Blue Cross and Blue Shield of Minnesota medical policies do not imply that members should not receive specific services based on the recommendation of their provider. These policies govern coverage and not clinical practice. Providers are responsible for medical advice and treatment of patients. Members with specific health care needs should consult an appropriate health care professional.

ADVANCED THERAPIES FOR PHARMACOLOGICAL TREATMENT OF PULMONARY HYPERTENSION

Description: Pulmonary hypertension (PH) refers to the presence of abnormally high pulmonary vascular pressure. The World Health Organization (WHO) classifies patients with PH into the following five groups based on etiology:

- WHO Group 1: Pulmonary arterial hypertension (PAH)
- WHO Group 2: Pulmonary hypertension due to left heart disease
- WHO Group 3: Pulmonary hypertension due to lung diseases and/or hypoxemia
- WHO Group 4: Chronic thromboembolic pulmonary hypertension (CTEPH)
- WHO Group 5: Pulmonary hypertension with unclear multifactorial mechanisms

Pulmonary Arterial Hypertension (PAH; WHO Group 1)
PAH is a rare and debilitating disease characterized by abnormal proliferation and contraction of pulmonary artery smooth muscle cells. This condition causes a decrease in the size of the pulmonary artery lumen, decreased reactivity of the vascular bed, increased pulmonary vascular resistance (PVR), elevated pressure in the pulmonary circulation (initially with normal left-sided pressures), and leads to overload-induced progressive right ventricular dilation and low cardiac output.

Idiopathic PAH is more prevalent in women, and is the most common type of PAH. Familial PAH often results from a mutation in bone morphogenetic protein receptor-2 (BMPR2) and is inherited as an autosomal dominant disease. PAH is also associated with congenital heart disease, connective tissue diseases, drugs and toxins, human immunodeficiency virus (HIV), portal hypertension, hemoglobinopathies, and myeloproliferative disorders.
Management of PAH
Conventional therapies are considered in all patients with PAH regardless of etiology. These therapies include diuretics, oxygen therapy, anticoagulants, digoxin, and exercise. Digoxin has been shown to have beneficial effects when used with caution (i.e., patients may be at higher risk for digitalis toxicity and require close monitoring). Patients with a positive vasoreactivity test can be given a trial of calcium channel blockers, whereas patients with a negative vasoreactivity test require advanced therapy.

Advanced therapies, according to therapeutic class, that are FDA-approved for the treatment of adults with PAH include:
- Prostacyclin analogues
  - Epoprostenol (Flolan or Veletri®)
  - Treprostinil (Remodulin®, Tyvaso®, or Orenitram™)
  - Iloprost (Ventavis®)
- Endothelin receptor antagonists
  - Bosentan (Tracleer®)
  - Ambrisentan (Letairis®)
  - Macitentan (Opsumit®)
- Phosphodiesterase type 5 inhibitors
  - Sildenafil (Revatio®)
  - Tadalafil (Adcirca®)
- Soluble guanylate cyclase stimulator
  - Riociguat (Adempas®)

No advanced therapy is FDA-approved for pharmacological treatment of PAH in pediatric patients. Combination advanced therapy has been suggested and is under investigation. Pulmonary endarterectomy, lung transplantation, and combined heart-lung transplantation have been performed in patients refractory to medical management. Objective assessments to measure treatment response include improvement in exercise capacity (6-minute walk test, cardiopulmonary exercise test, treadmill test), hemodynamics, and survival.

Non-Pulmonary Arterial Hypertension (Non-PAH) Pulmonary Hypertension (WHO Groups 2-5)
Non-PAH PH is more prevalent than PAH, with PH due to left heart disease being the most common form of PH. Treatment of non-PAH PH should be directed at the underlying disease. Use of PAH-specific therapies for non-PAH PH have been studied and generally found to be of no benefit. Patients with non-PAH PH may experience adverse effects with the use of PAH-specific therapies, including increased fluid retention, pulmonary edema, and ventilation perfusion mismatch.

Management of Chronic Thromboembolic Pulmonary Hypertension (CTEPH; WHO Group 4)
CTEPH primarily occurs after acute or chronic pulmonary embolism. Patients with CTEPH are treated with diuretics and oxygen as needed and with extended or lifelong anticoagulant therapy. Eligible patients
undergo pulmonary endarterectomy, which may be curative. Medical treatment is recommended when surgery is contraindicated due to significant distal disease or comorbidity, or when pulmonary artery pressures remain elevated after surgery. In 2013, riociguat (Adempas®) became the first drug to be approved by the FDA for the treatment of adults with persistent/recurrent CTEPH after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.

Policy:

I. **Advanced Therapies for Pharmacological Treatment of Pulmonary Arterial Hypertension (PAH; WHO Group 1)**
   
   A. Advanced therapies for PAH may be considered **MEDICALLY NECESSARY** for patients who meet **ALL** of the following criteria:
      1. Mean pulmonary artery pressure greater than 25 mm Hg; **AND**
      2. Pulmonary capillary wedge pressure, left atrial pressure, or left ventricular end-diastolic pressure less than or equal to 15 mm Hg; **AND**
      3. Pulmonary vascular resistance greater than 3 Wood units; **AND**
      4. Confirmation of PAH by complete right heart catheterization; **AND**
      5. Exclusion of significant chronic hypoxemic lung disease or chronic thromboembolic disease; **AND**
      6. A negative response to acute pulmonary vasodilator testing OR a contraindication to calcium-channel antagonists.

   B. The following advanced therapies for PAH may be considered **MEDICALLY NECESSARY** when used as monotherapy for patients diagnosed with PAH (as described in section A above):
      1. Epoprostenol (Flolan® or Veletri®) continuous intravenous infusion;
      2. Treprostinil (Remodulin®) continuous subcutaneous or intravenous infusion;
      3. Treprostinil (Tyvaso®) inhalation via nebulizer;
      4. Treprostinil (Orenitram ™) extended-release oral;
      5. Iloprost (Ventavis®) inhalation via nebulizer;
      6. Bosentan (Tracleer®) oral;
      7. Ambrisentan (Letairis®) oral;
      8. Macitentan (Opsumit®) oral;
      9. Sildenafil (Revatio®) oral;
      10. Tadalafil (Adcirca®) oral;
      11. Riociguat (Adempas®) oral.

   C. Combination therapy (i.e., two or more advanced therapies) for PAH may be considered **MEDICALLY NECESSARY** when **ALL** of the following conditions are met:
      1. The patient has failed to demonstrate an adequate response to monotherapy; **AND**
      2. Drugs are from different therapeutic classes, excluding the
combination of a soluble guanylate cyclase inhibitor (e.g., riociguat [Adempas®]) and a phosphodiesterase type 5 inhibitor (e.g., sildenafil [Revatio®] or tadalafil [Adcirca®]), which are contraindicated as combined treatment; AND

3. Each drug may be considered medically necessary for the treatment of PAH (as described in section B above).

D. Combination therapy (i.e., two or more advanced therapies) for PAH is considered INVESTIGATIVE as first-line treatment.

II. Advanced Therapies for Pharmacological Treatment of Non-PAH Pulmonary Hypertension (PH; WHO Groups 2-5)

A. The use of riociguat may be considered MEDICALLY NECESSARY for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH; WHO Group 4) in patients with either of the following conditions:
   1. Persistent or recurrent pulmonary hypertension after surgical thrombectomy; OR
   2. Inoperable CTEPH.

B. The use of riociguat is considered INVESTIGATIVE for the treatment of all other non-PAH pulmonary hypertension conditions, including but not limited to:
   1. Pulmonary hypertension associated with left heart diseases (WHO Group 2);
   2. Pulmonary hypertension associated with lung diseases and/or hypoxemia (including chronic obstructive pulmonary disease) (WHO Group 3);
   3. Miscellaneous conditions (i.e., sarcoidosis, histocytosis X and lymphangiomatosis) (WHO Group 5)

C. The use of epoprostenol, treprostinil, iloprost, bosentan, ambrisentan, macitentan, sildenafil, or tadalafil is considered INVESTIGATIVE for the treatment of non-PAH pulmonary hypertension conditions, including but not limited to:
   1. Pulmonary hypertension associated with left heart diseases (WHO Group 2);
   2. Pulmonary hypertension associated with lung diseases and/or hypoxemia (including chronic obstructive pulmonary disease) (WHO Group 3);
   3. Pulmonary hypertension due to chronic thrombotic and/or embolic disease (WHO Group 4);
   4. Miscellaneous conditions (i.e., sarcoidosis, histocytosis X and lymphangiomatosis) (WHO Group 5)

III. Other Advanced Therapies

The use of tadalafil 10 mg (Cialis®) and vardenafil 10 mg (Levitra®) is considered INVESTIGATIVE for the treatment of PAH (WHO Group 1) and non-PAH pulmonary hypertension (WHO Groups 2-5).

Coverage: Blue Cross and Blue Shield of Minnesota medical policies apply generally to all Blue Cross and Blue Plus plans and products. Benefit plans vary in coverage and some plans may not provide coverage for
certain services addressed in the medical policies.

Medicaid products and some self-insured plans may have additional policies and prior authorization requirements. Receipt of benefits is subject to all terms and conditions of the member’s summary plan description (SPD). As applicable, review the provisions relating to a specific coverage determination, including exclusions and limitations. Blue Cross reserves the right to revise, update and/or add to its medical policies at any time without notice.

For Medicare NCD and/or Medicare LCD, please consult CMS or National Government Services websites.

Refer to the Pre-Certification/Pre-Authorization section of the Medical Behavioral Health Policy Manual for the full list of services, procedures, prescription drugs, and medical devices that require Pre-certification/Pre-Authorization. Note that services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial of claims may result if criteria are not met.

Coding:

The following codes are included below for informational purposes only, and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

**HCPCS:**

J1325 Injection, epoprostenol, 0.5 mg  
J3285 Injection, treprostinil, 1 mg  
J7686 Treprostinil, inhalation solution, FDA-approved final product, noncompounded, administered through DME, unit dose form, 1.74 mg  
K0455 Infusion pump used for uninterrupted parenteral administration of medication, (e.g., epoprostenol or treprostinol)  
Q4074 Iloprost, inhalation solution, FDA-approved final product, noncompounded, administered through DME, unit dose form, up to 20 mcg  
S0090 Sildenafil citrate, 25 mg  
S0155 Sterile dilutant for epoprostenol, 50 ml

**Policy History:**

Developed July 8, 2009

**Most recent history:**

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