



Corporate Medical Policy

Pulmonary Hypertension, Drug Management

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Description of Procedure or Service

Pulmonary Hypertension

Pulmonary hypertension (PH) refers to the presence of abnormally high pulmonary vascular pressure. 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)

1. Pulmonary arterial hypertension (PAH)
 - 1.1. Idiopathic (IPAH)
 - 1.2. Familial (FPAH)
 - 1.3. Associated with (APAH)
 - 1.3.1. Connective tissue disorder
 - 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's 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
2. Pulmonary hypertension with left heart disease
 - 2.1. Left-sided atrial or ventricular heart disease
 - 2.2. Left-sided valvular heart disease

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

Pulmonary Arterial Hypertension (WHO Group 1)

Pulmonary arterial hypertension (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, a 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.

Idiopathic pulmonary hypertension (IPAH) is more prevalent in women, and 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. 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 mmHg; a pulmonary capillary wedge pressure, or left ventricular end-diastolic pressure less than or equal to 15 mmHg; and a pulmonary vascular resistance greater than 3 Wood units.

Non-Pulmonary Arterial Hypertension PH (WHO Groups 2-5)

PH associated with elevated left heart filling pressures are more prevalent than PAH. Treatment should be directed at the underlying left heart disease. Use of PAH-specific treatments for non-PAH PH has been suggested but there are no clinical trial data to support these hypotheses. There are potential adverse side effects of PAH-specific therapies in such patients including increased fluid retention, pulmonary edema, and ventilation perfusion mismatch.

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

Hemodynamic derangement—pulmonary artery systolic pressure and right ventricular function can be estimated by echocardiography. Right heart catheterization is performed to accurately measure the hemody-

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dynamic 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 are considered in all patients with PAH regardless of the etiology; 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 CCBs. Patients with a negative vasoreactivity test require advanced therapy with prostacyclin analogues, endothelin receptor antagonists, or phosphodiesterase type 5 (PDE5) inhibitors. Combination advanced therapy has been suggested and is under investigation, but the data are insufficient to draw conclusions. 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-mile walk test, cardiopulmonary exercise test, treadmill test), hemodynamics, and survival.

The following summarizes the advanced therapies for treatment of PAH (WHO Group 1):

Prostaglandin Analogues

epoprostenol sodium (Flolan[®]) is administered by continuous IV infusion via central venous catheter using an ambulatory infusion pump. FDA approved indications are for long-term treatment of primary pulmonary hypertension and pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA Class III-IV patients who do not respond adequately to conventional therapy.

treprostinil sodium (Remodulin[®]) is administered by continuous subcutaneous or intravenous infusion. It is approved for treatment of PAH in patients with NYHA Class II-IV symptoms, to diminish symptoms associated with exercise and in patients who require transition from Flolan, to reduce the rate of clinical deterioration.

iloprost (Ventavis[®]) is delivered by inhalation via nebulizer for treatment of pulmonary arterial hypertension (WHO Group 1) in patients with NYHA Class III-IV symptoms.

Endothelin Receptor Antagonists

bosentan (Tracleer[™]) is taken orally for the treatment of pulmonary arterial hypertension (WHO Group 1) in WHO Class III or IV symptoms to improve exercise ability and decrease the rate of clinical worsening.

ambrisentan (LETAIRIS[®]) is taken orally for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO Class II or III symptoms to improve exercise capacity and delay clinical worsening.

Phosphodiesterase (PDE5) Inhibitors

sildenafil citrate (REVATIO[®]) is taken orally for treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise ability.

tadalafil (CIALIS[®]). No FDA approved indications for PAH or clinical evidence to support use for PAH.

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Vardenafil (LEVITRA®). No FDA approved indications for PAH or clinical evidence to support use for PAH.

It is important to emphasize the approved treatment for pulmonary arterial disease (PAH; WHO Group 1) have serious side effects and have not shown to be effective in patients with other forms of pulmonary hypertension.

*****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

Please refer to certificate for availability of benefits. This policy relates only to the services or supplies described herein. Benefits may vary according to benefit design, therefore certificate language should be reviewed before applying the terms of the 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, IV infusion;
- Iloprost (VENTAVIS®) Inhalation via nebulizer;
- bosentan (TRACLEER®) oral;
- ambrisentan (LETAIRIS®) oral;
- sildenafil citrate (REVATIO®) oral.

When Pulmonary Hypertension Drug Management is not covered

Combination therapy is considered **investigational** for the treatment of pulmonary arterial hypertension, except when changing from one treatment to another.

The use of epoprostenol, treprostinil, iloprost, bosentan, ambrisentan, or sildenafil is considered **investigational** for the treatment of non-PAH PH conditions (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;

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- Miscellaneous group (i.e. sarcoidosis, histiocytosis X and lymphangiomatosis).

The use of tadalafil (CIALIS®) and vardenafil (LEVITRA®) is considered investigational for the treatment of pulmonary arterial hypertension (WHO Group 1) and non-PAH PH conditions (WHO Groups 2-5).

Policy Guidelines

Treatment with epoprostenol requires three steps as follows:

- Initial dose-ranging study, which is typically performed as an inpatient. The pulmonary capillary wedge pressure is monitored, the infusion rate of the drug is increased until dose-limiting pharmacologic effects such as nausea, vomiting or headache are elicited. Some practitioners may consider the initial dose-ranging study optional.
- Insertion of central venous catheter and attachment to portable infusion pump. Since rebound pulmonary hypertension may recur if the drug is abruptly withdrawn, the drug labeling advises that all patients should have access to a backup infusion pump and intravenous infusion set.
- Ongoing maintenance of portable infusion pump and treatment of complications related to the pump. Complications include catheter thrombosis, sepsis, and pump malfunction. In the 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.

New York Heart Association (NYHA) Functional Classification

Class I	Ordinary physical activity does not cause symptoms
Class II	Comfortable at rest, ordinary physical activity causes symptoms
Class III	Comfortable at rest, less than ordinary activity causes symptoms
Class IV	Symptoms at rest

World Health Organization (WHO) Functional Classification for PAH

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	Unable to perform any physical activity without symptoms; dyspnea and/or fatigue present at rest; discomfort increased by any physical activity

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

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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 Codes: J1325, J3285, K0455, 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

Specialty Matched Consultant Advisory Panel - 5/2003

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

Badesch DB, Abman SH, Aherarn 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

Policy Implementation/Update Information

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| 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. |

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- 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)

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.