Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product line, group, or contract. Some medications may be subject to precertification, age, quantity, or formulary restrictions (ie limits on non-preferred drugs). Individual member benefits must be verified.

This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be updated, but also when applying it to current requests for coverage.

Members are advised to use participating pharmacies in order to receive the highest level of benefits.

**Intent:**
The intent of this policy is to communicate the medical necessity criteria for sildenafil (Revatio®), tadalafil (Adcirca®), riociguat (Adempas®), ambrisentan (Letairis®), bosentan (Tracleer®), macitentan (Opsumit®), treprostinil (Orenitram®/Tyvaso®), iloprost (Ventavis®) and selexipag (Uptravi®) as provided under the member's prescription drug benefit.

**Description:**
Pulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure greater than or equal to 25 mmHg at rest. PH is categorized into 5 groups based on similar clinical presentation, pathological findings, hemodynamic characteristics, and treatment strategies.

<table>
<thead>
<tr>
<th>Group</th>
<th>Clinical classification</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pulmonary artery hypertension (PAH)</td>
<td>Idiopathic (IPA), heritable (HPA), drug and toxin induced, associated (APA) [connective tissue disease, HIV, portal hypertension, congenital heart disease (eg Eisenmenger's syndrome, systemic-to-pulmonary shunts), schistosomiasis]</td>
</tr>
<tr>
<td>2</td>
<td>PH due to left heart disease</td>
<td>Left ventricular systolic or diastolic dysfunction, valvular disease, congenital/ acquired left heart inflow/ outflow tract obstruction, congenital cardiomyopathies, congenital/</td>
</tr>
<tr>
<td></td>
<td>PH due to lung disease and/or hypoxia</td>
<td>Chronic obstructive pulmonary disease, interstitial lung disease, sleep-disordered breathing</td>
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</tr>
<tr>
<td>3</td>
<td>Chronic thromboembolic PH (CTEPH) and other pulmonary artery obstruction</td>
<td>CTEPH, other obstructions (eg angiosarcoma, tumors, arteritis)</td>
</tr>
<tr>
<td>4</td>
<td>PH with unclear and/or multifactorial mechanisms</td>
<td>Hematological disorders, sarcoidosis, metabolic disorders</td>
</tr>
</tbody>
</table>

PAH is a rare disease, with an estimated prevalence of 15-50 cases per million. The mean age at diagnosis is around 45 years, although the onset of symptoms can occur at any age. Despite the true relative prevalence of IPAH, HPAH and APAH being unknown, it is likely that IPAH accounts for at least 40% of PAH cases, with APAH accounting for the majority of the remaining cases. Due to the non-specific nature of the symptoms, PAH is unfortunately most frequently diagnosed when patients have reached an advanced stage of disease (WHO Functional Class III and IV). The goal of therapy for PAH is achieving good exercise capacity, good quality of life, good right ventricular function, and low mortality risk. Medications used to treat PAH include high dose calcium channel blockers in those who are vasoreactive or phosphodiesterase-5 inhibitors, endotherlin receptor antagonists, prostacyclin receptor analogs, prostacyclin receptor agonists, and guanylate cyclase stimulators.

CTEPH has an estimated prevalence of 3.2 cases per million. The mean age at diagnosis is 63 years. Surgery is the preferred treatment for CTEPH. For those in whom surgery is not an option or in whom surgery has failed, guanylate cyclase stimulators may be indicated.

**Sildenafil (Revatio®), tadalafil (Adcirca®), riociguat (Adempas®), macitentan (Osumit®), bosentan (Tracleer®), ambrisentan (Letairis®), and treprostinil (Orenitram®/Tyvaso®)** are indicated for the treatment of pulmonary arterial hypertension (World Health Organization [WHO] Group I) to improve exercise ability.

**Riociguat (Adempas®)** is also indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (World Health Organization [WHO] group 4), after surgical treatment or inoperable chronic thromboembolic pulmonary hypertension, to improve exercise capacity and WHO functional class.

**Ambrisartan (Letairis®)** is also indicated in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.

**Selexipag (Uptravi®)** is indicated for the treatment of PAH (WHO Group I) to delay disease progression and reduce hospitalization.

**Iloprost (Ventavis)** is indicated for the treatment of PAH (WHO group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms, and lack of deterioration.

**Sildenafil (Revatio®) and tadalafil (Adcirca®)** are selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase-5 (PDE5) in the smooth muscle of the
pulmonary arteries, where cGMP is degraded by PDE5. As a result, increases cGMP within the pulmonary arteries, causing relaxation and vasodilation of the pulmonary arteries.

**Riociguat (Adempas®)** has a dual mode of action for vasodilation. It sensitizes soluble guanylate cyclase (sGC) to endogenous nitric oxide (NO) by stabilizing the NO-sGC binding and also directly stimulates sGC independent of NO.

**Macitentan (Opsumit®), bosentan (Tracleer®), and ambrisentan (Letairis®)** block endothelin (ET)–1 from binding to endothelin receptor subtypes ET$_A$ and ET$_B$ on vascular endothelium and smooth muscle. Stimulation of these receptors is associated with vasoconstriction, fibrosis, proliferation, hypertrophy, and inflammation.

**Treprostinil (Orenitram®, Tyvaso®), and iloprost (Ventavis®)** are prostacyclin analogues. The major pharmacologic actions are direct vasodilation of pulmonary and systemic arterial vascular beds, inhibition of platelet aggregation, and inhibition of smooth muscle cell proliferation.

**Selexipag (Uptravi®)** is a prostacyclin receptor agonist that works at the same pathway as the prostacyclin analogues, but activates the IP receptor. It is one of two orally administered agents that work within the prostacyclin pathway.

**Policy:**

Tadalafil (Adcirca®) and sildenafil (Revatio®) are approved when all of the following inclusion criteria are met:

A. Documentation of a diagnosis of pulmonary arterial hypertension (PAH) WHO Group I with New York Heart Association (NYHA) Functional Class II or III; and
B. Diagnosis confirmed by catheterization (right-heart or Swan-Ganz) or echocardiography; and
C. Documentation of mean pulmonary artery pressure greater than 25 mm Hg at rest or greater than 30 mm Hg with exertion; and
D. No concurrent use of nitrates or other contraindicated medications for the drug requested, unless recommended by a cardiologist or pulmonologist; and
E. Inadequate response or inability to tolerate generic sildenafil (applies to Revatio® only)

**Bosentan (Tracleer®), Ambrisentan (Letairis®) and macitentan (Opsumit®)** are approved when ALL of the following inclusion criteria are met:

A. Diagnosis of pulmonary arterial hypertension (PAH) WHO Group I with New York Heart Association (NYHA) Functional Class II – IV; and
B. Diagnosis confirmed by catheterization (right-heart or Swan-Ganz) or echocardiography; and
C. Mean pulmonary artery pressure greater than 25 mm Hg at rest or greater than 30 mm Hg with exertion

**Treprostinil (Orenitram®, treprostinil (Tyvaso®) and iloprost (Ventavis®)** are approved when ALL of the following inclusion criteria are met:

A. Diagnosis of pulmonary arterial hypertension (PAH) WHO Group I with New York Heart Association (NYHA) Functional Class II – IV; and
B. Diagnosis confirmed by catheterization (right-heart or Swan-Ganz) or echocardiography; and
C. Mean pulmonary artery pressure greater than 25 mm Hg at rest or greater than 30 mm Hg with exertion

**Riociguat (Adempas®)** is approved when ALL of the following criteria are met:
A. Member has a diagnosis of ONE of the following:
   1. Pulmonary arterial hypertension (PAH) WHO Group I with New York Heart Association (NYHA) Functional Class II – IV; or
   2. Persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (WHO Group 4) after surgical treatment or inoperable CTEPH; and

B. Diagnosis confirmed by catheterization (right-heart or Swan-Ganz) or echocardiography; and

C. Documentation of mean pulmonary artery pressure greater than 25 mm Hg at rest or greater than 30 mm Hg with exertion; and

D. No concurrent use of specific (i.e. sildenafil) or non-specific (i.e. dipyridamole, theophylline) phosphodiesterase inhibitors; and

E. No concurrent use of nitrates or nitric oxide donors (i.e. amyl nitrite)

Selexipag (Uptravi®) is approved when ALL of the following documentation is provided:

A. Diagnosis of pulmonary arterial hypertension (PAH) WHO Group I with New York Heart Association (NYHA) Functional Class II-IV; and

B. Diagnosis confirmed by catheterization (right-heart or Swan-Ganz) or echocardiography; and

C. Documentation of mean pulmonary artery pressure greater than 25 mm Hg at rest or greater than 30 mm Hg with exertion; and

D. Inadequate response or inability to tolerate TWO of the following:
   1. Endothelin Receptor Antagonist
   2. Phosphodiesterase Type 5 Inhibitor (sildenafil if naïve to the class)
   3. Riociguat (Adempas®); and

E. Not taken in combination with a prostanoid/prostacyclin analogue (e.g. epoprostenol, iloprost, treprostinil)

Initial authorization: 6 months

Reauthorization criteria: Documentation of stabilization or improvement as evaluated by a cardiologist or pulmonologist

Reauthorization duration: 12 months

Black Box Warning:

Adempas®, Opsumit®, Tracleer® and Letairis®:
All available through risk evaluation and mitigation strategy (REMS) program.

Embryo-fetal toxicity:
Do not administer riociguat, macitentan, ambrisentan, or bosentan to a pregnant patient because they may cause fetal harm.

Female patients of reproductive potential: Exclude pregnancy prior to starting treatment and monthly during treatment. Prevent pregnancy during treatment and for 1 month after stopping treatment by using acceptable methods of contraception.

Tracleer®:
Hepatotoxicity:
Measure liver aminotransferases prior to initiation of treatment and then monthly.

Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 x ULN.
Guidelines:
Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are) covered under the prescription drug benefits of the Company's products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are experimental/investigational or cosmetic are benefit contract exclusions for all products of the Company.

References:


<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adcirca®</td>
<td>tadalafil</td>
</tr>
<tr>
<td>Adempas®</td>
<td>riociguat</td>
</tr>
<tr>
<td>Letaris®</td>
<td>ambrisentan</td>
</tr>
<tr>
<td>Opsumit®</td>
<td>macitentan</td>
</tr>
<tr>
<td>Orenitram®</td>
<td>treprostinil</td>
</tr>
<tr>
<td>Revatio®</td>
<td>sildenafil</td>
</tr>
<tr>
<td>Tracleer®</td>
<td>bosentan</td>
</tr>
<tr>
<td>Tyvaso®</td>
<td>treprostinil</td>
</tr>
<tr>
<td>Upravi®</td>
<td>selexipag</td>
</tr>
<tr>
<td>Ventavis®</td>
<td>iloprost</td>
</tr>
</tbody>
</table>

Applicable Drugs:
Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

Cross References:
N/A

Policy Version Number: 12.00

P&T Approval Date: January 11, 2018

Policy Effective Date: April 01, 2018

Next Required Review Date: January 11, 2019

The Policy Bulletins on this web site were developed to assist Independence Blue Cross (“Independence”) in administering the provisions of the respective benefit programs, and do not constitute a contract. If you have coverage through the Independence organization, please refer to your specific benefit program for the terms, conditions, limitations and exclusions of your coverage. Independence does not provide health care services, medical advice or treatment, or guarantee the outcome or results of any medical services/treatments. The facility and professional providers are responsible for providing medical advice and treatment. Facility and professional providers are independent contractors and are not employees or agents of Independence.