

Corporate Medical Policy

Pulmonary Hypertension, Drug Management

File Name:	pulmonary_hypertension_drug_management
Origination:	06/1998
Last CAP Review:	3/2020
Next CAP Review:	3/2021
Last Review:	3/2020

Description of Procedure or Service

Pulmonary hypertension (PH) is a chronic, progressive condition characterized by abnormally high arterial pressure in the lung vasculature. Increased pulmonary pressure can be caused by primary abnormalities in the pulmonary vascular system, or can be caused by other abnormalities in the cardiac or pulmonary organs that lead to secondary elevations in pulmonary arterial pressure. A definitive diagnosis of PH is usually made following measurement of pulmonary arterial pressure by right heart catheterization. A pulmonary arterial pressure of at least 25 mm Hg confirms the diagnosis. Advanced pharmacologic therapies for PH are specialty medications specifically intended to impact the natural history of the disease, rather than supportive medications that treat disease manifestations. These medications have been approved by the U.S. Food and Drug Administration (FDA) for 2 classes of PH: pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). PAH is a rare and debilitating disease associated with abnormal proliferation of smooth muscle cells in the pulmonary arterial system, causing progressive right ventricular dilation and low cardiac output. Advanced therapy medications approved for PAH can be used as single agents or in combination. CTEPH is characterized by residual organized thrombi obstructing the pulmonary vasculature following acute or chronic pulmonary embolism. Currently, only one medication, the soluble guanylate cyclase stimulator riociguat, has been FDA-approved for treatment of CTEPH.

Clinical symptoms of PH are related to right-sided heart failure and impaired oxygen delivery by the lungs. Warning signs are nonspecific, but often present as a constellation of symptoms including dyspnea on exertion, fatigue, weakness, and syncope. High pulmonary pressures lead to increased work of the right ventricle. This chronic hemodynamic overload leads to low cardiac output and progressive right ventricular dilatation. In advanced disease, signs of right-sided heart failure occur, such as abdominal distension, hepatic congestion, and pedal edema. Without treatment, the disease is progressive and eventually fatal; however, the natural history and rapidity of progression is variable. Premature death most commonly results from complications of right heart failure.

A subset of patients are considered to have pulmonary arterial hypertension (PAH), a rare and debilitating disease associated with progressive right ventricular dilation and low cardiac output. Several advanced therapies, including prostacyclin analogues, endothelin receptor antagonists, phosphodiesterase type 5 (PDE5) inhibitors, and a soluble guanylate cyclase stimulator are available to treat PAH. Combination advanced therapy has also been proposed.

Another subset of patients is considered to have chronic thromboembolic pulmonary hypertension (CTEPH), characterized by residual organized thrombi obstructing the pulmonary vasculature. Most patients have a history of acute pulmonary embolism. Standard treatment for CTEPH can include pulmonary endarterectomy. The soluble guanylate cyclase stimulator, riociguat, is the only medication currently U.S. Food and Drug Administration (FDA) approved to treat CTEPH.

Pulmonary Hypertension, Drug Management

Pulmonary Hypertension

The World Health Organization (WHO) classifies patients with PH into five groups based on etiology. These groups differ in their clinical presentation, diagnostic findings, and response to treatment. It is important to note the changes in defining and classifying pulmonary hypertension in the following revised WHO Classification of PH developed by the 2009 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) 2009 Expert Consensus Task Force on Pulmonary Hypertension. Patients in Group 1 are considered to have pulmonary arterial hypertension (PAH), and the remaining four groups are considered to have PH.

Revised WHO Classification of Pulmonary Hypertension (PH)

Group 1. Pulmonary arterial hypertension (PAH)

- 1.1. Idiopathic (IPAH)
- 1.2. Familial (FPAH)
- 1.3. Associated with (APAH)
 - 1.3.1. Collagen vascular disease
 - 1.3.2. Congenital systemic-to-pulmonary shunts
 - 1.3.3. Portal hypertension
 - 1.3.4. HIV infection
 - 1.3.5. Drugs and toxins
 - 1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, chronic myeloproliferative disorders, splenectomy)
- 1.4. Associated with significant venous or capillary involvement
 - 1.4.1. Pulmonary veno-occlusive disease (PVOD)
 - 1.4.2. Pulmonary capillary hemangiomatosis (PCH)
- 1.5. Persistent pulmonary hypertension of the newborn

Group 2. Pulmonary hypertension with left heart disease

- 2.1. Left-sided atrial or ventricular heart disease
- 2.2. Left-sided valvular heart disease

Group 3. Pulmonary hypertension associated with lung diseases and/or hypoxemia

- 3.1. Chronic obstructive pulmonary disease
- 3.2. Interstitial lung disease
- 3.3. Sleep disordered breathing
- 3.4. Alveolar hypoventilation disorders
- 3.5. Chronic exposure to high altitude
- 3.6. Developmental abnormalities

Group 4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease (CTEPH)

- 4.1. Thromboembolic obstruction of proximal pulmonary arteries
- 4.2. Thromboembolic obstruction of distal pulmonary arteries
- 4.3. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)

Pulmonary Hypertension, Drug Management

Group 5. Miscellaneous: Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis, chronic hemolytic anemia).

In 2013, based on the consensus of an international group of experts at the Fifth World Symposium on Pulmonary Hypertension, modifications to the classification of PAH were proposed. A key difference from the earlier classification, which is still used by the American College of Cardiology Foundation/American Heart Association (ACCF/AHA), is the category of “Group 1 prime,” defined as pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH), and “Group 1 double-prime,” defined as persistent pulmonary hypertension of the newborn (PPHN). The ACCF/AHA nomenclature lists these conditions as subcategories of Group 1. Further, the 2013 World Symposium classification moved PH associated with chronic hemolytic anemia to Group 5, PH with unclear multifactorial mechanisms. The updated classification of Group 1 PAH, with key changes in **bold**, is as follows:

1. Pulmonary arterial hypertension (PAH)
 - 1.1 Idiopathic PAH
 - 1.2 Heritable PAH
 - 1.21 BMPR2
 - 1.22 ALK-1, ENG, SMAD9, CAV1, KCNK3**
 - 1.23 Unknown
 - 1.3 Drug and toxin-induced
 - 1.4 Associated with:
 - 1.4.1 Connective tissue disorder
 - 1.4.2 HIV infection
 - 1.4.3 Portal hypertension
 - 1.4.4 Congenital heart diseases
 - 1.4.5 Schistosomiasis
- 1’. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)**
- 1”. Persistent pulmonary hypertension of the newborn (PPHN)**

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), and 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. Premature death commonly results from right heart failure.

Idiopathic PAH is the most common type of PAH and is more prevalent in women than in men. 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, HIV, portal hypertension, hemoglobinopathies, and myeloproliferative disorders. The diagnosis of PAH requires confirmation with a complete right heart catheterization. The current hemodynamic definition of PAH is a mean pulmonary artery pressure greater than 25 mm Hg; a pulmonary capillary wedge pressure, or left ventricular end-diastolic pressure of 15 mm Hg or less; and a PVR greater than 3 Wood units.

Baseline Assessment of Pulmonary Arterial Hypertension

A baseline assessment to determine severity of PAH is often performed before initiation of therapy.

This assessment includes the following measures as key determinants of disease severity:

Functional impairment—The functional significance of PAH is determined by measuring exercising capacity and determining New York Heart Association (NYHA) or WHO functional class. The WHO functional classification recognizes the importance of near syncope and syncope. Syncope is thought to worsen the

Pulmonary Hypertension, Drug Management

prognosis in patients with PAH. Although not explicitly stated, PAH patients who have experienced a syncopal episode are generally assigned to WHO functional class IV.

The New York Heart Association Classification- functional classification

- Class I Patients with no limitation of activities; they suffer no symptoms from ordinary activities.
- Class II Patients with slight, mild limitation of activity; they are comfortable with rest or mild exertion.
- Class III Patients with marked limitation of activity; they are comfortable only at rest
- Class IV Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest

World Health Organization functional classification for pulmonary arterial hypertension

- Class I No limitation of clinical activity; ordinary physical activity does not cause dyspnea or fatigue
- Class II Slight limitation in physical activity; ordinary physical activity produces dyspnea, fatigue, chest pain, or near-syncope; no symptoms at rest
- Class III Marked limitation of physical activity; less than ordinary physical activity produces dyspnea, fatigue, chest pain, or near-syncope; no symptoms at rest
- Class IV Inability to perform any physical activity without symptoms; dyspnea and/or fatigue present at rest; discomfort increased by any physical activity

Hemodynamic derangement-pulmonary artery systolic pressure and right ventricular function can be estimated by echocardiography. Right heart catheterization is performed to accurately measure the hemodynamic parameters and confirm PAH. Right heart catheterization is often deferred until advanced therapy is indicated because it is an invasive procedure. Patients with PAH typically undergo an invasive hemodynamic assessment and an acute vasoreactivity test prior to the initiation of advanced therapy.

The acute *vasoreactivity* test involves administration of a short-acting vasodilator, then measuring the hemodynamic response with a right heart catheter. Agents commonly used include epoprostenol, adenosine, and inhaled nitric oxide. An acute vasoreactivity test is considered positive if mean pulmonary artery pressure decreases at least 10 mmHg and to a value less than 40 mmHg, with an increased or unchanged cardiac output, and a minimally reduced or unchanged systemic blood pressure. Patients with a positive vasoreactivity test are candidates for a trial of calcium channel blocker therapy. In contrast, patients with a negative vasoreactivity test should be treated with alternative agents; calcium channel blockers (CCBs) have not shown to be beneficial in these patients and may be harmful.

Medical Management

Conventional therapies considered in all patients with PH regardless of etiology include medications to treat heart failure (diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, digoxin), oxygen therapy, 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 (CCBs). Patients with a negative vasoreactivity test require advanced therapy with prostacyclin analogues, endothelin receptor antagonists, phosphodiesterase type 5 (PDE5) inhibitors, or a soluble guanylate cyclase stimulator. Combination advanced therapy has been suggested and is currently under investigation. Lung transplantation and combined heart-lung transplantation have been performed in patients with PH that is refractory to medical management. There are also specific therapies for each WHO group. For example, anticoagulation is a treatment option in WHO groups 1 and 4, and both anticoagulation and surgical thrombectomy are treatment options for appropriate patients in group 4. Objective assessments to measure treatment response include improvement in exercise capacity (6-mile walk test, cardiopulmonary exercise test, treadmill test), hemodynamics, and survival.

It is important to emphasize that the approved treatments for PAH (WHO Group 1) have serious adverse effects. With the exception of riociguat, which is also FDA-approved to treat chronic thromboembolic PH (WHO Group 4), none have been shown to be effective in patients with other forms of PH.

Pulmonary Hypertension, Drug Management

Chronic Thromboembolic PH

In the WHO classification, CTEPH comprises Group 4. The 2003 WHO and current ACCF/AHA classifications divide CTEPH into 3 groups: proximal, distal, and nonthrombotic, eg, caused by tumor, parasites, or foreign material. The first 2 groups distinguish proximal CTEPH, which may be treated with pulmonary thromboendarterectomy, from distal CTEPH, which is inaccessible to surgery; however, this distinction can be difficult to make in clinical practice. Additionally, clinical presentation, radiologic findings, and management of CTEPH vary across etiology. For these reasons, the updated 2009 WHO classification includes only a single CTEPH category with no subcategories.

Disease Description

CTEPH primarily occurs after acute or chronic pulmonary embolism. Progressive pulmonary vascular remodeling (thrombi organization, fibrous stenosis, and microvascular changes) obstructs pulmonary arteries, leading to PH and right heart failure. Estimated CTEPH incidence among patients who survive an acute pulmonary embolism ranges from 0.6% to 3.8%. However, many patients have no clinical history of pulmonary embolism, and CTEPH is likely underdiagnosed. Additional risk factors include splenectomy, chronic inflammatory states, and hypercoagulability due to the presence of anticardiolipin antibody or elevated factor VIII levels. Diagnosis is made by ventilation-perfusion scan showing large areas of mismatch (segmental or larger). Pulmonary angiography confirms the diagnosis and indicates operability (ie, the extent of proximal and distal disease).

Baseline Assessment of CTEPH

Functional Impairment

Functional classification is determined using both NYHA and WHO classifications previously described. Patients who are ineligible for pulmonary endarterectomy because of distal disease may be candidates for lung transplantation if functional status is adequate (eg, functional class IV decreases the likelihood of receiving a transplant). Patients who are eligible for pulmonary endarterectomy but are considered high risk due to poor functional status (class IV) may have improved surgical outcomes if pretreated with intravenous epoprostenol.

Hemodynamic Derangement

CTEPH is characterized by a mean pulmonary artery pressure greater than 25 mm Hg. European guidelines also require pulmonary capillary wedge pressure of 15 mm Hg or less and PVR greater than 2 Wood units. In patients with poor hemodynamics (eg, pulmonary artery pressure >50 mm Hg) who are eligible for pulmonary endarterectomy, pretreatment with intravenous epoprostenol is recommended to improve surgical outcomes.

Medical Management of CTEPH

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. Current guidelines recommend medical treatment using PAH therapies when pulmonary endarterectomy is contraindicated (due to significant distal disease or comorbidity) and when pulmonary artery pressures remain elevated after pulmonary endarterectomy (due to residual distal pathology).

The single medication currently FDA-approved for treatment of CTEPH is riociguat. Riociguat is a first-in-class oral soluble guanylate cyclase stimulator. It stimulates soluble guanylate cyclase both directly and indirectly, by increasing sensitivity of the enzyme to nitric oxide. Thus, riociguat may be effective in conditions in which endogenous nitric oxide (a vasodilator) is depleted.

**Please note, this policy specifically addresses Flolan (epoprostenol sodium) intravenous infusion, Remodulin (treprostinil) subcutaneous or intravenous infusion, Tyvaso (treprostinil) inhalation, and Ventavis (iloprost) inhalation. The following oral pulmonary arterial hypertension (PAH) drugs; Adcirca

Pulmonary Hypertension, Drug Management

(tadalafil), Adempas (riociguat), Letairis (ambrisentan), Opsumit (macitentan), Orenitram (treprostinil), Revatio (sildenafil), Tracleer (bosentan), and Uptravi (selexipag) are each addressed separately in an individual pharmacy policy as referenced below.

Related Pharmacy Policy:

Oral Pulmonary Arterial Hypertension (PAH)

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for drug management of primary or secondary pulmonary hypertension when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Pulmonary Hypertension Drug Management is covered

The following therapies may be considered **medically necessary** for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1):

- epoprostenol sodium (FLOLAN[®]) continuous IV infusion;
- treprostinil sodium (REMODULIN[®]) continuous SC infusion, or IV infusion;
- iloprost (VENTAVIS[®]) inhalation via nebulizer;
- treprostinil (TYVASO[®]) via inhalation system

When Pulmonary Hypertension Drug Management is not covered

The use of epoprostenol, treprostinil, iloprost, bosentan, ambrisentan, macitentan, sildenafil, tadalafil, and vardenafil is considered **investigational** for the treatment of non-PAH PH conditions (PH; WHO Groups 2-5), including but not limited to:

- Pulmonary hypertension associated with left heart diseases;
- Pulmonary hypertension associated with lung diseases and/ or hypoxemia (including chronic obstructive pulmonary disease);
- Pulmonary hypertension due to chronic thrombotic and/or embolic disease;
- Miscellaneous group (i.e., sarcoidosis, histiocytosis X and lymphangiomatosis).

Pulmonary Hypertension, Drug Management

Use of other advanced therapies for the pharmacologic treatment of pulmonary arterial hypertension (PAH; WHO Group 1) that are not FDA-approved for this indication, including but not limited to imatinib, simvastatin, and atorvastatin, is considered **investigational**.

Policy Guidelines

Treatment with epoprostenol requires 3 steps: initial dose-ranging, catheter insertion and portable pump attachment, and catheter and pump maintenance.

- An initial dose-ranging study is typically performed as an inpatient. The pulmonary capillary wedge pressure is monitored, and the drug infusion rate is increased until dose-limiting pharmacologic effect such as nausea, vomiting, or headaches elicited. Some practitioners may consider the initial dose-ranging study optional.
- Insertion of central venous catheter and attachment to portable infusion pump. Because rebound pulmonary hypertension may recur if the drug is abruptly withdrawn, the drug labeling advises that all patients have access to a backup infusion pump and intravenous infusion set.
- For ongoing maintenance of portable infusion pump and treatment of complications related to the pump, complications include catheter thrombosis, sepsis, and pump malfunction. In clinical trials, a cold pouch and frozen gel packs were used to facilitate extended use at ambient temperatures.

Treatment with iloprost requires the use of a specialized dispensing device.

Oral treprostinil should only be prescribed by a physician with expertise in treating pulmonary arterial hypertension, including administration of infused prostanoids.

For combination treatment, riociguat should not be combined with a phosphodiesterase type 5 inhibitor (sildenafil, tadalafil, vardenafil).

For individuals who have PAH who receive monotherapy using tyrosine kinase inhibitors (TKIs) or statins, the evidence includes no randomized controlled trials (RCT) on TKIs and 4 RCTs and a meta-analysis on statins. Relevant outcomes are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity. A meta-analysis of RCTs evaluating statins for PAH did not find significantly better outcomes (i.e., mortality, 6MWD) with study medication than placebo. For imatinib, a TKI, there are no placebo-controlled studies evaluating efficacy. However, a 2016 safety study identified a high rate of adverse events in patients who took imatinib. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have PAH and inadequate response to monotherapy who receive add-on combined therapy using 2 drug classes FDA-approved for treatment of PAH, the evidence includes RCTs and meta-analyses. Relevant outcomes are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity. The most recent and comprehensive meta-analysis of RCTs was published in 2016. It included 17 RCTs comparing add-on combination therapy with monotherapy with at least 12 weeks of follow-up. The meta-analysis found significantly lower rates of clinical worsening and hospitalizations with add-on combination therapy, but mortality rates did not differ significantly between groups. In all RCTs selected for the 2016 meta-analysis, the combination therapy involved different drug combinations from different classes, although the specific combination of riociguat and phosphodiesterase type 5 inhibitors is contraindicated. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have PAH who receive initial combined therapy using 2 drug classes FDA-approved for treatment of PAH, the evidence includes 2 RCTs. Relevant outcomes are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity. In the first study (AMBITION trial), among patients in the primary analysis set, there was a significantly lower rate of clinical failure at six months in the combination therapy group than in the monotherapy group. Clinical failure was defined as a complex composite endpoint that included death, hospitalizations, functional improvement and other measures of disease progression. Study limitations include change in enrollment criteria during the trial and use of a complex composite outcome with

Pulmonary Hypertension, Drug Management

multiple components. The other RCT did not find significant differences in outcomes between a group receiving initial combined therapy and the group receiving monotherapy at 16 weeks; this study had a small sample size and may have been underpowered to assess secondary outcomes. Multiple reviews of the AMBITION trial with an emphasis on functional improvement (6MWT) have led to guideline recommendations for making ambrisentan plus tadalafil and appropriate initial treatment option. The evidence is sufficient to determine the effects of the technology on health outcomes.

For individuals who have inoperable CETPH or PH after surgery who receive a soluble guanylate cyclase stimulator (eg, riociguat), the evidence includes 1 RCT. Relevant outcomes are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity. The double-blind RCT found that functional outcomes at 16 weeks improved significantly more in the group receiving riociguat than placebo. Both groups had a high proportion of adverse events, and 1 death was attributed to riociguat. In an extension study, the estimated 1-year survival rate was 97%. Thirteen deaths occurred, none of which was attributed to study medication. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome. **Please note, riociguat is an oral drug which is addressed in the Pharmacy policy titled, “Oral Pulmonary Hypertension.”

For individuals who have operable CTEPH who receive perioperative prostacyclin analogues, endothelin receptor antagonists, or riociguat, the evidence includes 1 small RCT on bosentan, retrospective noncomparative studies on epoprostenol and iloprost, and no trials on riociguat. Relevant outcomes are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity. The few studies, with small numbers of patients and limited comparative data, do not provide sufficient evidence to determine whether mortality and pulmonary vascular resistance are reduced with any of these medications. The evidence is insufficient to determine the effects of the technology on health outcomes. **Please note, riociguat is an oral drug which is addressed in the Pharmacy policy titled, “Oral Pulmonary Arterial Hypertension (PAH)”.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: J1325, J3285, J7686, K0455, K0730, Q4074, S0090, S0155, S9347

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual - 1/30/98

Medical Policy Advisory Group - 12/99

BCBSA Medical Policy Reference Manual - 8/18/00, 5.01.09

Medical Policy Advisory Group - 10/2000

Specialty Matched Consultant Advisory Panel - 5/2001

BCBSA Medical Policy Reference Manual - 10/8/02, 5.01.09

Pulmonary Hypertension, Drug Management

Specialty Matched Consultant Advisory Panel - 5/2003

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.09, 12/17/03.

Badesch DB, Abman SH, Aheram GS, Barst RJ, McCrory DC, Simonneau G, et al. Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004; 126: 35-62. Retrieved 3/22/07 from http://www.chestjournal.org/cgi/reprint/126/1_suppl/35S

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.09, 4/25/06

Pohar R, Clark M, Spry C. *Drugs for Pulmonary Arterial Hypertension: A Systematic Review of the Clinical-Effectiveness of Combination Therapy*. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009

McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *J Am Coll Cardiol* 2009;53:1573-619

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.09, 4/24/09

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.09, 5/13/2010

Specialty Matched Consultant Advisory Panel – 3/2011

Senior Medical Director review 4/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.09, 8/11/11

Specialty Matched Consultant Advisory Panel- 3/2012

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.09, 9/13/12

Specialty Matched Consultant Advisory Panel- 3/2013

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.09, 9/12/13

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.09, 3/13/14

Specialty Matched Consultant Advisory Panel- 4/2014

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.09, 3/12/15

Specialty Matched Consultant Advisory Panel- 3/2015

Specialty Matched Consultant Advisory Panel- 3/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.09, 5/19/16

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.09, 6/16/16

Specialty Matched Consultant Advisory Panel- 3/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.09, 10/27/17

Specialty Matched Consultant Advisory Panel- 3/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.09, 10/10/18

Specialty Matched Consultant Advisory Panel- 3/2019

Pulmonary Hypertension, Drug Management

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.09, 10/17/19

Specialty Matched Consultant Advisory Panel- 3/2020

Policy Implementation/Update Information

- 6/98 Original policy adopted from BCBSA
- 8/99 Reformatted, Medical Term Definitions added.
- 12/99 Medical Policy Advisory Group
- 10/00 Revised to include eligible indications for secondary pulmonary hypertension. The term, "Primary" was removed from the document name to be consistent with the File Name. System coding changes. Medical Policy Advisory Group - Approved.
- 5/01 Changes in formatting.
- 5/01 Specialty Matched Consultant Advisory Panel review (5/2001). No change in policy.
- 5/03 Specialty Matched Consultant Advisory Panel review 5/2003. Codes K0455, ID032, ID033 deleted from the policy. Code S0114 added to the policy. Key words added. Added information regarding the use of Treprostinil Sodium (Remodulin) and Bosentan (Tracleer). Changed name of the policy from Epoprostenol Sodium for Treatment of Pulmonary Hypertension to Pulmonary Hypertension, Drug Management. Sources added to policy.
- 6/16/2005 Specialty Matched Consultant Advisory Panel review on 5/26/2005. Reference added. Billing/Coding Documentation Information section updated for consistent policy language. Codes Q4077, S0155, and S9347 added to Billing/Coding section. DRU4065 added as key word.
- 7/2/07 Statement added to Description section to indicate that Treprostinil sodium can be administered subcutaneously *or intravenously*. Following statement added to Description section: Iloprost (Ventavis) is a synthetic analogue of prostacyclin and is delivered as an inhaled solution. It is indicated for the treatment of pulmonary arterial hypertension in patients with NYHA Class III or IV symptoms or pulmonary hypertension related to chronic thromboembolic disease. Information regarding Iloprost added to the When Covered section. Items 4 and 5 added to the When Not Covered section to indicate pulmonary hypertension drugs are considered investigational for asthma and lung resection. Deleted codes Q4077 and S0114. Added codes J3285, K0455 and Q4080. References updated. Specialty Matched Consultant Advisory Panel review meeting 5/25/07. Reaffirm policy.
- 7/20/09 Description section extensive revised-added WHO information and added the drugs ambrisentan, sildenafil citrate, tadalafil and vardenafil. Policy statement revised to read: BCBSNC will provide coverage for drug management of primary or secondary pulmonary hypertension when it is determined to be medically necessary because the medical criteria and guidelines shown below are met. The coverage criteria sections revised. Moved the table of NYHA classes from the When Covered section to the Policy Guidelines section and added a table of WHO functional classifications. Added code S0090 to Billing/Coding section. Specialty Matched Consultant Advisory Panel review 5/13/09. (adn)
- 1/5/10 HCPCS Code Q4080 replaced with Code Q4074.
- 6/22/10 Policy Number(s) removed (amw)
- 01/01/11 Under Description section under Advanced Therapy and Prostacyclin Analogues-added Tyvaso as approved inhalation treatment. Moved PAH (Who Group I) statement paragraph that begins "The diagnosis of PAH requires confirmation with a complete right heart catheterization" from the Description section to Policy Guidelines. Also moved non-pulmonary arterial hypertension PH (Who Groups 2-5) statement paragraph that begins "PH associated with elevated left heart filling pressures are more prevalent than PAH" from the Description section to Policy Guidelines. Moved statement paragraph that begins "Treatment with epoprostenol requires three steps as follows" from

Pulmonary Hypertension, Drug Management

- Policy Guidelines to Description section. Under When Covered section, added Tadalafil (ADCIRCA), oral as medically necessary oral therapy for PAH conditions. Under When Not Covered section, added Tadalafil as investigational for the treatment of non-PAH PH conditions. Added new HCPCS code J7686 for 2011. HCPCS codes J1325, J3285, J7686, Q4074 will require prior review as of 4/1/2011. Notification given 1/1/2011 for effective date 4/1/2011. (lpr)
- 4/12/11 Specialty Matched Consultant Advisory Panel review 3/2011. Deleted information in the “When Pulmonary Hypertension Drug Management is not Covered” section regarding combination drug therapy. References added. (mco)
- 3/30/12 Under Description section: Phosphodiesterase (PDE5) Inhibitors, added statement that Sildenafil (Revatio) and Tadalafil (Adcirca) should not be used in combination with nitrates. Extensively revised Policy Guidelines section. Specialty Matched Consultant Advisory Panel 3/21/2012. (lpr)
- 11/27/12 Under “When Not Covered” section added: “Use of other advanced therapies for the pharmacologic treatment of pulmonary arterial hypertension (PAH/WHO Group 1), including but not limited to imatinib and simvastatin, is considered investigational.” Notification given 11/27/12 for effective date 2/26/13. (lpr)
- 4/16/13 Specialty Matched Consultant Advisory panel review meeting 3/20/13. No change to policy statement. (lpr)
- 10/29/13 Added e.g. to indicate availability of epoprostenol and sildenafil generic formulations under “When Covered” section. Atorvastatin is investigational under “When Not Covered” section. Reference added. (lpr)
- 5/13/14 Removed references to the oral drugs from “When Covered” section since pharmacy has the “Oral Pulmonary Hypertension” policy which includes these drugs. Revised and updated Description Policy Guidelines sections. Reference updated. Specialty matched consultant advisory panel review meeting 4/30/2014. No changes to policy statement. (lpr)
- 4/28/15 Updated Description section. Reference added. Specialty Matched Advisory Panel review 3/25/15. No change to policy statement. (lpr)
- 7/26/16 Specialty Matched Consultant Advisory Panel review 3/30/16. No change to policy statement. Reference added. (lpr)
- 4/28/17 Updated Description and Policy Guidelines sections. Reference added. Specialty Matched Advisory Panel review 3/29/2017. Under Description section, Chronic Thromboembolic PH on page 4, designated that CTEPH is in WHO Group 4. Under Policy Guidelines section, page 6, clarified that Riociguat for CTEPH is addressed under the Pharmacy policy titled “Oral Pulmonary Hypertension.” No change to policy statement. (lpr)
- 11/10/17 Updated Policy Guidelines section. No change to policy statement. Reference added. (lpr)
- 4/13/18 Specialty Matched Consultant Advisory Panel review 3/2018. No change to policy statement. (krc)
- 4/16/19 Reference added. Specialty Matched Consultant Advisory Panel review 3/20/2019. No change to policy statement. (krc)
- 5/26/20 Dosing specifications added to Policy Guidelines. Edits made throughout policy for improved structure and clarity. Reference added. Specialty Matched Consultant Advisory Panel review 3/18/2020. (krc)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.