ENDOTHELIN RECEPTOR ANTAGONISTS:
LETAIRIS® (ambrisentan) oral tablet
OPSUMIT® (macitentan) oral tablet
TRACLEER® (bosentan) oral tablet

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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**Description:**

Letairis (ambrisentan), Tracleer (bosentan), and Opsumit (macitentan) are endothelin receptor antagonists (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH) World Health Organization (WHO) Group I. Goals of treatment are to improve exercise ability, decrease clinical worsening, and to delay disease progression. Disease progression includes: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening (measured as decreased 6-minute walk distance, worsened symptoms and need for additional treatment).

Studies establishing effectiveness of Letairis (ambrisentan) included predominantly patients with New York Heart Association (NYHA) Functional Class II-III symptoms whose etiologies included idiopathic or heritable PAH and PAH associated with connective tissue diseases. Studies establishing effectiveness of Tracleer (bosentan)
ENDOTHELIN RECEPTOR ANTAGONISTS (cont.)

included predominantly patients with NYHA Functional Class II-IV symptoms whose etiologies of PAH were idiopathic or heritable, associated with connective tissue diseases, and associated with congenital heart disease with left-to-right shunts. Effectiveness of Osimt (macitentan) was established in PAH patients with predominantly NYHA Functional Class II-III symptoms and etiologies of idiopathic and heritable, caused by connective tissue disorders, and caused by congenital heart disease with repaired shunts.

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 I is called PAH and WHO Groups II through V 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 I 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 I) 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 (VEGF). VEGF is a signal protein that stimulates creation of new blood vessels which restore oxygen supply to tissues when blood flow is inadequate.

The pathogenesis of pulmonary hypertension from left heart disease (WHO Group II) 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 in the lungs causing pulmonary edema and pleural effusions. In hypoxic pulmonary hypertension (WHO Group III), low levels of oxygen are thought to cause vasoconstriction of pulmonary arteries. In chronic thromboembolic pulmonary hypertension (CTEPH or WHO Group IV), 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 I).

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.

ET-1 is a potent autocrine and paracrine peptide. There are two receptor subtypes for ET-1 binding, ETA and ETB. Binding of ET-1 to its receptors is thought to play a role in vasoconstriction, fibrosis, proliferation, hypertrophy, and inflammation. The primary actions of stimulating ETA receptor are vasoconstriction and cell proliferation, while the predominant actions of stimulating ETB receptor are vasodilation, antiproliferation, and clearance of ET-1. In PAH (WHO Group I), the local endothelin system is up-regulated and is involved in vascular hypertrophy and in organ damage; it is important to note that other factors besides the ET system are involved in the overall pathogenesis of PAH (WHO Group I).

All patients using Tracleer and female patients using Letairis or Opsumit are subject to a Risk Evaluation and Mitigation Strategies (REMS) program that requires provider, patient, and dispensing pharmacy to be enrolled into the program. Only providers and pharmacies enrolled into the REMS may prescribe and dispense the drug, respectively, to individuals who are also in the program. A REMS program attempts to manage known or potentially serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) for some drugs to ensure that the benefits of a drug outweigh its risks.

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**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 I - 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 II - 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 III - 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 IV - 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
ENDOTHELIN RECEPTOR ANTAGONISTS (cont.)

- WHO Group V - 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 1
  No limitation in physical activity; ordinary physical activity does not cause dyspnea or fatigue

- Functional Class 2
  Slight limitations in physical activity; ordinary physical activity produces dyspnea, fatigue, chest pain, or near-syncope; no symptoms at rest

- Functional Class 3
  Marked limitation of physical activity; less than ordinary physical activity produces dyspnea, fatigue, chest pain, or near-syncope; no symptoms at rest

- Functional Class 4
  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) – oral
  Bosentan (Tracleer) – oral
  Macitentan (Opsumit) – oral

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

- Prostanoids – direct vasodilation of pulmonary & systemic arterial vascular beds, inhibit platelet aggregation
  Epoprostenol (Flolan, Veletri, generics) – continuous IV
  Iloprost (Ventavis) – inhalational delivery
  Treprostinil (Tyvaso, Remodulin) – can be SQ or IV (Remodulin), inhalational delivery (Tyvaso)

- Soluble Guanylate Cyclase Stimulators – stimulate Nitric Oxide cGMP pathway to increase cGMP
  Riociguat (Adempas) – oral
Drug related events:

\textit{Ineffective / failure}

Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

\textbf{Adverse Drug Event: Allergic reaction / Hypersensitivity / Intolerance}

Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual’s outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals’ body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

\textit{Allergic reaction / hypersensitivity} – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

\textit{Intolerance} – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

\textbf{Contraindication}

Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer’s labelled recommendation and is considered investigational or experimental

\textbf{Non-adherence}

Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record
ENDOTHELIN RECEPTOR ANTAGONISTS (cont.)

Precertification:

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

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.

Criteria:

See “Resources” section for FDA-approved dosage.

- Precertification for Letairis (ambrisentan) oral tablet, Opsumit (macitentan) oral tablet, and Tracleer (bosentan) oral tablet requires completion of the specific request form in its entirety. 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 will be returned.

Criteria for Letairis (ambrisentan) oral tablet:

- **Initial therapy:** FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Letairis is considered medically necessary when ALL of the following criteria are met:

  1. Individual is 18 years or older

  2. Individual has medical record documentation of a confirmed diagnosis of pulmonary arterial hypertension WHO Group I with Functional Class II or III symptoms

  3. Documentation that the individual has been seen by a provider affiliated with a Pulmonary Hypertension Association (PHA) accredited Pulmonary Hypertension Care Center (PHCC) as either a Center of Comprehensive Care (CCC) or as a Regional Clinical Program (RCP) within 6 months of the request and the diagnosis of PAH has been confirmed by that provider. Individuals with ongoing therapy must have at least one yearly appointment with a CCC or RCP center.

  4. Diagnosis of PAH has been confirmed by provider affiliated with a PHCC that is PHA accredited with documentation of ALL of the following:
ENDOTHELIN RECEPTOR ANTAGONISTS (cont.)

- Right heart catheterization documents a mean pulmonary artery pressure greater than 25 mm Hg at rest; a pulmonary arterial wedge pressure of less than or equal to 15 mm Hg and a pulmonary vascular resistance greater than 3 Wood units
- Vasoreactivity testing with results
- WHO Functional Class
- Chronic lung diseases and other causes of hypoxemia are mild or absent
- Venous thromboembolic disease is absent
- Individual does not have other disorders, including systemic disorders (e.g., sarcoidosis), hematologic disorders (e.g., myeloproliferative diseases), and metabolic disorders (e.g., glycogen storage disease) that would put them into WHO group V PH (unclear multifactorial causes)

5. Individual cannot use generic oral sildenafil due to ONE of the following:
   - Generic was not effective (see Definitions section)
   - Experienced an adverse drug event (see Definitions section)
   - Generic is contraindicated (see Definitions section)

6. ALL of the following baseline tests have been obtained before initiation:
   - Hemoglobin and Hematocrit

7. Absence of ALL of the following contraindications:
   - Idiopathic pulmonary fibrosis, with or without pulmonary hypertension

8. Absence of ALL of the following exclusions:
   - Moderate to severe hepatic impairment
   - Woman who is breast feeding an infant or child
   - Individual with severe anemia
   - Severe renal impairment
   - Individual on dialysis

1 For a list of PHA-certified providers, go to www.phassociation.org/patients/findadoctor.
2 If an individual has not be seen within 6 months but needs to continue therapy or begin initial therapy, a limited authorization will be given initially to allow for sufficient time for the individual to be evaluated by a provider affiliated with a CCC or RCP. The diagnosis of PAH must be confirmed by the CCC or RCP provider. Individuals with ongoing therapy must have at least one yearly appointment with a CCC or RCP 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 provider for a second opinion.

Continuation of coverage (renewal request): Letairis is considered medically necessary with documentation of ALL of the following:

1. The individual has benefited from therapy but remains at high risk
2. The condition has not progressed or worsened while on therapy
3. Individual has not developed any contraindications or other exclusions to its continued use
Letairis for all other indications not previously listed is considered experimental or investigational based upon:

1. Lack of final approval from the Food and Drug Administration, and
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.

This includes but is not limited to the following:
- Idiopathic pulmonary fibrosis
- Digital ulcers
- Systemic Sclerosis
- Eisenmenger syndrome
- Raynaud phenomenon
- Use of other advanced therapies for the pharmacologic treatment of PAH (WHO group I) that are not FDA approved for this indication
- Use of these agents for the treatment of pulmonary hypertension (WHO groups II-V), including but not limited to:
  - Pulmonary hypertension associated with left heart diseases
  - Pulmonary hypertension associated with lung diseases and/or hypoxemia (including chronic obstructive pulmonary disease)
  - Pulmonary hypertension due to chronic thrombotic and/or embolic disease
  - Miscellaneous group (i.e., sarcoidosis, histocytosis X, or lymphangiomatosis)
- Treatment with dosing or frequency outside the FDA-approved dosing and frequency

Criteria for Opsumit (macitentan) oral tablet:

- Initial therapy: FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Opsumit is considered medically necessary when ALL of the following criteria are met:
  
  1. Individual is 18 years of age or older
  2. Individual has medical record documentation of a confirmed diagnosis of pulmonary arterial hypertension WHO Group I with Functional Class II or III symptoms
  3. Documentation that the individual has been seen by a provider affiliated with a Pulmonary Hypertension Association (PHA) accredited Pulmonary Hypertension Care Center (PHCC) ¹ as either a Center of Comprehensive Care (CCC) or as a Regional Clinical Program (RCP) within 6 months ² of the request and the diagnosis of PAH has been confirmed by that provider. Individuals with ongoing therapy must have at least one yearly appointment with a CCC or RCP center.
  4. Diagnosis of PAH has been confirmed by provider affiliated with a PHCC that is PHA accredited with documentation of ALL of the following:
ENDOTHELIN RECEPTOR ANTAGONISTS (cont.)

- Right heart catheterization documents a mean pulmonary artery pressure greater than 25 mm Hg at rest; a pulmonary arterial wedge pressure of less than or equal to 15 mm Hg and a pulmonary vascular resistance greater than 3 Wood units
- Vasoreactivity testing with results
- WHO Functional Class
- Chronic lung diseases and other causes of hypoxemia are mild or absent
- Venous thromboembolic disease is absent
- Individual does not have other disorders, including systemic disorders (e.g., sarcoidosis), hematologic disorders (e.g., myeloproliferative diseases), and metabolic disorders (e.g., glycogen storage disease) that would put them into WHO group V PH (unclear multifactorial causes)

5. Individual cannot use generic oral sildenafil due to ONE of the following:
   - Generic was not effective (see Definitions section)
   - Experienced an adverse drug event (see Definitions section)
   - Generic is contraindicated (see Definitions section)

6. **ALL** of the following baseline tests have been obtained before initiation:
   - Hemoglobin and Hematocrit
   - Liver enzymes

7. Absence of **ALL** of the following exclusions:
   - Idiopathic pulmonary fibrosis, with or without pulmonary hypertension
   - Woman who is breast feeding an infant or child
   - Individual with severe anemia
   - Drugs known to increase OR decrease blood concentration of Opsumit have been discontinued or doses have adjusted if clinically appropriate to do so

1. For a list of PHA-certified providers, go to [www.phassociation.org/patients/findadoctor](http://www.phassociation.org/patients/findadoctor).
2. If an individual has not be seen within 6 months but needs to continue therapy or begin initial therapy, a limited authorization will be given initially to allow for sufficient time for the individual to be evaluated by a provider affiliated with a CCC or RCP. The diagnosis of PAH must be confirmed by the CCC or RCP provider. Individuals with ongoing therapy must have at least one yearly appointment with a CCC or RCP 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 provider for a second opinion.

- **Continuation of coverage (renewal request):** Opsumit is considered **medically necessary** with documentation of **ALL** of the following:
  4. The individual has benefited from therapy but remains at high risk
  5. The condition has not progressed or worsened while on therapy
  6. Individual has not developed any contraindications or other exclusions to its continued use

- Opsumit for all other indications not previously listed is considered **experimental or investigational** based upon:
ENDOTHELIN RECEPTOR ANTAGONISTS (cont.)

1. Lack of final approval from the Food and Drug Administration, and
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.

This includes but is not limited to the following:
- Idiopathic pulmonary fibrosis
- Digital ulcers
- Systemic Sclerosis
- Eisenmenger syndrome
- Raynaud phenomenon
- Use of other advanced therapies for the pharmacologic treatment of PAH (WHO group I) that are not FDA approved for this indication
- Use of these agents for the treatment of pulmonary hypertension (WHO groups II-V), including but not limited to:
  - Pulmonary hypertension associated with left heart diseases
  - Pulmonary hypertension associated with lung diseases and/or hypoxemia (including chronic obstructive pulmonary disease)
  - Pulmonary hypertension due to chronic thrombotic and/or embolic disease
  - Miscellaneous group (i.e., sarcoidosis, histocytosis X, or lymphangiomatosis)
- Treatment with dosing or frequency outside the FDA-approved dosing and frequency

Criteria for Tracleer (bosentan) oral tablet:

- **Initial therapy**: FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Tracleer is considered **medically necessary** when ALL of the following criteria are met:

  1. Individual is 18 years of age or older

  2. Individual has medical record documentation of a confirmed diagnosis of pulmonary arterial hypertension WHO Group I with Functional Class II - IV symptoms

  3. Documentation that the individual has been seen by a provider affiliated with a Pulmonary Hypertension Association (PHA) accredited Pulmonary Hypertension Care Center (PHCC) \(^1\) as either a Center of Comprehensive Care (CCC) or as a Regional Clinical Program (RCP) within 6 months \(^2\) of the request and the diagnosis of PAH has been confirmed by that provider. Individuals with ongoing therapy must have at least one yearly appointment with a CCC or RCP center.

  4. Diagnosis of PAH has been confirmed by provider affiliated with a PHCC that is PHA accredited with documentation of ALL of the following:
     - Right heart catheterization documents a mean pulmonary artery pressure greater than 25 mm Hg at rest; a pulmonary arterial wedge pressure of less than or equal to 15 mm Hg and a pulmonary vascular resistance greater than 3 Wood units
ENDOTHELIN RECEPTOR ANTAGONISTS (cont.)

- Vasoreactivity testing with results
- WHO Functional Class
- Chronic lung diseases and other causes of hypoxemia are mild or absent
- Venous thromboembolic disease is absent
- Individual does not have other disorders, including systemic disorders (e.g., sarcoidosis), hematologic disorders (e.g., myeloproliferative diseases), and metabolic disorders (e.g., glycogen storage disease) that would put them into WHO group V PH (unclear multifactorial causes)

5. Individual cannot use generic oral sildenafil due to ONE of the following:
   - Generic was not effective (see Definitions section)
   - Experienced an adverse drug event (see Definitions section)
   - Generic is contraindicated (see Definitions section)

6. ALL of the following baseline tests have been obtained before initiation:
   - Hemoglobin and Hematocrit

7. Absence of ALL of the following contraindications:
   - Use with Cyclosporine
   - Use with Glyburide
   - Hypersensitivity to bosentan or any component of the product

8. Absence of ALL of the following exclusions:
   - Moderate to severe hepatic impairment
   - Woman who is breast feeding an infant or child

1 For a list of PHA-certified providers, go to www.phassociation.org/patients/findadoctor.
2 If an individual has not be seen within 6 months but needs to continue therapy or begin initial therapy, a limited authorization will be given initially to allow for sufficient time for the individual to be evaluated by a provider affiliated with a CCC or RCP. The diagnosis of PAH must be confirmed by the CCC or RCP provider. Individuals with ongoing therapy must have at least one yearly appointment with a CCC or RCP 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 provider for a second opinion.

- **Continuation of coverage (renewal request):** Tracleer is considered medically necessary with documentation of ALL of the following:
  1. The individual has benefited from therapy but remains at high risk
  2. The condition has not progressed or worsened while on therapy
  3. Individual has not developed any contraindications or other exclusions to its continued use

- Tracleer for all other indications not previously listed is considered experimental or investigational based upon:
  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
ENDOTHELIN RECEPTOR ANTAGONISTS (cont.)

4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.

This includes but is not limited to the following:
- Idiopathic pulmonary fibrosis
- Digital ulcers
- Systemic Sclerosis
- Eisenmenger syndrome
- Raynaud phenomenon
- Use of other advanced therapies for the pharmacologic treatment of PAH (WHO group I) that are not FDA approved for this indication
- Use of these agents for the treatment of pulmonary hypertension (WHO groups II-V), including but not limited to:
  - Pulmonary hypertension associated with left heart diseases
  - Pulmonary hypertension associated with lung diseases and/or hypoxemia (including chronic obstructive pulmonary disease)
  - Pulmonary hypertension due to chronic thrombotic and/or embolic disease
  - Miscellaneous group (i.e., sarcoidosis, histocytosis X, or lymphangiomatosis)
- Treatment with dosing or frequency outside the FDA-approved dosing and frequency

Resources:


ENDOTHELIN RECEPTOR ANTAGONISTS (cont.)


FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
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<tbody>
<tr>
<td><strong>LETAIRIS</strong> is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%).</td>
<td>Initiate treatment at 5 mg once daily with or without food, and consider increasing the dose to 10 mg once daily if 5 mg is tolerated. Tablets should not be split, crushed, or chewed. Tablet: 5 mg and 10 mg</td>
</tr>
<tr>
<td><strong>OPSUMIT</strong> is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). OPSUMIT also reduced hospitalization for PAH.</td>
<td>10 mg once daily. Doses higher than 10 mg once daily have not been studied in patients with PAH and are not recommended. Tablet: 10 mg</td>
</tr>
<tr>
<td><strong>TRACLEER</strong> is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%). Considerations for use: Consider whether benefits offset the risk of hepatotoxicity in WHO Class II patients. Early hepatotoxicity may preclude future use as disease progresses.</td>
<td>Initiate at 62.5 mg twice daily with or without food for 4 weeks, and then increase to 125 mg twice daily. Patients with low body weight (&lt;40 kg) and &gt;12 years old: Initial and maintenance dose is 62.5 mg twice daily. Reduce the dose and closely monitor patients developing aminotransferase elevations &gt;3 × ULN. Discontinue Tracleer 36 hours prior to initiation of ritonavir. Patients on ritonavir: Initiate Tracleer at 62.5 mg once daily or every other day. Tablet: 62.5 mg and 125 mg</td>
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