LOUISIANA BLUE

aprocitentan (Tryvio™)

Policy # 00920
Original Effective Date: 04/01/2025
Current Effective Date: 04/01/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider aprocitentan (Tryvio™)‡ 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.to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for aprocitentan (Tryvio) will be considered when the following criteria are met:

- Patient has a diagnosis of resistant hypertension; AND
- Patient is 18 years of age or older; AND
- Patient is on a stabilized dose and receiving concomitant therapy with ALL of the following unless there is clinical evidence or patient history that suggests the required products will be ineffective or cause an adverse reaction to the patient:
    - Maximally tolerated blocker of the renin-angiotensin system [angiotensin-converting enzyme (ACE) inhibitor (e.g., enalapril, lisinopril) or angiotensin II receptor blocker (ARB) (e.g., candesartan, valsartan)]; AND
    - Maximally tolerated calcium channel blocker (e.g., amlodipine, diltiazem, verapamil); AND
    - Maximally tolerated diuretic (e.g., hydrochlorothiazide, metolazone, triamterene); AND

  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient has tried and failed (e.g., intolerance or inadequate response) at least ONE other GENERIC formulary antihypertensive agent in a different pharmacological class, including, but not limited to a mineralocorticoid receptor agonist (e.g., eplerenone, spironolactone), beta blocker (e.g., atenolol, carvedilol, metoprolol), alpha adrenergic blocker (e.g., doxazosin, prazosin), central alpha-adrenergic agonist (clonidine, methyldopa), direct vasodilator (e.g., hydralazine, minoxidil), or direct renin inhibitor (aliskiren); AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

- If the patient is a female of reproductive potential, provider attests that the patient is NOT currently pregnant and is willing to use effective contraception; AND
- Patient has an estimated glomerular filtration rate (eGFR) ≥ 15 mL/min/1.73 m^2
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of aprocitentan (Tryvio) when the patient is not on a stabilized dose and receiving concomitant therapy with a maximally tolerated blocker of the renin-angiotensin system, a maximally tolerated calcium channel blocker, AND a maximally tolerated diuretic to be **not medically necessary.****

Based on review of available data, the Company considers the use of aprocitentan (Tryvio) when the patient has not tried and failed at least ONE other GENERIC formulary antihypertensive agent in a different pharmacological class to be **not medically necessary.****

Based on review of available data, the Company considers the use of aprocitentan (Tryvio) when the patient has an estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m^2 to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of aprocitentan (Tryvio) when the patient selection criteria are not met (except those noted to be **not medically necessary****) to be **investigational.***

Background/Overview

Tryvio, an endothelin receptor antagonist (ERA), is indicated for the treatment of hypertension in combination with other antihypertensive drugs, to lower blood pressure in adults who are not adequately controlled on other medications. Lowering blood pressure reduces the risk of fatal and non-fatal cardiovascular (CV) events, primarily strokes and myocardial infarctions (MIs). Tryvio is available as 12.5 mg tablets, and the recommended dose of Tryvio is one tablet once daily. Tryvio has a Boxed Warning regarding embryofetal toxicity and is contraindicated in pregnancy. Prescribers should verify that females of reproductive potential are not pregnant prior to treatment initiation. Effective contraception should also be used. Due to the risk of birth defects, Tryvio is only available through a restricted distribution program called the TRYVIO REMS. 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 Tryvio pharmacokinetics is unknown. In addition, patients with renal impairment are at increased risk of edema/fluid retention

Tryvio is the only ERA indicated for the treatment of hypertension (in combination with other antihypertensive drugs). There are many medications available for the treatment of hypertension, most of which come at a lower price tag than Tryvio due to their generic availability. These include thiazide-like diuretics (e.g., chlorthalidone, hydrochlorothiazide, metolazone), loop diuretics (e.g., furosemide, ethacrynic acid), potassium-sparing diuretics (e.g., amiloride, triamterene), mineralocorticoid receptor antagonists (e.g., spironolactone, eplerenone), ACE inhibitors (e.g., enalapril, lisinopril, ramipril, trandolapril), ARBs (e.g., candesartan, irbesartan, valsartan), a direct renin inhibitor (i.e., aliskiren), dihydropyridine CCBs (e.g., felodipine, amlodipine), non-dihydropyridine CCBs (e.g., diltiazem, verapamil), beta blockers (e.g., atenolol, bisoprolol, metoprolol, acebutolol), alpha-adrenergic blockers (e.g., doxazosin, prazosin, terazosin), central alpha-adrenergic agonists (e.g., clonidine, guanfacine, methyldopa), and direct vasodilators (e.g., hydralazine, minoxidil).

Guidelines have not been updated to include Tryvio. The American College of Cardiology (ACC)/ American Heart Association (AHA) guideline for the prevention, detection, evaluation, and management of high blood pressure in adults (2017) generally recommended initiation of antihypertensive drug therapy with thiazide diuretics, CCBs, and ACE inhibitors or ARBs. Beta blockers also have a significant role in certain clinical scenarios such as ischemic heart disease. A scientific statement released by the AHA defines resistant hypertension (RH) as above-goal elevated blood pressure (BP) in a patient despite the concurrent use of 3 antihypertensive drug classes, commonly including a long-acting calcium channel blocker, a blocker of the renin-angiotensin system (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker), and a diuretic. The antihypertensive drugs should be administered at maximum or maximally tolerated daily doses. Management of RH includes maximization of lifestyle interventions, use of long-acting thiazide-like diuretics (chlorthalidone or indapamide), addition of a mineralocorticoid receptor antagonist (spironolactone or eplerenone), and, if BP remains elevated, stepwise addition of antihypertensive drugs with complementary mechanisms of action to lower BP. The role of Tryvio in the management of hypertension is limited to adults with resistant hypertension as an add-on to other standard antihypertensives (CCBs, ACE inhibitors or ARBs, thiazide diuretics). Tryvio is an alternative to other later-line antihypertensive therapies in adults with resistant hypertension who have not responded to optimized standard initial antihypertensive therapy.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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

aprocitentan (Tryvio™)

Policy # 00920
Original Effective Date: 04/01/2025
Current Effective Date: 04/01/2025

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Tryvio was evaluated in a multipart, phase 3 multicenter study in adults with systolic blood pressure (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 Tryvio at either 12.5 mg, 25 mg, or placebo 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 Tryvio 25 mg once daily for 32 weeks. At the end of the 32 weeks, patients were re-randomized to receive either Tryvio 25 mg or placebo, once daily, during a 12-week double-blind withdrawal period (part 3).

The primary efficacy endpoint was the change in sitting systolic blood pressure (SiSBP) from baseline to Week 4 during part 1, measured at trough by unattended automated office blood pressure (uAOBP). Tryvio 12.5 mg was statistically superior to placebo in reducing SiSBP at Week 4 (part 1) (least squares [LS] mean reduction of -15.4 mmHg vs. -11.6 mmHg, respectively; LS mean treatment difference of -3.8 mmHg [P = 0.0043]). The treatment effect was consistent for sitting diastolic blood pressure (SiDBP) (least squares [LS] mean reduction of -15.4 mmHg vs. -11.6 mmHg, respectively; LS mean treatment difference of -3.8 mmHg [P = 0.0043]). The persistence of the blood pressure-lowering effect of Tryvio was demonstrated in part 3 of the trial, in which patients on Tryvio were re-randomized to placebo or Tryvio 25 mg 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 Tryvio 25 mg 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.

It should be noted that Tryvio is not approved for use at a 25 mg dose. The 25 mg dose did not demonstrate a meaningful improvement in blood pressure reduction as compared to the 12.5 mg dose and had an increased risk of edema/fluid retention.

aprocitentan (Tryvio™)

Policy # 00920
Original Effective Date: 04/01/2025
Current Effective Date: 04/01/2025

References

1. Tryvio [package insert]. Idorsia Pharmaceuticals, Ltd. Radnor, Pennsylvania. Updated April 2024.
2. Tryvio Drug Evaluation. Express Scripts. Updated June 12, 2024.
3. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018;138:e484-e594.
4. Carey RM, Calhoun DA, Bakris GL, et al. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. Hypertension. 2018;72(5):e53-e90.

Policy History

Original Effective Date: 04/01/2025
Current Effective Date: 04/01/2025
03/06/2025 Medical Policy Committee review
03/12/2025 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 03/2026

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.