A. SUBJECT
Pulmonary Arterial Hypertension
- Endothelin Receptor Antagonist
  - Ambrisentan (Letairis)
  - Bosentan (Tracleer)
  - Macitentan (Opsumit)
- Phosphodiesterase Type 5 inhibitors
  - Tadalafil (Adcirca)
  - Sildenafil citrate (Revatio) Oral and Infusion
- Soluble Guanylate Cyclase (sGC) Stimulator
  - Riociguat (Adempas)
- Peripheral Vasodilators
  - Treprostinil (Remodulin) Infusion
  - Treprostinil (Tyvaso) Inhalation
  - Epoprostenol (Flolan, Velentri) Infusion
  - Iloprost (Ventavis) Inhalation
  - Treprostinil (Orenitram)
- Prostacyclin receptor agonist
  - Selexipag (Uptravi) Oral

B. BACKGROUND
The CareSource Medication Policies are therapy class policies that are used as a guide when determining health care coverage for our members with benefit plans covering prescription drugs. Medication Policies are written on selected prescription drugs requiring prior
authorization or Step-Therapy. The Medication Policy is used as a tool to be interpreted in conjunction with the member’s specific benefit plan.

**Endothelin Receptor Antagonists** are competitive antagonist at endothelin receptor types ETA and ETB. Endothelin-1 (ET-1) is a neurohormone, the effects of which are mediated by binding to ETA and ETB receptors in the endothelium and vascular smooth muscle. ET-1 concentrations are elevated in plasma and lung tissue of patients with pulmonary arterial hypertension, suggesting a pathogenic role for ET-1 in this disease.

**Phosphodiesterase Type 5 inhibitors** inhibit the phosphodiesterase type 5 (PDE5), the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP). Pulmonary arterial hypertension is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations in the pulmonary vascular smooth muscle. PDE5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 increases the concentrations of cGMP resulting in relaxation of pulmonary vascular smooth muscle cells and vasodilation of the pulmonary vascular bed.

**Soluble Guanylate Cyclase (sGC) Stimulator** stimulates soluble guanylate cyclase (sGC), an enzyme in the cardiopulmonary system and the receptor for nitric oxide (NO). When NO binds to sGC, the enzyme catalyzes synthesis of the signaling molecule cyclic guanosine monophosphate (cGMP). Intracellular cGMP plays an important role in regulating processes that influence vascular tone, proliferation, fibrosis and inflammation. Pulmonary hypertension is associated with endothelial dysfunction, impaired synthesis of nitric oxide and insufficient stimulation of the NO-sGC-cGMP pathway. Riociguat has a dual mode of action. It sensitizes sGC to endogenous NO by stabilizing the NO-sGC binding. Riociguat also directly stimulates sGC via a different binding site, independently of NO.

**Peripheral Vasodilators** are direct vasodilators of pulmonary and systemic arterial vascular beds, and inhibition of platelet aggregation.

**Prostacyclin receptor (IP receptor)** are agonist that is structurally distinct from prostacyclin. Selexipag is hydrolyzed by carboxylesterase 1 to yield its active metabolite, which is approximately 37-fold as potent as selexipag. Selexipag and the active metabolite are selective for the IP receptor versus other prostanoid receptors (EP1-4, DP, FP and TP).

The intent of the **pulmonary arterial hypertension (PAH)** program is to encourage appropriate selection of patients for therapy according to product labeling and/or clinical guidelines and/or clinical studies, and also to encourage use of preferred agents.

C. **DEFINITIONS**

- **Chronic Thromboembolic Pulmonary Hypertension (CTEPH):** High blood pressure in the pulmonary arteries that lasts six months or longer. The condition often happens after there is a pulmonary embolism.

- **Pulmonary Thromboendarterectomy:** (also known as PTE). The surgery treating chronic thromboembolic pulmonary hypertension (CTEPH).

D. **POLICY**

**I. Diagnosis Criteria:**

A. Prescribed by a pulmonologist or cardiologist

B. The treatment of pulmonary hypertension is considered medically necessary when **ALL** of the following criteria are met.
1. Documented diagnosis of pulmonary arterial hypertension confirmed by right heart catheterization and ALL of the following:
   1.1 Pretreatment mean pulmonary arterial pressure at rest ≥ 25 mmHg
   1.2 Pretreatment pulmonary capillary wedge pressure ≤ 15 mmHg
   1.3 Pretreatment pulmonary vascular resistance > 3 Wood units
2. World Health Organization functional class II, III or IV symptoms
3. Diagnosis of primary pulmonary hypertension, or has pulmonary hypertension secondary to ANY of the following conditions:
   3.1 World Health Organization group 1 pulmonary arterial hypertension, associated with one (1) or more of the following:
      a. Chronic hemolytic anemia
      b. Congenital heart disease
      c. Connective tissue diseases, including systemic sclerosis
      d. Drugs or toxins (e.g., fenfluramine, methamphetamine, cocaine)
      e. Family history, including mutation in BMPR2 gene
      f. HIV infection
      g. Idiopathic pulmonary arterial hypertension
      h. Portal hypertension
      i. Pulmonary capillary hemangiomatosis
      j. Pulmonary veno-occlusive disease
      k. Schistosomiasis
   3.2 Recurrent or persistent CTEPH diagnosed by right heart catheterization and has undergone PEA or has inoperable CTEPH

II. Treatment Criteria:
CareSource will approve the use of ambrisentan (Letairis) and bosentan (Tracleer), and macitentan (Opsumit) consider their use as medically necessary for pulmonary arterial hypertension, when the following criteria have been met for:
A. Endothelin Receptor Antagonist
   1. Prior Authorization Criteria:
      1.1 Patient must be 18 years or older for Letairis or 12 years of age and older for Tracleer and Opsumit
      1.2 WHO Group 1 with NYHA class II or III for Letairis and Opsumit or II through IV for Tracleer
      1.3 Pulmonary arterial pressure not adequately controlled using an oral vasodilator (e.g. calcium channel blocker) at maximal doses OR the patient was not vasodilator sensitive as determined by an epoprostenol, adenosine, or inhaled nitric oxide challenge

B. Phosphodiesterase Type 5 inhibitors and Soluble Guanylate Cyclase (sGC) Stimulator tadalafil (Adcirca), sildenafil citrate (Revatio), and riociguat (Adempas)
   1. Prior Authorization Criteria:
      1.1 Patient must be 18 years or older
      1.2 WHO Group 1 with NYHA Functional class II or III symptoms
      1.3 PAP pressures not adequately controlled using an oral vasodilator (e.g. calcium channel blocker) at maximal doses or the patient was not vasodilator sensitive as determined by an epoprostenol, adenosine, or inhaled nitric oxide challenge

C. Peripheral Vasodilators Prior Authorization Criteria:
   1. Epoprostenol sodium (Flolan, Veleti) continuous intravenous infusion is
considered **medically necessary** as a treatment for individuals who meet **ALL** of the following criteria:

1.1 Age 18 years or older

1.2 Treatment as indicated by: New York Heart Association or World Health Organization functional class III symptoms and patient has not responded to specific oral therapies for pulmonary hypertension (e.g., bosentan, sildenafil) or New York Heart Association or World Health Organization functional class IV symptom

1.3 PAP pressures not adequately controlled using an oral vasodilator (e.g. calcium Channel blocker) at maximal doses or the patient was not vasodilator sensitive as determined by an epoprostenol, adenosine, or inhaled nitric oxide challenge

2. **Treprostinil sodium (Remodulin)** continuous subcutaneous infusion and continuous intravenous infusion is considered **medically necessary** as a treatment for individuals who meet **ALL** of the following criteria:

2.1 Age 18 years or older

2.2 PAP pressures not adequately controlled using an oral vasodilator (e.g. calcium Channel blocker) at maximal doses or the patient was not vasodilator sensitive as determined by an epoprostenol, adenosine, or inhaled nitric oxide challenge

2.3 Transition from another therapy for pulmonary arterial hypertension is needed, as indicated by **one (1) or more** of the following:

   a. Patient is not a candidate for or has failed to respond to other oral medications (e.g., ambrisentan, bosentan, sildenafil, tadalafil)

   b. Patient requires transition from epoprostenol

3. **Iloprost (Ventavis)** Inhalation Solution or **treprostinil (Tyvaso)** Inhalation Solution considered **medically necessary** as a treatment for individuals who meet **ALL** of the following criteria:

3.1 Age 18 years or older

3.2 New York Heart Association or World Health Organization functional class III or IV (Tyvaso is not approved for class IV) symptoms

3.3 Patient has received but not adequately responded to conventional treatment or was not candidate for conventional treatment (e.g., oxygen, anticoagulants, calcium channel blockers, diuretics).

3.4 Patient is not a candidate for or has failed to respond to **tadalafil** (Adcirca) **sildenafil citrate** (Revatio) or **riociguat** (Adempas)

4. **Treprostinil** (Orenitram) extended-release oral tablets are considered **medically necessary** as a treatment for individuals who meet **ALL** of the following criteria:

4.1 Age 18 years or older

4.2 Patient has received but not adequately responded to conventional treatment or was not a candidate for conventional treatment (e.g., oxygen, anticoagulants, calcium channel blockers, diuretics).

4.3 Patient has received but not adequately responded to other oral medications (e.g., ambrisentan, bosentan, sildenafil, tadalafil)

4.4 World Health Organization functional class II or III symptoms

D. **Selexipag (Uptravi)** oral tablets are considered **medically necessary** as a treatment for individuals who meet **ALL** of the following criteria:

1. **Prior Authorization Criteria:**

   1.1 Patient must be 18 years or older

   1.2 WHO Group 1 with NYHA class II or III

   1.3 Pulmonary arterial pressure not adequately controlled using an oral...
vasodilator (e.g., calcium channel blocker) at maximal doses OR the patient was not vasodilator sensitive as determined by an epoprostenol, adenosine, or inhaled nitric oxide challenge.

### Functional Assessment of Pulmonary Arterial Hypertension

<table>
<thead>
<tr>
<th>New York Heart Association functional classification</th>
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<tbody>
<tr>
<td><strong>Class 1:</strong> Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.</td>
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<tr>
<td><strong>Class 2:</strong> Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.</td>
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<td><strong>Class 3:</strong> Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.</td>
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<td><strong>Class 4:</strong> Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients</td>
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<thead>
<tr>
<th>World Health Organization functional assessment classification</th>
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<tbody>
<tr>
<td><strong>Class I:</strong> Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.</td>
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<tr>
<td><strong>Class II:</strong> Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.</td>
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<tr>
<td><strong>Class III:</strong> Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.</td>
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<td><strong>Class IV:</strong> Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.</td>
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ALL other uses of PAH agents above are considered experimental/investigational and therefore, will follow CareSource’s Off-Label policy.

**Note:** Documented diagnosis must be confirmed by portions of the individual’s medical record which will confirm the presence of disease and will need to be supplied with prior authorization request. These medical records may include, but not limited to test reports, chart notes from provider’s office or hospital admission notes.

Refer to the product package insert for dosing, administration and safety guidelines.

For Medicare Plan members, reference the below link to search for Applicable National Coverage Descriptions (NCD) and Local Coverage Descriptions (LCD):

If there is no NCD or LCD present, reference the CareSource Policy for coverage.

**CONDITIONS OF COVERAGE**

<table>
<thead>
<tr>
<th>HCPCS</th>
<th>J3285 – Treprostinil (Remodulin)</th>
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<tbody>
<tr>
<td>J3490, Q4074</td>
<td>Iloprost (Ventavis),</td>
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<tr>
<td>J1325</td>
<td>Epoprostenol (Flolan, Veletri)</td>
</tr>
<tr>
<td>J7686 –</td>
<td>Treprostinil, inhalation solution (Tyvaso)</td>
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</tbody>
</table>
J8499 – Treprostinil (Orenitram), Letairis, Tracleer, Adcirca, Revatio, Opsumit, Adempas, Uptravi

CPT

Step Therapy
Under some plans, including plans that use an open or closed formulary, some of the medications in this policy may be subject to step-therapy. Refer to the CareSource formulary tool or PDL for further guidance.

PLACE OF SERVICE
Office, Outpatient, Home
**Preferred place of service is in the home
This medication can be self-administered and can be billed through the pharmacy benefit

Note: CareSource supports administering inject able medications in various setting, as long as those services are furnished in the most appropriate and cost effective setting that are supportive of the patient’s medical condition and unique needs and condition. The decision on the most appropriate setting for administration is based on the member’s current medical condition and any required monitoring or additional services that may coincide with the delivery of the specific medication.

AUTHORIZATION PERIOD
Approved authorizations are valid for one (1) year. Continued treatment may be considered when the member has shown biological response to treatment. ALL authorizations are subject to continued eligibility.

D. REVIEW/REVISION HISTORY
Date Issued: 06/15/2011
Date Reviewed: 06/15/2011, 05/13/2014, 07/09/2015, 08/18/2015
Date Revised: 05/13/2014 – combined all PAH agents into one policy
05/19/2015 – Add Orenitram and Soluble Guanylate Cyclase (sGC) Stimulator to policy with other criteria changes.
07/09/2015 – Revised guidelines for therapy aligning with CMS
08/18/2015 – Revised guidelines to include diagnosis criteria
5/17/2016 – Add Uptravi new oral agent

E. REFERENCES
   http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/125036s044lbl.pdf (May 1, 2011)
   2006; 114:1417-1431.
5. Barst, R.J, MD et. al. and STRIDE-2 Study Group, Treatment of Pulmonary Arterial Hypertension with the Selective Endothelin-A Receptor Antagonist Sitaxsentan.
   http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/125036s044lbl.pdf (May 1, 2011)
21. American Heart Association, http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp

The Medical Policy Statement detailed above has received due consideration as defined in the Medical Policy Statement Policy and is approved.