PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Endothelin Receptor Antagonists
- Tracleer® (bosentan tablets and oral suspension – Actelion)
- Letairis® (ambrisentan tablets – Gilead, generics)
- Opsumit® (macitentan tablets – Actelion)

APPROVAL DATE: 09/11/2019

OVERVIEW
Tracleer, Letairis and Opsumit are oral endothelin receptor antagonists (ERAs) that are used for the treatment of pulmonary arterial hypertension (PAH).1,2 Tracleer is indicated for the treatment of PAH (World Health Organization [WHO] Group 1) in adults to improve exercise ability and decrease the rate of clinical worsening and in pediatric patients ≥ 3 years of age with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability.1 In adults, trials establishing effectiveness included mainly patients with WHO Functional Class II to IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue disease (21%), and PAH associated with congenital heart disease with left-to-right shunts. Letairis is indicated for the treatment of PAH (WHO Group 1) to improve exercise ability and delay clinical worsening; and 2) for use in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.2 Studies establishing effectiveness included predominantly those with WHO Functional Class II to III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%).2 Opsumit is indicated for the treatment of PAH (WHO Group 1) to reduce the risks of disease progression and hospitalization for PAH.3 The effectiveness was established in a long-term study involving patients with PAH who mainly had WHO Functional Class II to III symptoms who were treated for an average of 2 years. Patients had idiopathic and heritable PAH (57%), PAH due to connective tissue disorders (31%), and PAH due to congenital heart disease with repaired shunts (8%).

Disease Overview
PAH is a serious but rare condition impacting approximately fewer than 20,000 patients in the US. It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized. In this progressive disorder the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment.4,5 In time, right-sided heart failure and/or death may occur. Common PAH symptoms include shortness of breath, fatigue, chest pain, dizziness and fainting, along with impairment in activity tolerance. It is more prevalent in women. Patients of all ages may develop the disease; however, the mean age of diagnosis typically happens between 36 to 50 years. Children may also have PAH. The condition may occur due to various underlying medical conditions or as a disease that uniquely impacts the pulmonary circulation; both genetic and environmental factors may be involved. PAH is defined as a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg with a pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg measured by cardiac catheterization. The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved. Lung transplantation may be recommended if pharmacological or medical therapies fail, based upon patient status. The WHO categorizes PAH into stages, which is also referred to as the functional class (Class I to IV) and is an adaptation of the New York Heart Association (NYHA) system to evaluate activity tolerance.
Chronic thromboembolic pulmonary hypertension (CTEPH) is a persistent obstruction of pulmonary arteries and is often a complication of pulmonary embolism. It is classified within Group 4 pulmonary hypertension. Symptoms include progressive dyspnea on exertion, as well as fatigue, syncope, hemoptysis, and signs of right heart failure. Pulmonary endarterectomy is the treatment of choice for most patients with CTEPH. However, around 40% of patients are deemed inoperable for various reasons. Medication therapy may also be recommended. Anticoagulant therapy is also given.

**Guidelines**

In 2009, the American College of Cardiology Foundation (ACCF) Task Force on Expert Consensus Documents and the American Heart Association (AHA), developed in collaboration with the American College of Chest Physicians (ACCP), American Thoracic Society (ATS) and the Pulmonary Hypertension Association, published an expert consensus document on pulmonary hypertension. The hemodynamic definition of PAH is a mean pulmonary artery pressure (mPAP) greater than 25 mmHg; a pulmonary capillary wedge pressure (PCWP), left atrial pressure (LAP) or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mmHg; and a pulmonary vascular resistance (PVR) greater than 3 Wood units. Many different medication from varying therapies classes and different routes of administration are recognized. In 2019, and updated CHEST guideline and Expert Panel Report regarding therapy for pulmonary arterial hypertension in adults was released. Evidence for use of the many medications available is also detailed.

**Other Uses with Supportive Evidence**

The BENEFiT (Bosentan Effects in iNopErable Forms of chronic Thromboembolic pulmonary hypertension) study was a double-blind trial involving 156 patients with CTEPH who were randomized to placebo or Tracleer therapy (target dose of 125 mg BID) for 16 weeks. Benefits were noted in some hemodynamic parameters (e.g., decreased pulmonary vascular resistance). Adempas, a soluble guanylate cyclase stimulator, is the only agent indicated for the treatment of adults with CTEPH (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class. The agent is also indicated for PAH (WHO Group 1) to improve exercise capacity, improve WHO functional class, and to delay clinical worsening. Adempas has a Boxed Warning regarding embryo-fetal toxicity and is contraindicated in patients using nitrates or nitric oxide donors in any forms, as well as in patients using PDE inhibitors. The main adverse effects of Adempas are symptomatic hypotension.

Tracleer has been used in patients with systemic sclerosis who have digital ulcers. In a randomized, prospective, multicenter, placebo-controlled, double-blind study patients (n = 122) with limited or diffuse systemic sclerosis (scleroderma) were randomized in a 2:1 ratio to receive Tracleer or placebo for 16 weeks. Patients receiving Tracleer had a 48% reduction in the mean number of new ulcerations (1.4 vs. 2.7 new ulcers; P = 0.0083), the primary efficacy endpoint. The effect was more substantial in patients with digital ulcers at study entry. However, no differences were noted in the healing of established ulcers. Another trial showed a reduction in the occurrence of new digital ulcers in patients given Tracleer for 24 weeks. Many other agents are utilized in digital ulcers. In 2017 the European League Against Rheumatism (EULAR) updated recommendations for the treatment of systemic sclerosis. Tracleer has efficacy from two high-quality randomized controlled trials to reduce the number of new digital ulcers in patients with systemic sclerosis. Tracleer should be considered to reduce the number of new digital ulcers in systemic sclerosis, especially in patients who have multiple digital ulcers despite use of calcium channel blockers, phosphodiesterase type 5 (PDE5) inhibitors or iloprost therapy. A consensus of systemic sclerosis experts published an article that discusses therapy for digital ulcers. The algorithm for digital ulcer prevention lists the following as first-line, second-line, third-line, and fourth-line treatment respectively: CCBs, PDE5 inhibitors, ERAs, and prostanoids. For the prevention of severe digital ulcers, selective sympathetecomy may occasionally be recommended. For active treatment
CCBs are used first line, followed by PDE5 inhibitors. A review on Raynaud’s phenomenon and its manifestations (e.g., digital ulcers) also mentions similar medications. Other data describing use of epoprostenol are available.

Safety
All agents are in Pregnancy Category X and have a Boxed Warning regarding teratogenicity. Tracleer has a Boxed Warning regarding hepatotoxicity. All agents have a Boxed Warning regarding embryofetal toxicity.

POLICY STATEMENT
Prior authorization is recommended for prescription benefit coverage of Tracleer, Letairis, and Opsumit. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tracleer, Letairis, and Opsumit, as well as the monitoring required for adverse events and long-term efficacy, approval requires the agents to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 years in duration unless otherwise noted below.

Documentation: In the Pulmonary Arterial Hypertension – Endothelin Receptor Antagonists Prior Authorization Policy, documentation is required for initiation of therapy where noted in the criteria as [documentation required]. Documentation may include, but is not limited to, chart notes and catheterization laboratory reports. For a patient case in which the documentation requirement of the right heart catheterization upon prior authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this Pulmonary Arterial Hypertension – Endothelin Receptor Antagonist Prior Authorization Policy is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Tracleer, Opsumit, and Letairis is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1]. Approve for the duration noted if the patient meets ONE of the following (A or B):
   A) Initial Therapy. Approve for 3 years if the patient meets all of the following criteria (i, ii, and iii):
      i. The patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
      ii. The agent is prescribed by or in consultation with a cardiologist or a pulmonologist; AND
      iii. The patient meets the following criteria (a and b):
         a) The patient has had a right heart catheterization [documentation required] (see documentation section above); AND
         b) The results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; OR
   B) Patients Currently Receiving the Requested Endothelin Receptor Antagonist (i.e., Tracleer, Letairis or Opsumit). Approve for 3 years if the patient meets the following criteria (i, ii, and iii):
      i. The patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
ii. The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND

iii. The patient meets the following criteria (a and b):
   a) The patient has had a right heart catheterization; AND
   b) The results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH.

Other Uses with Supportive Evidence

Coverage of Tracleer is also recommended in those who meet the following criteria:

2. Chronic Thromboembolic Pulmonary Hypertension (CTEPH). Approve Tracleer for 3 years if the patient meets the following criteria (A and B):
   A) The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
   B) The patient meets ONE of the following conditions (i, ii, or iii):
      i. The patient has tried Adempas; OR
      ii. The patient has a specific contraindication to use of Adempas according to the prescribing physician.
         Note: Examples of contraindications to use of Adempas include that the patient is receiving nitrates or nitric oxide donors, the patient is receiving a phosphodiesterase inhibitor such as sildenafil or tadalafil, or that the patient is hypotensive or is at risk for hypotension; OR
      iii. The patient is currently receiving Tracleer.

3. Digital Ulcers/Systemic Sclerosis. Approve Tracleer for 3 years if the patient meets the following criteria (A or B):
   A) The patient has tried two other therapies for this condition such as calcium channel blockers (CCBs), phosphodiesterase type 5 (PDE5) inhibitors, alpha-adrenergic blockers, nitroglycerin, or angiotensin converting enzyme (ACE) inhibitors.
      Note: Examples of CCBs include amlodipine, felodipine, and nifedipine; an example of an alpha-adrenergic blocker is prazosin; and examples of PDE5 inhibitors include sildenafil and Levitra® (vardenafil tablets); OR
   B) The patient has tried one vasodilator/prostanoid therapy
      Note: Examples of vasodilator/prostanoid therapies include epoprostenol injection and alprostadil injection.

Conditions Not Recommended for Approval

Letairis, Tracleer and Opsumit have has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

References

2. Letairis® tablets [prescribing information]. Foster City, CA: Gilead Sciences; August 2019.


