BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 5/19/2016**
SECTION: DRUGS	**LAST REVIEW DATE: 2/13/2020**
	LAST CRITERIA REVISION DATE: 2/13/2020
	ARCHIVE DATE:

PULMONARY ARTERIAL HYPERTENSION MEDICATIONS:
ADCIRCA® (tadalafil), ALYQ (tadalafil), and TADALAFIL oral tablet
ADEMPAS® (riociguat) oral tablet
LETAIRIS® (ambrisentan) and AMBRISENTAN oral tablet
OPSUMIT® (macitentan) oral tablet
ORENITRAM® (trepostinil) oral tablet
REVATIO® (sildenafil) and SILDENAFIL oral tablet and oral suspension
TRACLEER® (bosentan) and BOSENTAN oral tablet and oral tablet for suspension
TYVASO® (treprostinil) inhalation solution
UPTRAVI® (selexipag) oral tablet
VENTAVIS® (iloprost) inhalation solution

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.

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.

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 5/19/2016
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PULMONARY ARTERIAL HYPERTENSION MEDICATIONS

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.**

Section A: Applies for all Pulmonary Arterial Hypertension agents:

- **Criteria for initial therapy:** Pulmonary Arterial Hypertension 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

2. Right heart catheterization documents **ALL** of the following:
   - Mean pulmonary artery pressure > 25 mm Hg at rest
   - Pulmonary arterial/capillary wedge pressure ≤ 15 mm Hg
   - Pulmonary vascular resistance > 3 Wood units

3. Baseline vasoreactivity testing was negative or non-responsive

4. Chronic lung diseases and other causes of hypoxemia are mild or absent

5. Individual does not have other disorders, that would put them into WHO group 5 PH, including:
   - systemic disorders (e.g., sarcoidosis)
   - hematologic disorders (e.g., myeloproliferative diseases), and
   - metabolic disorders (e.g., glycogen storage disease)

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

7. Meets other initial criteria as described below in Sections B-G below
   - See section B – for Revatio, Sildenafil, Adcirca, Alyq, or Tadalafil
   - See section C – for Letairis, Ambrisentan, Tracleer, Bosentan, or Opsumit
   - See section D – for Adempas
   - See section E – for Orenitram
   - See section F – for Uptravi
   - See section G – for Inhaled Tyvaso or Ventavis
   - See Evidence Based Coverage – for Flolan, Veletri, Remodulin

PULMONARY ARTERIAL HYPERTENSION MEDICATIONS

- **Criteria for continuation of coverage (renewal request):** Pulmonary Arterial Hypertension 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

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

  3. Individual has been adherent with the medication

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

  5. There are no significant interacting drugs

  6. Meets other continuation criteria as described in Sections B-G below
     - See section B – for Revatio, Sildenafil, Adcirca, Alyq, or Tadalafil
     - See section C – for Letairis, Ambrisentan, Tracleer, Bosentan, or Opsumit
     - See section D – for Adempas
     - See section E – for Orenitram
     - See section F – for Uptravi
     - See section G – for Inhaled Tyvaso or Ventavis
     - See Evidence Based Coverage – for Flolan, Veletri, Remodulin

Section B: Phosphodiesterase type-5 (PDE5) inhibitors: Revatio (sildenafil), Sildenafil generic, Adcirca (tadalafil), Alyq (tadalafil), Tadalafil generic

- **Criteria for initial therapy:** Revatio, Sildenafil, Adcirca, Alyq, or Tadalafil 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 pulmonary arterial hypertension (PAH, WHO Group I) with Functional Class II-III symptoms (WHO Group and Functional Class category must be submitted with request. See Definitions section)

  3. Individual is 18 years of age or older

4. **For Revatio and Adcirca:** Individual has failure, contraindication or intolerance to **ONE** of the following:
   - generic oral Revatio (Sildenafil)
   - generic oral Adcirca (Alyq or Tadalafil 20mg)

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Revatio, Sildenafil, Adcirca, Alyq, or Tadalafil 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:
   - Sudden loss of vision in one or both eyes
   - Sudden decrease or loss of hearing
   - Priapism
   - Pulmonary edema
   - Vaso-occlusive crisis

Renewal duration: 12 months

Section C: Endothelin receptor antagonists (ERAs): Letairis (ambrisentan), Ambrisentan, Tracleer (bosentan), Bosentan, Opsumit (macitentan)

- **Criteria for initial therapy:** Letairis, Ambrisentan, Tracleer, Bosentan, or Opsumit 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:

   - **Ambrisentan (brand Letairis or generic) monotherapy or with tadalafil (brand Adcirca or Alyq, or generic):** An individual 18 years of age or older with a confirmed diagnosis of pulmonary arterial hypertension (PAH, WHO Group 1) with Functional Class II-III symptoms (WHO Group and Functional Class category must be submitted with request. See Definitions section)

   - **For Bosentan (brand Tracleer or generic) with or without a PDE5 inhibitor**: An individual 3 years of age or older with a confirmed diagnosis of idiopathic or congenital pulmonary arterial hypertension (PAH, WHO Group 1) **OR** an adult with PAH (WHO Group 1) with Functional Class II-IV symptoms (WHO Group and Functional Class category must be submitted with request. See Definitions section)

   - **For Opsumit monotherapy or with PDE5 inhibitor or inhaled prostanoid**: An individual 18 years of age or older with a confirmed diagnosis of pulmonary arterial hypertension (PAH, WHO

Group 1) with Functional Class II-III symptoms (WHO Group and Functional Class category must be submitted with request. See Definitions section)

3. For each agent: Individual is enrolled in the appropriate Risk Evaluation and Mitigation Strategy (REMS) program

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

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

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Letairis, Ambrisentan, Tracleer, Bosentan, 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:
   - Pulmonary veno-occlusive disease
   - Fluid retention requiring hospitalization for decompensating heart failure
   - Severe anemia
   - Pulmonary edema with pulmonary veno-occlusive disease
   - 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. Individual is 18 years of age or older

3. For a woman, regardless of reproductive potential, is enrolled in the Risk Evaluation and Mitigation Strategy (REMS) program

4. A confirmed diagnosis of **ONE** of the following:
   - 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

- 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 (WHO Group and Functional Class category must be submitted with request. See Definitions section) used as monotherapy or with an endothelin receptor antagonist or prostanoid

5. Individual has failure, intolerance, or contraindication to oral generic sildenafil

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:
   - Pulmonary edema with pulmonary veno-occlusive disease
   - Severe bleeding
   - Liver toxicity

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. Individual is 18 years of age or older

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

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

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

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:
   - Severe bleeding

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:
   - Center of Comprehensive Care (CCC)[1, 2]
   - Regional Clinical Program (RCP)[1, 2]
   - An equivalent center[2]

3. Individual is 18 years of age or older

4. 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 (WHO Group and Functional Class category must be submitted with request. See Definitions section)

5. Individual has failure, intolerance or contraindication to generic oral sildenafil

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

Initial approval duration:
- If the individual has **NOT** been seen by a PHA-certified or equivalent provider within 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:
   - Pulmonary edema with pulmonary veno-occlusive disease

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

Section G: Inhaled Prostanoid: Ventavis (iloprost), Tyvaso (treprostinil)

- **Criteria for initial therapy:** Ventavis (iloprost) or Tyvaso (treprostinil) 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. 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:
   - Center of Comprehensive Care (CCC)[1, 2]
   - Regional Clinical Program (RCP)[1, 2]
   - An equivalent center [2]

3. Individual is 18 years of age or older

4. 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 (WHO Group and Functional Class category must be submitted with request. See Definitions section)

PULMONARY ARTERIAL HYPERTENSION MEDICATIONS

Initial approval duration:

- If the individual has **NOT** been seen by a PHA-certified or equivalent provider within 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):** Ventavis (iloprost) or Tyvaso (treprostinil) 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:
   - Symptomatic hypotension
   - Syncope
   - Bleeding
   - Pulmonary venous hypertension
   - Pulmonary edema
   - Bronchospasm

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 those 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.

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)

PULMONARY ARTERIAL HYPERTENSION MEDICATIONS

- 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

PULMONARY ARTERIAL HYPERTENSION MEDICATIONS

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

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

PULMONARY ARTERIAL HYPERTENSION MEDICATIONS

Contraindications to Pulmonary Arterial Hypertension Medications:

Agents:	FDA-labeled contraindications
Adcirca Alyq Revatio Sildenafil Tadalafil	4. Use with any form of organic nitrate, either regularly or intermittently 5. Use with a Guanylate Cyclase (GC) stimulator riociguat (Adempas) 6. 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 PDE5 inhibitors, dipyridamole or theophylline) ▪ Use of nitrates or nitric oxide donors (such as amyl nitrite) in any form ▪ 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

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

PULMONARY ARTERIAL HYPERTENSION MEDICATIONS

Resources:

Revatio (sildenafil) product information accessed 02-06-20 at DailyMed

Sildenafil product information accessed 02-06-20 at DailyMed

Adcirca (tadalafil) product information accessed 02-06-20 at DailyMed

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