BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 5/19/2016**
SECTION: DRUGS	**LAST REVIEW DATE: 2/17/2022**
	LAST CRITERIA REVISION DATE: 2/17/2022
	ARCHIVE DATE:

PULMONARY HYPERTENSION MEDICATIONS:
ADCIRCA® (tadalafil) oral
ADEMPAS® (riociguat) oral
ALYQ (tadalafil) oral
Ambrisentan oral
Bosentan oral
LETAIRIS® (ambrisentan) oral
OPSUMIT® (macitentan) oral
ORENITRAM® (treprostinil) oral
REVATIO® (sildenafil) oral
Sildenafil oral
Tadalafil oral
TRACLEER® (bosentan) oral
TYVASO® (treprostinil) inhalation
UPTRAVI® (selexipag) oral
VENTAVIS® (iloprost) inhalation

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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PULMONARY HYPERTENSION MEDICATIONS

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

Criteria:

Section A. Applies for ALL Pulmonary Hypertension agents:

- **Criteria for initial therapy:** Pulmonary Hypertension (PH) agent is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Pulmonologist **or** a Pulmonary Hypertension Association (PHA)-certified **or** equivalent provider **or** Cardiologist

  2. Age of individual is consistent with the FDA approved product labeling

  3. Confirmed diagnosis of **ONE** of the following:
     a. For Pulmonary Arterial Hypertension: right heart catheterization documents **ALL** of the following:
        i. Mean pulmonary artery pressure (mPAP) > 20 mm Hg at rest
        ii. Pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg
        iii. Pulmonary vascular resistance (PVR) ≥ 3 Wood units

     b. For Chronic thromboembolic pulmonary hypertension: right heart catheterization documents **ALL** of the following:
        i. Mean pulmonary artery pressure (mPAP) > 20 mm Hg at rest
        ii. Pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg
        iii. Pulmonary vascular resistance (PVR) ≥ 3 Wood units

iv. Thromboembolic occlusion of the proximal or distal pulmonary vasculature presumed to be causing the pulmonary hypertension

4. Baseline vasoreactivity testing was negative or non-responsive (**does not apply** for Chronic thromboembolic pulmonary hypertension)

5. Requested agent will be utilized as **ONE** of the following:
    a. Initial monotherapy
    b. Initial dual therapy when the request is for ambrisentan and tadalafil (See Section B and C)
    c. Add-on to existing therapy when **BOTH** of the following are present:
        i. Individual is experiencing unacceptable or deteriorating clinical status despite pharmacotherapy
        ii. Requested agent is in a different pharmacologic class with a different mechanism of action

6. There are **NO** FDA-label contraindications (See Definitions section)

7. For agents that have a Risk Evaluation and Mitigation Strategy (REMS) program, individual, provider, and dispensing Pharmacy are enrolled

8. There are no significant interacting drugs

9. Meets <u>other initial criteria</u> as described below in Sections B-G below
    a. See section B – for Revatio, Sildenafil, Adcirca, Alyq, or Tadalafil
    b. See section C – for Ambrisentan, Letairis, Bosentan, Tracleer, or Opsumit
    c. See section D – for Adempas
    d. See section E – for Orenitram
    e. See section F – for Uptravi
    f. See section G – for Inhaled Tyvaso
    g. See section H – for Inhaled Ventavis
    h. See Evidence Based Coverage Guideline – for Flolan, Veletri, Remodulin

- **<u>Criteria for continuation of coverage (renewal request)</u>:** Pulmonary Hypertension (PH) agent is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Pulmonologist **or** a Pulmonary Hypertension Association (PHA)-certified **or** equivalent provider **or** Cardiologist

2. Individual's condition responded while on therapy
    a. Response is defined as **ONE** of the following:
        i. Is clinically stable or condition would destabilize if not continued
        ii. 6MWD stabilized or improved
        iii. NYHA Functional Class symptoms stabilized or improved
        iv. Reduced hospitalizations for PH

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use

5. There are no significant interacting drugs

6. For agents that have a Risk Evaluation and Mitigation Strategy (REMS) program, individual, provider, and dispensing Pharmacy are enrolled

7. Meets other continuation criteria as described in Sections B-G below
   a. See section B – for Revatio, Sildenafil, Adcirca, Alyq, or Tadalafil
   b. See section C – for Ambrisentan, Letairis, Bosentan, Tracleer, or Opsumit
   c. See section D – for Adempas
   d. See section E – for Orenitram
   e. See section F – for Uptravi
   f. See section G – for Inhaled Tyvaso
   g. See section H – for Inhaled Ventavis
   h. See Evidence Based Coverage Guideline – for Flolan, Veletri, Remodulin

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guidelines:

  1. **Off-Label Use of Non-cancer Medications**

  2. **Off-Label Use of Cancer Medications**

Section B. Phosphodiesterase type-5 (PDE5) inhibitors: ADCIRCA (tadalafil) ALYQ (tadalafil) REVATIO (sildenafil) Sildenafil generic Tadalafil generic

- **Criteria for initial therapy:** Adcirca (tadalafil), Alyq (tadalafil), tadalafil generic, Revatio (sildenafil) or sildenafil generic are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Meets other initial criteria as described in Section A above

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2. A confirmed diagnosis of pulmonary arterial hypertension (PAH, WHO Group I) with Functional Class II-III symptoms (documentation of WHO Group and Functional Class category must be submitted with request. See Definitions section)

3. **For Revatio (sildenafil) and Adcirca (tadalafil):** Individual has failure, contraindication per FDA label or intolerance to **ONE** of the following:
    a. generic oral sildenafil
    b. oral Alyq (tadalafil) or generic oral tadalafil 20mg

4. **Additional for Adcirca, Alyq, and generic tadalafil only:** Individual does not have severe renal impairment (creatinine clearance less than 30 mL/min or on hemodialysis)

5. Individual does not have severe hepatic impairment (Child-Pugh Class C)

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Adcirca, Alyq, Tadalafil, Revatio or Sildenafil, therapy are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Meets continuation criteria as described in Section A above

2. Has not developed significant adverse effects such as:
    a. Sudden loss of vision in one or both eyes
    b. Sudden decrease or loss of hearing
    c. Priapism or erection lasting more than 4-hours
    d. Pulmonary edema
    e. Vaso-occlusive crisis

3. **Additional for Adcirca, Alyq, and generic tadalafil only:** Individual does not have severe renal impairment (creatinine clearance less than 30 mL/min or on hemodialysis)

4. Individual does not have severe hepatic impairment (Child-Pugh Class C)

Renewal duration: 12 months

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Section C. Endothelin receptor antagonists (ERAs):
Ambrisentan generic
Bosentan generic
LETAIRIS (ambrisentan)
OPSUMIT (macitentan)
TRACLEER (bosentan)

- **Criteria for initial therapy:** Letairis (ambrisentan), Ambrisentan generic, Opsumit (macitentan), Tracleer (bosentan) or Bosentan generic are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:
  1. Meets other initial criteria as described in Section A above

  2. A confirmed diagnosis of **ONE** of the following:
     a. **Ambrisentan (brand Letairis or generic) monotherapy or with tadalafil (See Section B for criteria):** An individual with a confirmed diagnosis of pulmonary arterial hypertension (PAH, WHO Group 1) with Functional Class II-III symptoms (documentation of WHO Group and Functional Class category must be submitted with request. See Definitions section)

     b. **For Bosentan (brand Tracleer or generic) monotherapy or with a PDE5 inhibitor (See Section B for criteria)**: An individual with a confirmed diagnosis of idiopathic or congenital pulmonary arterial hypertension (PAH, WHO Group 1) **OR** PAH (WHO Group 1) with Functional Class II-IV symptoms (documentation of WHO Group and Functional Class category must be submitted with request. See Definitions section)

     c. **For Opsumit monotherapy or with PDE5 inhibitor (See Section B for criteria) or with inhaled prostanoid (See Section G for criteria)**: An individual with a confirmed diagnosis of pulmonary arterial hypertension (PAH, WHO Group 1) with Functional Class II-III symptoms (documentation of WHO Group and Functional Class category must be submitted with request. See Definitions section)

  3. **For Letairis, Bosentan (brand Tracleer or generic) and Opsumit**: Individual has failure, contraindication per FDA label, or intolerance to generic ambrisentan

  Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Ambrisentan, Letairis, Bosentan, Tracleer, or Opsumit therapy are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Meets continuation criteria as described in Section A above

  2. Has not developed significant adverse effects such as:

a. Pulmonary veno-occlusive disease
b. Fluid retention requiring hospitalization for decompensating heart failure
c. Severe anemia
d. Pulmonary edema with pulmonary veno-occlusive disease
e. Liver toxicity

Renewal duration: 12 months

Section D. Guanylate cyclase stimulator: ADEMPAS (riociguat)

- **Criteria for initial therapy:** Adempas (riociguat) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Meets other initial criteria as described in Section A above

2. A confirmed diagnosis of **ONE** of the following:
    a. Persistent or recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH, WHO group 4) after surgical treatment or is not an operable candidate, to improve exercise capacity and WHO functional class

    b. Pulmonary arterial hypertension (PAH, WHO group 1) with Functional Class II-III symptoms to improve exercise capacity, improve WHO functional class and to delay clinical worsening (documentation of WHO Group and Functional Class category must be submitted with request. See Definitions section) used as **monotherapy or in combination with an endothelin receptor antagonist** (See Section C for criteria) **or prostanoid** (See Section G for criteria)

3. Individual does not have severe renal impairment (creatinine clearance less than 15 mL/min or on hemodialysis)

4. Individual does not have severe hepatic impairment (Child-Pugh Class C)

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Adempas (riociguat) therapy is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Meets continuation criteria as described in Section A above

2. Has not developed significant adverse effects such as:
    a. Pulmonary edema with pulmonary veno-occlusive disease
    b. Severe bleeding
    c. Liver toxicity

3. ndividual does not have severe renal impairment (creatinine clearance less than 15 mL/min or on hemodialysis)

4. Individual does not have severe hepatic impairment (Child-Pugh Class C)

Renewal duration: 12 months

Section E. Oral prostacyclin analogue: ORENITRAM (treprostinil)

- **Criteria for initial therapy:** Orenitram (treprostinil) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Meets other initial criteria as described in Section A above

  2. A confirmed diagnosis of pulmonary arterial hypertension (PAH, WHO group 1), with Functional Class II-III symptoms, to improve exercise capacity (documentation of WHO Group and Functional Class category must be submitted with request. See Definitions section)

  3. Individual has failure, contraindication per FDA label, or intolerance to oral generic sildenafil

  4. Individual has failure, contraindication per FDA label, or intolerance to use **ONE** oral Endothelin Receptor Antagonist [ambrisentan (brand Letairis or generic), bosentan (brand Tracleer or generic), Opsumit (macitentan)] **OR** Adempas (riociguat)

  5. Will not be used with other prostacyclin analogs (such as epoprostenol, iloprost) or prostacyclin receptor agonists (such as selexipag) or with other treprostinil dose forms (such as subcutaneous, intravenous, or inhalation)

  6. Individual does not have moderate hepatic impairment (Child-Pugh Class B) [**Note:** it is contraindicated for use in severe hepatic impairment]

  Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Orenitram (treprostinil) therapy is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Meets continuation criteria as described in Section A above

  2. Has not developed significant adverse effects such as:
     a. Severe bleeding

3. Individual does not have moderate hepatic impairment (Child-Pugh Class B) [**Note:** it is contraindicated for use in severe hepatic impairment]

Renewal duration: 12 months

Section F. Prostacyclin receptor agonist: UPTRAVI (selexipag)

- **Criteria for initial therapy:** Uptravi (selexipag) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Meets other initial criteria as described in Section A above

2. Provider is a physician specializing in the patient's diagnosis or is in consultation with a Pulmonologist or a Pulmonary Hypertension Association-certified or equivalent physician at a Pulmonary Hypertension Association (PHA) accredited Pulmonary Hypertension Care Center (PHCC)[1] that is **ONE** of the following:
    a. Center of Comprehensive Care (CCC)[1, 2]
    b. Regional Clinical Program (RCP)[1, 2]
    c. An equivalent center[2]

3. A confirmed diagnosis of pulmonary arterial hypertension (PAH, WHO Group 1) with Functional Class II-III symptoms to delay disease progression and reduce the risk of hospitalization (documentation of WHO Group and Functional Class category must be submitted with request. See Definitions section)

4. Individual has failure, contraindication per FDA label, or intolerance to generic oral sildenafil

5. Individual has failure, contraindication per FDA label, or intolerance to **ONE** oral Endothelin Receptor Antagonist [ambrisentan (brand Letairis or generic), bosentan (brand Tracleer or generic), Opsumit (macitentan)] **OR** Adempas (riociguat)

6. Will not be used with prostacyclin analogs prostacyclin analogs (such as epoprostenol, iloprost, treprostinil)

7. Individual does not have severe renal impairment (creatinine clearance less than 15 mL/min or on hemodialysis)

8. Individual does not have severe hepatic impairment (Child-Pugh Class C)

Initial approval duration:
- If the individual has **NOT** been seen by a PHA-certified or equivalent provider within the last 6 months **AND** the request is for initial **OR** continuation of therapy:
    - 60-day transition of care period to permit ample time to be seen by a PHA-certified or equivalent provider

- If seen by a PHA-certified or equivalent provider: 12 months

[1] For a list of PHA-certified providers, go to www.phassociation.org/patients/findadoctor.

[2] If an individual has not been seen within 6 months but needs to continue therapy or begin initial therapy, a limited authorization will be given to allow sufficient time for the individual to be evaluated by a PHA-accredited provider affiliated with a CCC or RCP or by a provider with advanced training in the management of pulmonary hypertension at an equivalent center. Individuals in an active course of treatment will be allowed a 60-day transition of care period to permit ample time to consult with a PHA-certified or equivalent provider. The diagnosis of PAH must be confirmed by the PHA-certified or equivalent provider. Individuals with ongoing therapy must have an appointment with a CCC or RCP center or equivalent center at least yearly or more often as deemed clinically appropriate by the provider.

➢ **Criteria for continuation of coverage (renewal request):** Uptravi (selexipag) therapy is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Meets continuation criteria as described in Section A above
2. Has not developed significant adverse effects such as:
   a. Pulmonary edema with pulmonary veno-occlusive disease
3. Individual does not have severe renal impairment (creatinine clearance less than 15 mL/min or on hemodialysis)
4. Individual does not have severe hepatic impairment (Child-Pugh Class C)

Renewal duration: If seen by a PHA-certified or equivalent provider: 12 months

Section G. INHALED TYVASO (treprostinil):

➢ **Criteria for initial therapy:** Inhaled Tyvaso (treprostinil) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Meets other initial criteria as described in Section A above
2. Provider is a physician specializing in the patient's diagnosis or is in consultation with a Pulmonologist or a Pulmonary Hypertension Association-certified or equivalent physician at a Pulmonary Hypertension Association (PHA) accredited Pulmonary Hypertension Care Center (PHCC)[1] that is **ONE** of the following:
   a. Center of Comprehensive Care (CCC)[1, 2]
   b. Regional Clinical Program (RCP)[1, 2]
   c. An equivalent center [2]
3. A confirmed diagnosis of **ONE** of the following:

a. Pulmonary arterial hypertension (PAH, WHO Group 1) with continued or advancing NYHA Functional Class III symptoms despite therapy with an Endothelin Receptor Antagonist [ambrisentan (brand Letairis or generic), bosentan (brand Tracleer or generic), Opsumit (macitentan)] or PDE5 inhibitor [sildenafil (brand Revatio or generic), tadalafil (brand Adcirca or Alyq or generic)] **OR** has NYHA Functional Class IV symptoms (documentation of WHO Group and Functional Class category must be submitted with request. See Definitions section)

b. Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability, predominately in patients with etiologies of idiopathic interstitial pneumonia (IIP) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) and WHO Group 3 connective tissue disease

4. Will not be used with other prostacyclin analogs (such as epoprostenol, iloprost, other forms of treprostinil) or prostacyclin receptor agonists (such as selexipag)

Initial approval duration:

- If the individual has **NOT** been seen by a PHA-certified or equivalent provider within the last 6 months **AND** the request is for initial **OR** continuation of therapy:
  - 60-day transition of care period to permit ample time to be seen by a PHA-certified or equivalent provider
- If seen by a PHA-certified or equivalent provider: 12 months

[1]For a list of PHA-certified providers, go to www.phassociation.org/patients/findadoctor.

[2] If an individual has not been seen within 6 months but needs to continue therapy or begin initial therapy, a limited authorization will be given to allow sufficient time for the individual to be evaluated by a PHA-accredited provider affiliated with a CCC or RCP or by a provider with advanced training in the management of pulmonary hypertension at an equivalent center. Individuals in an active course of treatment will be allowed a 60-day transition of care period to permit ample time to consult with a PHA-certified or equivalent provider. The diagnosis of PAH must be confirmed by the PHA-certified or equivalent provider. Individuals with ongoing therapy must have an appointment with a CCC or RCP center or equivalent center at least yearly or more often as deemed clinically appropriate by the provider.

➢ **Criteria for continuation of coverage (renewal request):** Inhaled Tyvaso (treprostinil) therapy is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Meets continuation criteria as described in Section A above

2. Has not developed significant adverse effects such as:
   a. Symptomatic hypotension
   b. Syncope
   c. Bleeding

Renewal duration: 12 months, if seen by a PHA-certified or equivalent provider

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Section H. INHALED VENTAVIS (iloprost):

- **Criteria for initial therapy:** Inhaled Ventavis (iloprost) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:
  1. Meets other initial criteria as described in Section A above

  2. Provider is a physician specializing in the patient's diagnosis or is in consultation with a Pulmonologist or a Pulmonary Hypertension Association-certified or equivalent physician at a Pulmonary Hypertension Association (PHA) accredited Pulmonary Hypertension Care Center (PHCC)[1] that is **ONE** of the following:
     a. Center of Comprehensive Care (CCC)[1, 2]
     b. Regional Clinical Program (RCP)[1, 2]
     c. An equivalent center [2]

  3. A confirmed diagnosis of pulmonary arterial hypertension (PAH, WHO Group 1) with continued or advancing NYHA Functional Class III symptoms despite therapy with an Endothelin Receptor Antagonist [ambrisentan (brand Letairis or generic), bosentan (brand Tracleer or generic), Opsumit (macitentan)] or PDE5 inhibitor [sildenafil (brand Revatio or generic), tadalafil (brand Adcirca or Alyq or generic)] **OR** has NYHA Functional Class IV symptoms (documentation of WHO Group and Functional Class category must be submitted with request. See Definitions section)

  4. Will not be used with other prostacyclin analogs (such as epoprostenol, treprostinil) or prostacyclin receptor agonists (such as selexipag)

  5. Individual does not have chronic obstructive pulmonary disease, severe asthma, or acute pulmonary infection

  Initial approval duration:
  - If the individual has **NOT** been seen by a PHA-certified or equivalent provider within the last 6 months **AND** the request is for initial **OR** continuation of therapy:
    - 60-day transition of care period to permit ample time to be seen by a PHA-certified or equivalent provider
  - If seen by a PHA-certified or equivalent provider: 12 months

[1] For a list of PHA-certified providers, go to www.phassociation.org/patients/findadoctor.

[2] If an individual has not been seen within 6 months but needs to continue therapy or begin initial therapy, a limited authorization will be given to allow sufficient time for the individual to be evaluated by a PHA-accredited provider affiliated with a CCC or RCP or by a provider with advanced training in the management of pulmonary hypertension at an equivalent center. Individuals in an active course of treatment will be allowed a 60-day transition of care period to permit ample time to consult with a PHA-certified or equivalent provider. The diagnosis of PAH must be confirmed by the PHA-certified or equivalent provider. Individuals with ongoing therapy must have an appointment with a CCC or RCP center or equivalent center at least yearly or more often as deemed clinically appropriate by the provider.

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- **Criteria for continuation of coverage (renewal request):** Inhaled Ventavis (iloprost) therapy is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Meets continuation criteria as described in Section A above

  2. Has not developed significant adverse effects such as:
     a. Symptomatic hypotension
     b. Syncope
     c. Bleeding
     d. Pulmonary venous hypertension
     e. Pulmonary edema
     f. Bronchospasm

  3. Individual does not have chronic obstructive pulmonary disease, severe asthma, or acute pulmonary infection

  Renewal duration: 12 months, if seen by a PHA-certified or equivalent provider

Description:

Pulmonary hypertension (PH) may be described by restricted or reduced blood flow through the pulmonary artery, pulmonary vein, or pulmonary capillaries, leading to complaints of shortness of breath, dizziness, fainting, fatigue, chest pain, palpitations, leg swelling and other symptoms. PH is a severe progressive disease with markedly decreased exercise tolerance, heart failure and ultimately death. The rate of progression is highly variable.

PH may be categorized, using the WHO scheme, into five classes or groups based on etiology and may be further characterized using the NYHA Functional Class system modified for PH that is based on activity level and symptoms in an attempt to classify severity of disease clinically. It should be noted that while together all groups are called pulmonary hypertension, WHO Group 1 is called PAH and WHO Groups 2 through 5 are called PH. Other factors are also used to determine an individual's risk category and assessment of prognosis. WHO NYHA Functional Class I are individuals least affected by their disease while those in WHO Functional Class IV are most affected.

PAH is placed in WHO Group 1 and includes a large number of etiologies. It is important to distinguish PAH from other types of PH as PH from other causes is thought to differ pathophysiologically from PAH and may be managed differently.

The pathogenesis of PAH (WHO Group 1) is complex and incompletely understood; it is thought to involve an imbalance between vasoconstriction, vasodilation, and abnormal cellular proliferation. It includes genetic, inflammatory, and environmental factors that alter vascular structure and function in smooth muscle, endothelial cells, and adventitia. Included in this complexity are endothelial dysfunction (favoring vasoconstriction, thrombosis, and mitogenesis); increased levels of thromboxane A2, endothelin-1 (ET-1), and serotonin (5HT) which stimulate vasoconstriction, cell proliferation, and thrombosis; decreased levels of prostacyclin, nitric oxide, and vasoactive intestinal peptide (VIP) which favor vasoconstriction, cell proliferation, and thrombosis; and low

levels of other mediators such as vascular endothelial growth factor (VGEF). VEGF is a signal protein that stimulates creation of new blood vessels which restores oxygen supply to tissues when blood flow is inadequate.

The pathogenesis of pulmonary hypertension from left heart disease (WHO Group 2) is completely different. There is no obstruction to blood flow in the lungs. Instead, the left heart fails to pump blood efficiently, leading to pooling of blood causing pulmonary edema and pleural effusions. In hypoxic pulmonary hypertension (WHO Group 3), low levels of oxygen are thought to cause vasoconstriction of pulmonary arteries. In chronic thromboembolic pulmonary hypertension (CTEPH or WHO Group 4), the blood vessels are blocked or narrowed with blood clots. These last two groups also share some similar pathophysiology as seen in PAH (WHO Group 1).

A baseline assessment to determine PAH severity is performed before initiating therapy. Therapy should not be administered unless a diagnostic right heart catheterization (RHC) and extensive investigations for the etiology of PH have been performed. This assessment includes the following three key measures:

1. Functional impairment: This is determined by measuring exercising capacity and determining WHO or NYHA Functional Class.

2. Hemodynamic derangement: The diagnosis of PH can be suspected based on echocardiography. However, a RHC is performed to accurately measure hemodynamic parameters and confirm PAH. Individuals with PAH typically undergo an invasive hemodynamic assessment and an acute vasoreactivity test before the initiation of advanced therapy. The hemodynamic definition of PAH is a mean pulmonary artery pressure greater than 25 mm Hg at rest. A pulmonary arterial wedge pressure or left ventricular end-diastolic pressure of less than 15 mm Hg is needed to exclude WHO Group II PH (due to left heart disease). PAH is also supported by increased pulmonary vascular resistance and transpulmonary gradient.

3. Acute vasoreactivity test: The test involves administration of a short-acting vasodilator, then measuring hemodynamic response with a right heart catheter. An acute vasoreactivity test is considered positive if mean pulmonary artery pressure decreases by at least 10 mm Hg and to a value less than 40 mm Hg, with an increased or no change in cardiac output and a minimally reduced or no change in systemic blood pressure.

Definitions:

Pulmonary Hypertension Association (PHA):
The largest and oldest pulmonary hypertension (PH) association in the world. PHA is a community-based nonprofit support, education, advocacy and awareness association for PH.

Pulmonary Hypertension Care Centers (PHCC):
Center of Comprehensive Care (CCC):
A PHA accredited highly organized, full-time PH center that proficiently evaluates individuals with PH based on published evidence-based guidelines and provides expert treatment of individuals with PAH with all of the FDA-approved therapies. CCC also make important contributions to PH research and education.

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Regional Clinical Program (RCP):
A PHA accredited center that proficiently evaluates individuals with PH based on published evidence-based guidelines and provides expert treatment of individuals with PAH with all non-parenteral therapies. A RCP must collaborate with its regional CCC by referring individuals that may benefit from opportunities unavailable at the RCP, including the initiation of advanced parenteral therapies and participation in clinical research protocols.

WHO Group, classification of Pulmonary Hypertension (PH):

- WHO Group 1 - Pulmonary arterial hypertension (PAH)
  - Idiopathic (IPAH)
  - Heritable / Familial
    - Activin receptor-like kinase (ALK1), endoglin (with or without hereditary hemorrhagic telangiectasia)
    - Bone Morphogenic Protein Receptor type II (BMPR)
    - Unknown
  - Drug- and toxin-induced
  - Associated with (APAH):
    - Chronic hemolytic anemia (including sickle cell disease)
    - Congenital heart diseases – systemic to pulmonary shunts
    - Connective tissue disease
    - HIV infection
    - Portal hypertension
    - Schistosomiasis
  - Persistent pulmonary hypertension of the newborn
  - Associated with significant venous or capillary involvement
    - Pulmonary capillary hemangiomatosis (PCH)
    - Pulmonary veno-occlusive disease (PVOD)

- WHO Group 2 - Pulmonary hypertension owing to left heart disease
  - Left-sided arterial or ventricular heart disease
  - Left-sided valvular heart disease
  - Diastolic dysfunction
  - Systolic dysfunction

- WHO Group 3 - Pulmonary hypertension owing to lung disease and/or hypoxia
  - Alveolar hypoventilation disorders
  - Chronic exposure to high altitude
  - Chronic obstructive pulmonary disease
  - Developmental abnormalities
  - Interstitial lung disease
  - Other pulmonary diseases with mixed restrictive and obstructive pattern
  - Sleep-disordered breathing

- WHO Group 4 - Pulmonary hypertension due to Chronic thromboembolic pulmonary hypertension (CTEPH)
  - Non-thrombotic pulmonary embolism (tumor, parasites, foreign material)

- Thromboembolic obstruction of distal pulmonary arteries
- Thromboembolic obstruction of proximal pulmonary arteries

- WHO Group 5 - Pulmonary hypertension with unclear multifactorial mechanisms
  - Hematologic diseases: myeloproliferative disease, splenectomy
  - Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid diseases
  - Systemic diseases: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
  - Others: tumor obstruction, fibrosing mediastinitis, chronic renal failure on dialysis, compression of pulmonary vessels, Hemoglobinopathies, Hereditary hemorrhagic telangiectasia

WHO Functional Class (modified New York Heart Association (NYHA) for PH):

Functional Class I
No limitation in physical activity; ordinary physical activity does not cause dyspnea or fatigue

Functional Class II
Slight limitations in physical activity; ordinary physical activity produces dyspnea, fatigue, chest pain, or near-syncope; no symptoms at rest

Functional Class III
Marked limitation of physical activity; less than ordinary physical activity produces dyspnea, fatigue, chest pain, or near-syncope; no symptoms at rest

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

Therapeutic classes of drugs used to treat pulmonary hypertension:

Calcium Channel Blockers – used in a very select group of individuals
Dihydropyridine class preferred

Endothelin receptor antagonists – bind to receptors in endothelium and vascular smooth muscle
Ambrisentan (Letairis and generics) – oral
Bosentan (Tracleer and generics) – oral
Macitentan (Opsumit) – oral

Phosphodiesterase type 5 (PDE5) inhibitors – inhibit Phosphodiesterase type-5 to increased cAMP
Sildenafil (Revatio, and generics) – oral (generics available) and IV (available as brand Revatio)
Tadalafil (Adcirca, Alyq, and generics) – oral

Prostanoids – direct vasodilation of pulmonary & systemic arterial vascular beds, inhibit platelet aggregation
Epoprostenol (Flolan, Veletri, and generics) – continuous IV
Iloprost (Ventavis) – inhaled delivery system
Treprostinil:
Orenitram ER – oral
Remodulin and generics – can be SQ or IV
Tyvaso – inhaled delivery system

PULMONARY HYPERTENSION MEDICATIONS

Soluble Guanylate Cyclase Stimulators – stimulate Nitric Oxide cGMP pathway to increase cGMP
Riociguat (Adempas) – oral

Selective prostacyclin receptor (IP receptor) agonist
Selexipag (Uptravi) – oral

2016 Eur Heart J: Risk assessment in pulmonary arterial hypertension:

Low Risk patients:	Intermediate Risk patients:	High Risk patients:
Functional Class I, II No RV failure No progression of Sx No syncope 6MWD > 440 m BNP < 50 ng/L NT-proBNP < 300 ng/L Echo: RA < 18 cm^2 no pericardial effusion RAP < 8 mmHg & CI $\geq$ 2.5 L/min/m^2	Functional Class III No RV failure Slow progression of Sx Occasional syncope during brisk/heavy exercise 6MWD 165-440 m BNP < 50-300 ng/L NT-proBNP < 300-1400 ng/L Echo: RA 18-26 cm^2 no/minimal effusion RAP 8-14 mmHg & CI 2-2.4 L/min/m^2	Functional Class IV RV failure Rapid progression Repeated syncope little/regular activity 6MWD < 165 m BNP > 300 ng/L NT-proBNP > 1400 ng/L Echo: RA > 26 cm^2 pericardial effusion RAP > 14 mmHg & CI < 2 L/min/m^2

Contraindications to Pulmonary Arterial Hypertension Medications:

Agents:	FDA-labeled contraindications
Adcirca Alyq Revatio Sildenafil Tadalafil	▪ Use with any form of organic nitrate, either regularly or intermittently ▪ Use with a Guanylate Cyclase (GC) stimulator riociguat (Adempas) ▪ History of known serious hypersensitivity reactions
Ambrisentan Letairis	▪ Pregnancy ▪ Idiopathic pulmonary fibrosis, with or without pulmonary hypertension (WHO Group 3)
Opsumit	▪ Pregnancy
Bosentan Tracleer	▪ Pregnancy ▪ Use with cyclosporine or glyburide ▪ Hypersensitivity to bosentan or any component of the product
Adempas	▪ Pregnancy ▪ Use with any type of Phosphodiesterase Inhibitor (this includes specific PDE5 inhibitors, or nonspecific PDE5 inhibitors such as dipyridamole or theophylline) ▪ Use of nitrates or nitric oxide donors (such as amyl nitrite) in any form ▪ Use with other soluble guanylate cyclase (sGC) stimulators, ex. Verquvo (vericiguat) ▪ Pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP)
Orenitram	▪ Severe hepatic impairment (Child-Pugh Class C)
Uptravi	▪ Use with gemfibrozil or other strong inhibitors of CYP2C8
Tyvaso Ventavis	▪ None listed

PULMONARY HYPERTENSION MEDICATIONS

The Child-Pugh classification system:
The Child-Pugh classification is a scoring system used to determine the prognosis with cirrhosis. Scoring is based upon several factors: albumin, ascites, total bilirubin, prothrombin time, and encephalopathy, as follows:

	Score: 1 point	Score: 2 points	Score: 3 points
Serum Albumin (g/dL)	>3.5	3.0 - 3.5	<3.0
Serum Bilirubin (mg/dL)	<2.0	2.0 - 3.0	>3.0
Prothrombin time (seconds)	1 - 4	4 - 6	>6
Ascites	none	moderate	severe
Encephalopathy	none	mild	severe

The three classes and their scores are:

- **Class A** is score 5 – 6: Well compensated
- **Class B** is score 7 – 9: Significant functional compromise
- **Class C** is score > 9: Decompensated disease

Resources:

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Adempas (riociguat) product information, revised by Bayer HealthCare Pharmaceuticals, Inc. 09-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed January 26, 2022.

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Uptravi (selexipag) product information, revised by Actelion Pharmaceuticals US, Inc. 10-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed January 26, 2022.

Ventavis (iloprost) product information, revised by Actelion Pharmaceuticals US, Inc. 01-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed January 26, 2022.

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