobin concentration and hematocrit have occurred following administration of other ERAs and were observed in the clinical trial with TRYVIO. Hemoglobin decreases usually presented early, stabilized thereafter, and were reversible after discontinuation. A decrease in hemoglobin of >2 g/dL from baseline was observed in 7% of patients compared to 1% of placebo patients. A decrease to below 10.0 g/dL was observed in 3% of TRYVIO-treated patients compared to 0 patients taking placebo. Initiation of TRYVIO is not recommended in patients with severe anemia. Measure hemoglobin prior to initiation of treatment and periodically during treatment as clinically indicated *[see Adverse Reactions (6.1)]*.

5.6 Decreased Sperm Counts

TRYVIO, like other ERAs, may have an adverse effect on spermatogenesis. Counsel men about potential effects on fertility *[see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)]*.

6 ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Embryo-fetal toxicity *[see Warnings and Precautions (5.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*
- Fluid retention *[see Warnings and Precautions (5.4)]*
- Hemoglobin decrease *[see Warnings and Precautions (5.5)]*
- Decreased sperm counts *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of TRYVIO was evaluated in a placebo-controlled phase 3 clinical study (PRECISION, NCT03541174) in adults with uncontrolled BP (systolic blood pressure [SBP] ≥140 mmHg) despite the use of at least three antihypertensive medications.

In this study, 724 patients received any dose of aprocitentan, with 633 patients treated for at least 26 weeks, 192 patients for at least 47 weeks, and 99 patients for at least 48 weeks.

The most frequently reported adverse reactions to TRYVIO during the 4-week double-blind placebo-controlled treatment period (part 1) of the PRECISION study are presented in Table 1.

Table 1 Adverse reactions reported with a frequency of ≥2% in TRYVIO-treated patients and greater (≥1%) than in placebo-treated patients during the initial 4-week double-blind placebo-controlled treatment (part 1)

Adverse Reaction	12.5 mg N = 243 %	Placebo N = 242 %
Edema/fluid retention	9.1	2.1
Anemia	3.7	0

Hypersensitivity Reactions

During the initial 4-week double-blind placebo-controlled treatment period (part 1), 0.8% of patients experienced an adverse reaction of hypersensitivity (i.e., rash, erythema, allergic edema) on TRYVIO compared to no reports in patients treated with placebo. One patient experienced allergic dermatitis requiring hospitalization while receiving aprocitentan 25 mg.

Laboratory Tests

Initiation of TRYVIO may cause an initial small decrease in estimated glomerular filtration rate (eGFR) that occurs within the first 6 weeks of starting therapy and then stabilizes.

In the initial 4-week double-blind treatment period, TRYVIO 12.5 mg caused a mean decrease of about 0.8 g/dL in hemoglobin compared to no change in the placebo patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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 *[see Contraindications (4.1)]*. Administration of macitentan, where approximately ≥50% of total exposure was to aprocitentan, was teratogenic in rats and rabbits at all doses tested *(see Data).* Available data from reports of pregnancy in clinical trials with TRYVIO are insufficient to rule out a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Advise pregnant patients of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

There is a Pregnancy Safety Study that monitors pregnancy outcomes in women exposed to TRYVIO during pregnancy. Healthcare providers should report any prenatal exposure to TRYVIO by calling 1-866-429-8964.

Data

Animal Data
In embryo-fetal development toxicity studies in pregnant rats and rabbits given macitentan (for which aprocitentan is a major metabolite) during the period of major organogenesis, cardiovascular and mandibular arch fusion malformations were observed at all doses studied. The lowest doses in rats and rabbits produced aprocitentan exposures that were equivalent to and 15-fold, respectively, the clinical exposures at the maximum recommended human dose (MRHD) based on area under the curve (AUC).

In pre- and post-natal development studies, female rats given macitentan (for which aprocitentan is a major metabolite) from late pregnancy through lactation showed reduced pup survival and impairment of the male fertility of the offspring at all doses. The lowest dose produced aprocitentan exposures approximately 2-fold the clinical exposures at the MRHD based on AUC.

8.2 Lactation

Risk Summary

There are no data on the presence of aprocitentan in human milk, the effects on the breastfed infant, or the effect on milk production. In rats, aprocitentan was excreted into milk during lactation *(see Data).* When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious adverse reactions in breastfed infants, advise women not to breastfeed during treatment with TRYVIO.

Data

A single ^{14}C-radiolabeled macitentan dose of 3 mg/kg was given orally to lactating Wistar rats. Aprocitentan was consistently observed in milk samples across all collection times after oral administration.

8.3 Females and Males of Reproductive Potential

Based on data from animal reproductive toxicity studies with other ERAs, TRYVIO can cause fetal harm, including birth defects and fetal death, when administered to a pregnant patient and is contraindicated during pregnancy *[see Contraindications (4.1), Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of patients prior to initiating TRYVIO. Patients who can become pregnant should exclude pregnancy with a negative pregnancy test monthly during treatment, and one month after discontinuation of treatment with TRYVIO. The patient should contact their physician immediately if onset of menses is delayed or pregnancy is suspected. If the pregnancy test is positive, the physician and patient must discuss the risks to the patient, the pregnancy, and the fetus *[see Warnings and Precautions (5.1), Dosage and Administration (2.2), Contraindications (4.1)]*.

Contraception

Patients using TRYVIO who can become pregnant should use acceptable contraception prior to initiation of treatment, during treatment, and for one month after discontinuation of treatment with TRYVIO *[see Warnings and Precautions (5.1)]*.

Infertility

Other ERAs have shown an adverse effect on spermatogenesis in humans and/or animals. TRYVIO, like other ERAs, may impair fertility in males of reproductive potential. It is not known whether effects on fertility would be reversible *[see Warnings and Precautions (5.6), Nonclinical Toxicology (13.1)].*

8.4 Pediatric Use

The safety and efficacy of TRYVIO in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in the PRECISION study of TRYVIO, 321 (44%) were 65 years and older, while 72 (10%) were 75 years and older. Edema/fluid retention was more common in these patients than younger patients *[see Warnings and Precautions (5.4)]*.

No dose adjustment is required in patients over the age of 65 years *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

TRYVIO is not recommended in patients with kidney failure (eGFR <15 mL/min) or on dialysis. The effect of kidney failure (eGFR <15 mL/min) or dialysis on aprocitentan pharmacokinetics is unknown *[see Clinical Pharmacology (12.3)]*. Patients with renal impairment are at increased risk of edema/fluid retention *[see Warnings and Precautions (5.4)]*.

No dose adjustment is required in patients with mild to severe renal impairment (eGFR ≥15 mL/min).

8.7 Hepatic Impairment

TRYVIO is not recommended in patients with moderate and severe hepatic impairment (Child-Pugh class B and C) because these patients may be at increased risk for poor outcomes from hepatotoxicity.

No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A) *[see Clinical Pharmacology (12.3)]*.

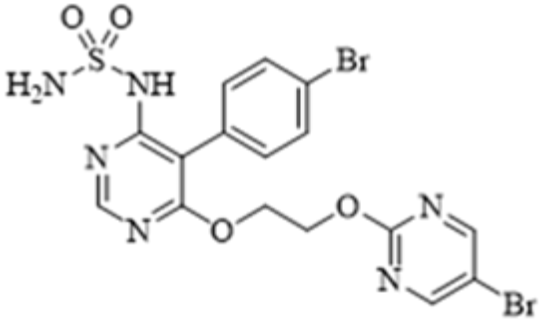
10 OVERDOSAGE

TRYVIO has been administered as a single dose of up to 600 mg, and as multiple doses of up to 100 mg daily, to healthy subjects (48 and 8 times the recommended dose, respectively). Adverse events of headache, nasal congestion, nausea, and upper respiratory tract infection were observed. In the event of an overdose, standard supportive measures should be taken, as required. Dialysis is unlikely to be effective because aprocitentan is highly protein-bound. Consult a Certified Poison Control Center for the most up-to-date information on the management of overdosage (1-800-222-1222 or www.poison.org).

11 DESCRIPTION

TRYVIO (aprocitentan) is an ERA. The chemical name of aprocitentan is N-[5-(4-bromophenyl)-6- [2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-sulfamide. It has a molecular formula of $C_{16}H_{14}Br_2N_6O_4S$ and a molecular weight of 546.2 g/mol.

The structural formula is:



Aprocitentan is a white to off-white powder that is insoluble in water.

TRYVIO is available as film-coated 12.5 mg strength tablets for oral administration. The inactive ingredients in TRYVIO are croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose.

The film coating contains the following inactive ingredients: hydroxypropyl cellulose, iron oxide black, iron oxide red, iron oxide yellow, polyvinyl alcohol, silica colloidal hydrated, talc, titanium dioxide, and triethyl citrate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Aprocitentan is an 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.

12.2 Pharmacodynamics

Aprocitentan exposure-response relationships and the time course of pharmacodynamic response are not fully characterized.

Cardiac Electrophysiology

At eight times the recommended dose, clinically significant QTc interval prolongation was not observed.

12.3 Pharmacokinetics

The aprocitentan mean (%CV) C_{max} is approximately 1.3 mcg/mL (19) following a single 25 mg dose (twice the recommended dose). The mean (%CV) aprocitentan AUC to the dosing interval ($AUC_{0\text{-}tau}$) is approximately 23 mcg·h/mL (17) following a single 25 mg dose. Aprocitentan plasma concentrations increased in a dose-proportional manner following once-daily administration of 5, 25, and 100 mg (0.4 times the recommended dose to 8 times the recommended dose). Aprocitentan steady state is reached by Day 8 with approximately 3-fold accumulation following once daily administration. Aprocitentan is primarily unchanged in plasma following oral TRYVIO administration.

Absorption

The absolute oral bioavailability of aprocitentan is unknown. The time to reach C_{max} is between 4 and 5 hours after administration of 25 mg aprocitentan (twice the recommended dose).

Effect of Food

No clinically significant differences in aprocitentan pharmacokinetics were observed following administration of a high-fat, high-calorie meal (approximately 150, 250, and 500–600 calories from protein, carbohydrate, and fat, respectively) in healthy subjects.

Distribution

The apparent volume of distribution of aprocitentan is approximately 20 L. Aprocitentan is >99% bound to plasma proteins, primarily albumin. Protein binding is not affected by renal or hepatic impairment. The aprocitentan blood-to-plasma ratio is 0.63.

Elimination

The aprocitentan effective half-life is approximately 41 hours, and the apparent clearance is approximately 0.3 L/h.

Metabolism

Aprocitentan is primarily metabolized by UGT1A1- and UGT2B7-mediated N-glucosidation and non-enzymatic hydrolysis.

Excretion

After a single dose of radiolabeled aprocitentan, approximately 52% of the dose was eliminated via urine (0.2% unchanged) and 25% via feces (6.8% unchanged).

Specific Populations

No clinically significant differences in the pharmacokinetics of aprocitentan were observed based on age (18–84 years), sex, race/ethnicity, body weight (44–196 kg), between patients and healthy subjects, mild to severe renal impairment (eGFR ≥15 mL/min), or mild to moderate hepatic impairment (Child-Pugh class A to B). The effect of kidney failure (eGFR <15 mL/min), dialysis, or severe hepatic impairment (Child-Pugh class C) on aprocitentan pharmacokinetics is unknown.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

No clinically significant differences in the pharmacokinetics of the following drugs were observed when used concomitantly with aprocitentan: midazolam (CYP3A4 substrate) or rosuvastatin (breast cancer resistance protein [BCRP] substrate).

In Vitro Studies

UDP-glucuronosyltransferase (UGT) inducers: Concomitant administration of aprocitentan with UGT inducers may decrease aprocitentan exposure.

CYP450 enzymes: Aprocitentan inhibits CYP3A4 and all members of the CYP2C family, but did not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2D6, and CYP2E1. Aprocitentan is an inducer of CYP3A4 but did not induce CYP1A2 or CYP2C9.

UGT enzymes: Aprocitentan is a substrate and inhibitor of UGT1A1 and UGT2B7.

Transporter systems: Aprocitentan is a substrate of P-glycoprotein (P-gp) and BCRP. However, inhibitors of these transporters are not anticipated to influence the PK of aprocitentan. Aprocitentan is an inhibitor of BCRP, bile salt export pump (BSEP), and sodium taurocholate co-transporting polypeptide (NTCP), but does not inhibit P-gp, organic cationic transporter (OCT)1, OCT2, human multi-drup and toxin compound extrusion (MATE)1, or MATE2K. Aprocitentan does not inhibit organic anion transporter (OAT)1, OAT3, OATP1B1, or OATP1B3 at therapeutic concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year carcinogenicity studies with macitentan (for which aprocitentan is a major metabolite) did not identify any carcinogenic potential at doses up to 100 mg/kg/day and 250 mg/kg/day in mice and rats, which produced aprocitentan exposures approximately 30-fold and 11-fold, respectively, the clinical aprocitentan exposure at the MRHD based on AUC.

Mutagenesis

Aprocitentan did not induce mutagenicity or genotoxicity in a standard battery of *in vitro* and *in vivo* assays that included a bacterial reverse mutation assay, a chromosome aberration test in human lymphocytes, and an *in vivo* bone marrow micronucleus test in rats.

Impairment of Fertility

In a fertility study in male rats given aprocitentan for 15 weeks at doses up to 250 mg/kg/day, no effect on fertility or spermatogenesis was observed at 52-fold the clinical exposure at the MRHD based on AUC. In repeated dose toxicity studies, treatment with aprocitentan resulted in testicular tubular degeneration/atrophy in male rats and dogs at high doses of 250 mg/kg/day and 25 mg/kg/day, respectively, which represents approximately 41- and 52-fold the clinical exposure at the MRHD, based on AUC, respectively. The testicular toxicity was not evident in male rats and dogs at 50 mg/kg/day and 5 mg/kg/day, respectively, which represents approximately 14- and 10-fold the clinical exposure at the MRHD based on AUC.

In female rats given aprocitentan prior to mating, minimally increased pre-implantation loss was observed at doses ≥50 mg/kg/day, which represent ≥23-fold the clinical exposure at the MRHD based on AUC. No impact on fertility was observed at 10 mg/kg/day, which represents 5-fold the clinical exposure at the MRHD based on AUC.

14 CLINICAL STUDIES

The efficacy of TRYVIO (aprocitentan) was evaluated in a multipart, phase 3 multicenter study (PRECISION, NCT03541174) in adults with SBP ≥140 mmHg who were prescribed at least three antihypertensive medications. The trial included a placebo run-in period, which was followed by three parts as described below. Prior to the placebo run-in period, all patients were switched to standard background antihypertensive therapy consisting of an angiotensin receptor blocker, a calcium channel blocker, and a diuretic, which was continued throughout the study. Patients with concomitant use of beta-blockers continued this treatment throughout the study.

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

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

Patients had a mean age of 62 years (range 24 to 84 years) and 60% were male. Patients were White (83%), African American (11%) or Asian (5%). Approximately 10% were Hispanic. The mean body mass index (BMI) was 34 kg/m^2 (range 18 to 64 kg/m^2). At baseline, 19% of patients had an eGFR 30–59 mL/min/1.73 m^2 and 3% had an eGFR 15–29 mL/min/1.73 m^2. At baseline, 24% of patients had a urine albumin-to-creatinine ratio (UACR) of 30–300 mg/g and 13% had a UACR >300 mg/g. Approximately 54% of patients had a medical history of diabetes mellitus, 31% ischemic heart disease, and 20% congestive heart failure. At baseline, 63% of patients reported taking four or more antihypertensive medications.

BP reductions compared to placebo based on uAOBP measurements at trough are shown in Table 2. TRYVIO 12.5 mg was statistically superior to placebo in reducing SiSBP at Week 4 (part 1). The treatment effect was consistent for sitting diastolic BP (SiDBP) (Table 2).

Table 2 Reduction in sitting trough BP (mmHg) at Week 4 of DB treatment

				Difference to placebo	
Treatment group	**N**	**Baseline* Mean**	**LS Mean**	**LS Mean**	**p-value**
SiSBP (primary endpoint)			**LS 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†
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)	–	–

* Observed baseline value.

† Statistically significant at the 2.5% level as prespecified in the testing strategy.

BP = blood pressure; CL = confidence limits; DB = double-blind; LS Mean = least squares mean; SiDBP = sitting diastolic blood pressure; SiSBP = sitting systolic blood pressure.

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 25 mg aprocitentan following a period during which all patients were treated with 25 mg. In patients re-randomized to placebo, the mean SiSBP increased, whereas in patients re-randomized to 25 mg 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 25 mg dose. The 25 mg dose has not demonstrated a meaningful improvement in blood pressure reduction as compared to the 12.5 mg dose and had an increased risk of edema/fluid retention *[see Warnings and Precautions (5.4)]*.

TRYVIO's BP-lowering effect appeared consistent among subgroups defined by age, sex, race, BMI, baseline eGFR, baseline UACR, medical history of diabetes, and between BP measurement methodologies (uAOBP and ambulatory BP measurements).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

TRYVIO tablets are available as:

- 12.5 mg: yellow to orange round, film-coated tablet, debossed with "AN" on one side and plain on the other side.
  - NDC 80491-8012-8, each blister contains 10 tablets
  - NDC 80491-8012-3, each bottle contains 30 tablets and has a child-resistant closure

16.2 Storage and Handling

Store at 20ºC to 25ºC (68ºF to 77ºF); excursions permitted from 15ºC to 30ºC (59ºF to 86ºF) *[see USP Controlled Room Temperature]*. Store in the original package. Dispense to patient in original container only. Replace cap securely each time after opening. Do not discard desiccant. Protect from light and moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

<u>Embryo-Fetal Toxicity</u>

Counsel patients who can become pregnant to use acceptable methods of contraception before treatment with TRYVIO, during treatment with TRYVIO, and for one month after

treatment discontinuation. Patients who can become pregnant should have pregnancy tests prior to initiation of TRYVIO, monthly during treatment, and one month after TRYVIO discontinuation *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)]*.

TRYVIO REMS

Because of the risk of birth defects, TRYVIO is only available through a restricted distribution program called the TRYVIO REMS. Under the TRYVIO REMS, prescribers and pharmacies must enroll in the REMS *[see Warnings and Precautions (5.2)]*.

Acceptable forms of contraception include, but are not limited to, IUD, contraceptive implants, tubal sterilization, or a combination of methods (either one hormone method with a barrier method or two barrier methods). Alternatively, if a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method.

Patients should be instructed to contact their healthcare provider if they suspect they may be pregnant. Patients should seek additional contraceptive advice from a gynecologist or similar expert as needed.

Educate and counsel patients who can become pregnant on the use of emergency contraception in the event of unprotected sex or contraceptive failure.

Advise pre-pubertal females and/or their guardian(s) to report any changes in their reproductive status immediately to their prescriber.

Review the Medication Guide and REMS educational materials with patients.

Lactation

Advise females not to breastfeed during treatment with TRYVIO *[see Use in Specific Populations (8.2)]*.

Hepatotoxicity

Educate patients on signs of hepatotoxicity. Advise patients that they should contact their healthcare provider if they have unexplained nausea, vomiting, right upper quadrant pain, fatigue, anorexia, jaundice, dark urine, fever, or itching.

Fluid Retention

Educate patients on signs of fluid retention. Advise patients that they should contact their healthcare provider if they have unusual weight increase or swelling of the ankles or legs.

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