BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

PULMONARY HYPERTENSION MEDICATIONS:
ADCIRCA (tadalafil) oral
ADEMPAS® (riociguat) oral
ALYQ (tadalafil) oral
Ambrisentan oral
Bosentan oral
LETAIRIS® (ambrisentan) oral
OPSUMIT® (macitentan) oral
OPSYNVI® (macitentan-tadalafil) oral
ORENITRAM® (treprostinil) oral
REVATIO (sildenafil) oral
Tadalafil oral
TADLIQ (tadalafil) oral
TRACLEER® (bosentan) oral
TYVASO® (treprostinil) inhalation
UPTRAVI® (selexipag) oral
VENTAVIS® (iloprost) inhalation
WINREVAIR™ (sotatercept-csrk) SQ injection
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**

ORIGINAL EFFECTIVE DATE: 05/19/2016 | ARCHIVE DATE: | LAST REVIEW DATE: 02/20/2025 | LAST CRITERIA REVISION DATE: 02/20/2025

PHARMACY COVERAGE GUIDELINE

PULMONARY HYPERTENSION MEDICATIONS

- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

Section A. Applies for ALL Pulmonary Hypertension agents:

- **Criteria for initial therapy:** Pulmonary Hypertension (PH) agent and/or generic equivalent (if available) are 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. Individual's age is consistent with the FDA approved product labeling

3. Individual has a confirmed diagnosis of **ONE** of the following:
    a. If FDA label approved 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. If FDA label approved 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. Individual's 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 (**Does not apply for** Winrevair (sotatercept))

8. There are no significant interacting drugs

9. Individual meets other initial criteria as described below in Sections B-I below
    a. See section B – for Revatio, Adcirca, Alyq, Tadliq, or Tadalafil
    b. See section C – for Ambrisentan, Letairis, Bosentan, Tracleer, Opsumit, or Opsynvi (macitentan and tadalafil)
    c. See section D – for Adempas
    d. See section E – for Winrevair
    e. See section F – for Orenitram
    f. See section G – for Uptravi
    g. See section H – for Inhaled Tyvaso
    h. See section I – for Inhaled Ventavis
    i. See Evidence Based Coverage Guideline – for Flolan, Veletri, Remodulin

- **Criteria for continuation of coverage (renewal request):** Pulmonary Hypertension (PH) agent and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

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 has responded while on therapy with response defined as **ONE** of the following:
    a. Individual clinically stable or condition would destabilize if not continued
    b. 6MWD stabilized or improved
    c. NYHA Functional Class symptoms stabilized or improved
    d. Reduced hospitalizations for PH
    e. Reduced pulmonary vascular resistance (PVR)
    f. Reduced NT-proBNP

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 (**Does not apply for** Winrevair (sotatercept))

7. Individual meets other continuation criteria as described in Sections B-I below
    a. See section B – for Revatio, Adcirca, Alyq, Tadliq, or Tadalafil
    b. See section C – for Ambrisentan, Letairis, Bosentan, Tracleer, Opsumit, or Opsynvi (macitentan and tadalafil)
    c. See section D – for Adempas

d. See section E – for Winrevair
e. See section F – for Orenitram
f. See section G – for Uptravi
g. See section H – for Inhaled Tyvaso
h. See section I – for Inhaled Ventavis
i. 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)
TADLIQ (tadalafil)
Tadalafil

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

1. Individual meets other initial criteria as described in Section A above

2. Individual has 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 Adcirca (tadalafil), Tadliq (tadalafil), and Revatio (sildenafil):** Individual has documented failure, contraindication per FDA label, intolerance or is not a candidate for **BOTH** of the following:
   a. Generic sildenafil
   b. Alyq (tadalafil) or generic tadalafil 20mg

4. **Additional for Adcirca (tadalafil), Alyq (tadalafil), Tadliq (tadalafil) 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)

6. Individual does not have pulmonary veno-occlusive disease (PVOD)

7. Individual does not have hereditary degenerative retinal disorders, including retinitis pigmentosa

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Adcirca (tadalafil), Alyq (tadalafil), Tadliq (tadalafil), tadalafil generic, Revatio (sildenafil), and/or generic equivalents (if available) therapy are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

  1. Individual meets continuation criteria as described in Section A above

  2. Individual 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. **For Adcirca (tadalafil), Tadliq (tadalafil), and Revatio (sildenafil):** Individual has documented failure, contraindication per FDA label, intolerance or is not a candidate for **BOTH** of the following:
     a. Generic sildenafil
     b. Alyq (tadalafil) or generic tadalafil 20mg

  4. **Additional for Adcirca (tadalafil), Alyq (tadalafil), Tadliq (tadalafil), 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)

  6. Individual does not have pulmonary veno-occlusive disease (PVOD)

  7. Individual does not have hereditary degenerative retinal disorders, including retinitis pigmentosa

  Renewal duration: 12 months

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

OPSYNVI (macitentan and tadalafil)
TRACLEER (bosentan)

- **Criteria for initial therapy:** Letairis (ambrisentan), ambrisentan generic, Tracleer (bosentan), bosentan generic, Opsumit (macitentan), Opsynvi (macitentan and tadalafil), and/or generic equivalents (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual meets other initial criteria as described in Section A above

  2. Individual has a confirmed diagnosis of **ONE** of the following:
     a. **Ambrisentan (brand Letairis or generic) monotherapy or combination therapy 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. **Bosentan (brand Tracleer or generic) monotherapy or combination therapy 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. **Opsumit (macitentan) monotherapy or combination therapy 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)

     d. **Opsynvi (macitentan and tadalafil):** An individual with a confirmed diagnosis of pulmonary arterial hypertension (PAH, WHO Group 1) with Functional Class II-III symptoms in an individual who has documented failure, contraindication per FDA label, intolerance, or is not a candidate for use of Opsumit (macitentan) with generic tadalafil. (Documentation of WHO Group and Functional Class category must be submitted with request. See Definitions section)

  3. Request for **brand Letairis, brand Opsumit, brand Tracleer, brand Opsynvi (macitentan and tadalafil) or bosentan generic**: Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **ambrisentan generic**

  Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Letairis (ambrisentan), ambrisentan generic, Tracleer (bosentan), bosentan generic, Opsumit (macitentan), Opsynvi (macitentan and tadalafil), and/or generic equivalents (if available) therapy are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

  1. Individual meets continuation criteria as described in Section A above

2. Request for continuation of **brand Letairis, brand Opsumit, brand Tracleer, brand Opsynvi**: Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

3. Individual 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

- 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 Guideline:

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

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

Section D. Guanylate cyclase stimulator: ADEMPAS (riociguat)

- **Criteria for initial therapy:** Adempas (riociguat) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual meets other initial criteria as described in Section A above

2. Individual has 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 a surgical candidate

    b. 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) **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) and/or generic equivalent (if available) therapy are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

  1. Individual meets continuation criteria as described in Section A above

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

  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: 12 months

- 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 Guideline:

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

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

Section E. Transforming growth factor beta pathway modulation: WINREVAIR (sotatercept-csrk)

- **Criteria for initial therapy:** Winrevair (sotatercept-csrk) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual meets other initial criteria as described in Section A above

  2. Individual has a confirmed diagnosis of pulmonary arterial hypertension (PAH, WHO group 1), with characteristic Functional Class II-III symptoms (Documentation of WHO Group and Functional Class category must be submitted with request. See Definitions section)

  3. Individual is on stable doses of a background pulmonary hypertension-specific therapy and diuretics for at least 3-months [**Note**: Background PAH-specific may consist of monotherapy or combination therapy with ERA, PDE5 inhibitors, soluble guanylate cyclase stimulators, and/or prostacyclin analogues or receptor agonists

  4. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
     a. 6-minute walk distance (6MWD) is between greater than or equal to 150 and less than or equal to 500 meters

b. Hemoglobin before each dose for the first 5 doses, or longer if values are unstable, and monitor periodically thereafter
c. Platelet count is greater than 50,000/mm^3 (or greater than 50 x 10^9/L)
d. Platelets before each dose for the first 5 doses, or longer if values are unstable, and monitor periodically thereafter
e. Negative pregnancy test in a woman of childbearing potential

5. Individual does not have
   a. Diagnosis of pulmonary hypertension WHO Groups 2, 3, 4, or 5
   b. Hemoglobin (Hgb) above gender-specific upper limit of normal (ULN)

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Winrevair (sotatercept-csrk) and/or generic equivalent (if available) therapy are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual meets continuation criteria as described in Section A above

2. Individual has not developed significant adverse effects such as:
   a. Erythrocytosis which increases risk for thromboembolic events and hyperviscosity
   b. Severe thrombocytopenia which increases risk for severe bleeding
   c. Serious bleeding events (gastrointestinal, intracranial)

3. Individual does not have
   a. Diagnosis of pulmonary hypertension WHO Groups 2, 3, 4, or 5
   b. Hemoglobin (Hgb) above gender-specific upper limit of normal (ULN)
   c. Platelet count is less than 50,000/mm^3 (or less than 50 x 10^9/L)

Renewal duration: 12 months

- 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 Guideline:

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

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

Section F. Oral prostacyclin analogue: ORENITRAM (treprostinil)

- **Criteria for initial therapy:** Orenitram (treprostinil) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual meets other initial criteria as described in Section A above

2 Individual has 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. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for oral generic sildenafil

4. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for use **ONE** oral Endothelin Receptor Antagonist [ambrisentan (brand Letairis or generic), bosentan (brand Tracleer or generic), Opsumit (macitentan)] **OR** Adempas (riociguat)

5. Agent 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 or severe hepatic impairment (Child-Pugh Class B or C)

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Orenitram (treprostinil) and/or generic equivalent (if available) therapy are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual meets continuation criteria as described in Section A above

2 Individual has not developed significant adverse effects such as: severe bleeding

3. Individual does not have moderate or severe hepatic impairment (Child-Pugh Class B or C)

Renewal duration: 12 months

- 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 Guideline:

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

Section G. Prostacyclin receptor agonist: UPTRAVI (selexipag)

- **Criteria for initial therapy:** Uptravi (selexipag) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual 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. Individual has 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)

4. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for generic oral sildenafil

5. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **ONE** oral Endothelin Receptor Antagonist [ambrisentan (brand Letairis or generic), bosentan (brand Tracleer or generic), Opsumit (macitentan)] **OR** Adempas (riociguat)

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

7. Individual does not have severe renal impairment (glomerular filtration rate less than 15 mL/min/1.73 m^2) or individuals undergoing dialysis

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) and/or generic equivalent (if available) therapy are considered ***medically necessary*** and will be approved when **ALL** of the following

criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual meets continuation criteria as described in Section A above

2. Individual has not developed significant adverse effects such as pulmonary edema with pulmonary veno-occlusive disease

3. Individual does not have severe renal impairment (glomerular filtration rate less than 15 mL/min/1.73 m^2) or individuals undergoing dialysis

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

- 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 Guideline:

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

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

Section H. Inhaled TYVASO (treprostinil):

TYVASO (treprostinil) inhalation solution, for oral inhalation
TYVASO DPI (treprostinil) inhalation powder, for oral inhalation

- **Criteria for initial therapy:** Inhaled Tyvaso (treprostinil) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual 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. Individual has a confirmed diagnosis of **ONE** of the following: (Documentation of WHO Group and Functional Class category must be submitted with request. See Definitions section for examples of agents)
    a. Pulmonary arterial hypertension (PAH, WHO Group 1) with **ONE** of the following:
        i. Continued or advancing NYHA Functional Class III symptoms despite therapy with an Endothelin Receptor Antagonist and/or PDE5 inhibitor (e.g., bosentan plus sildenafil)
        ii. Has NYHA Functional Class IV symptoms

    b. Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3)

4. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for use of **ONE** oral Endothelin Receptor Antagonist [ambrisentan (brand Letairis or generic), bosentan (brand Tracleer or generic), Opsumit (macitentan)] **OR** Adempas (riociguat)

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

6. Individual does not have severe hepatic impairment

7. **For Tyvaso DPI:** Medical record documentation that the individual is unable to use Tyvaso oral inhalational solution due to **ONE** of the following:
    a. Physical impairment
    b. Visual impairment

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) and/or generic equivalent (if available) therapy are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual meets continuation criteria as described in Section A above

2. Individual has not developed significant adverse effects such as:
    a. Symptomatic hypotension
    b. Syncope
    c. Bleeding
    d. Acute bronchospasm

3. Individual does not have severe hepatic impairment

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

- 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 Guideline:

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

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

Section I. Inhaled VENTAVIS (iloprost):

- **Criteria for initial therapy:** Inhaled Ventavis (iloprost) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual 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. Individual has a confirmed diagnosis of pulmonary arterial hypertension (PAH, WHO Group 1) with continued or advancing NYHA Functional Class III-IV symptoms despite therapy with an Endothelin Receptor Antagonist or PDE5 inhibitor (Documentation of WHO Group and Functional Class category must be submitted with request. See Definitions section for examples of agents)

  4. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for use of **ONE** oral Endothelin Receptor Antagonist [ambrisentan (brand Letairis or generic), bosentan (brand Tracleer or generic), Opsumit (macitentan)] **OR** Adempas (riociguat)

  5. Agent will not be used with other prostacyclin analogs (such as epoprostenol, treprostinil) or prostacyclin receptor agonists (such as selexipag)

  6. 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.

- **Criteria for continuation of coverage (renewal request):** Inhaled Ventavis (iloprost) and/or generic equivalent (if available) therapy are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

  1. Individual meets continuation criteria as described in Section A above

  2. Individual 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

- 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 Guideline:

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

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

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 World Health Organization (WHO) scheme, into five classes or groups based on etiology and may be further characterized using the New York Heart Association (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 pulmonary arterial hypertension (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 effected by their disease while those in WHO Functional Class IV are most effected.

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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:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

PHARMACY COVERAGE GUIDELINE

PULMONARY HYPERTENSION MEDICATIONS

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.

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)
    - Non-responders at vasoreactivity testing
    - Acute responders at vasoreactivity testing
  - Heritable / Familial[a]
    - Activin receptor-like kinase (ALK1), endoglin (with or without hereditary hemorrhagic telangiectasia)
    - Bone Morphogenic Protein Receptor type II (BMPR)
    - Unknown
  - Drug- and toxin-induced[a]
  - Associated with (APAH):
    - Connective tissue disease
    - HIV infection
    - Portal hypertension
    - Congenital heart diseases
    - Schistosomiasis
  - Associated with significant venous or capillary involvement
    - Pulmonary veno-occlusive disease (PVOD)
    - Pulmonary capillary hemangiomatosis (PCH)
  - Persistent pulmonary hypertension of the newborn
- WHO Group 2 - Pulmonary hypertension owing to left heart disease
  - Heart failure
    - with preserved ejection fraction
    - with reduced or mildly reduced ejection fraction [b]
  - Valvular heart disease
  - Congenital/acquired cardiovascular conditions leading to post-capillary pulmonary hypertension
- WHO Group 3 - Pulmonary hypertension owing to lung disease and/or hypoxia
  - Obstructive lung disease or emphysema
  - Restrictive lung disease
  - Lung disease with mixed restrictive and obstructive pattern
  - Hypoventilation syndromes

  - Hypoxia without lung disease (e.g., high altitude)
  - Developmental lung disorders
- WHO Group 4 - Pulmonary hypertension associated with pulmonary artery obstructions
  - Chronic thromboembolic pulmonary hypertension (CTEPH)
  - Other pulmonary artery obstructions [c]
- WHO Group 5 - Pulmonary hypertension with unclear and/or multifactorial mechanisms
  - Hematologic disorders [d]
  - Systemic disorders [e]
  - Metabolic disorders [f]
  - Chronic renal failure with or without hemodialysis
  - Pulmonary tumor thrombotic microangiopathy
  - Fibrosing mediastinitis

[a] Patients with heritable PAH or PAH associated with drugs and toxins might be acute responders.
b LV ejection fraction for HF with reduced ejection fraction: ≤40%; for HF with mildly reduced ejection fraction: 41–49%.
[c] Other causes of pulmonary artery obstructions include sarcomas (high or intermediate grade or angiosarcoma), other malignant tumors (e.g., renal carcinoma, uterine carcinoma, germ-cell tumors of the testis), non-malignant tumors (e.g., uterine leiomyoma), arteritis without connective tissue disease, congenital pulmonary arterial stenoses, and hydatidosis.
[d] Including inherited and acquired chronic hemolytic anemia and chronic myeloproliferative disorders.
[e] Including sarcoidosis, pulmonary Langerhans's cell histiocytosis, and neurofibromatosis type 1.
[f] Including glycogen storage diseases and Gaucher disease.

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:
Nifedipine – oral

Endothelin receptor antagonists (ERA) – 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 (Liqrev, Revatio, and generics) – oral (generics available) and IV (generics available)
Tadalafil (Adcirca, Alyq, Tadliq 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

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

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

Other
Bone morphogenic protein receptor type 2 (BMPR2)
– Member of transforming growth factor (TGF)-beta family of proteins
Winrevair (sotatercept) SQ: acts as a ligand trap for members of TGF-beta superfamily to restore balance between the growth promoting activin pathway and the growth inhibiting BMP pathway

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 RAP < 8 mmHg & CI $\geq$ 2.5 L/min/m^2 Echo: RA < 18 cm^2 no pericardial effusion	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 RAP 8-14 mmHg & CI 2-2.4 L/min/m^2 Echo: RA 18-26 cm^2 no/minimal pericardial effusion	Clinical and echocardiographic¶ evidence of RV failure (pericardial effusion, RV dysfunction, and right atrial enlargement) PaCO2 <32 mmHg RAP >20 mmHg CI <2 L/min/m^2 Rapid disease progression WHO functional class III/IV 6MWD <300 meters Peak VO2 <10.4 mL/kg/min Elevated BNP/NT-proBNP

Contraindications to Pulmonary Arterial Hypertension Medications:

Agents:	FDA-labeled contraindications
Adcirca Alyq Revatio Sildenafil Tadalafil Tadliq	▪ Use with any form of organic nitrate, either regularly or intermittently ▪ Use with a Guanylate Cyclase (GC) stimulator ex., riociguat (Adempas) ▪ History of known serious hypersensitivity reactions
Ambrisentan Letairis	▪ Pregnancy ▪ Idiopathic pulmonary fibrosis, with or without pulmonary hypertension (WHO Group 3)
Opsumit	▪ Pregnancy

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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 such as Adcirca, Revatio, 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)
Sotatercept	▪ None listed
Orenitram	▪ Severe hepatic impairment (Child-Pugh Class C)
Uptravi	▪ Use with gemfibrozil or other strong inhibitors of CYP2C8
Tyvaso Ventavis	▪ None listed

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:

Adcirca (tadalafil) tab product information, revised by United Therapeutics Corporation. 09-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 21, 2024.

Alyq (tadalafil) tab product information, revised by AvKARE, Inc. 01-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 21, 2024.

Tadliq (tadalafil) suspension product information, revised by CMP Pharma, Inc. 10-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 21, 2024.

Tadalafil tab product information, revised by Ajanta Pharma USA, Inc. 10-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 21, 2024.

Revatio (sildenafil) tab, power for oral suspension, & intravenous solution product information, revised by Viatris Specialty LLC. 10-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 21, 2024.

Letairis (ambrisentan) tab product information, revised by Gilead Sciences, Inc. 08-2019. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 21, 2024.

Ambrisentan tab product information, revised by Apotex Corp. 09-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 21, 2024.

Tracleer (bosentan) tab & tab for oral suspension product information, revised by Actelion Pharmaceutical US, Inc. 02-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 21, 2024.

Bosentan tab product information, revised by Zydus Pharmaceuticals USA, Inc. 02-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 21, 2024.

Opsumit (macitentan) tab product information, revised by Actelion Pharmaceuticals US, Inc. 04-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 21, 2024.

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Adempas (riociguat) tab product information, revised by Bayer HealthCare Pharmaceuticals, Inc. 01-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 21, 2024.

Orenitram (treprostinil) extended-release tab product information, revised by United Therapeutics Corporation. 11-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 21, 2024.

Tyvaso (treprostinil) solution for oral inhalation product information, revised by United Therapeutics Corporation. 05-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 9, 2024.

Tyvaso DPI treprostinil) powder for oral inhalation product information, revised by United Therapeutics Corporation. 10-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 21, 2024.

Uptravi (selexipag) tab & powder for intravenous solution product information, revised by Actelion Pharmaceuticals US, Inc. 07-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 21, 2024.

Ventavis (iloprost) solution for oral inhalation product information, revised by Actelion Pharmaceuticals US, Inc. 03-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 21, 2024.

Winrevair (sotatercept-csrk) for subcutaneous injection product information, revised by Merck Sharp & Dohme LLC. 03-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 21, 2024.

Hopkins W, Rubin LJ. Treatment and prognosis of pulmonary arterial hypertension in adults (Group 1). In: UpToDate, Mandel J, Finlay G (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through November 2024. Topic last updated December 04, 2024. Accessed December 09, 2024.

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Mullen MP. Pulmonary hypertension in children: Management and prognosis. In: UpToDate, Fulton DR, Armsby C (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through November 2024. Topic last updated August 26, 2024. Accessed December 09, 2024.

Humbert M, Kovacs G, Hoeper MM, et. al.: 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). European Heart Journal 2022; 43; 3618–3731. Accessed December 08, 2022. Re-evaluated December 09, 2024.

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Humbert M, McLaughlin V, Gibbs JSR, et al. Sotatercept for the treatment of pulmonary arterial hypertension: PULSAR open-label extension. Eur Respir J 2023; 61: 2201347. https://doi.org/10.1183/13993003.01347-2022. Accessed August 05, 2024. Re-evaluated December 09, 2024.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT04576988: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Compare the Efficacy and Safety of Sotatercept Versus Placebo When Added to Background Pulmonary Arterial Hypertension (PAH) Therapy for the Treatment of PAH. Available from: http://clinicaltrials.gov. Last update posted June 24, 2024. Last verified June 2024. Accessed August 05, 2024. Re-evaluated December 09, 2024.