VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Endothelin Receptor Antagonists

- Letairis® (ambrisentan tablets – Gilead, generics)
- Opsumit® (macitentan tablets – Actelion)
- Tracleer® (bosentan tablets [generic] and tablets for oral suspension – Actelion)

REVIEW DATE: 09/23/2020

OVERVIEW

Letairis, Opsumit and Tracleer are oral endothelin receptor antagonists indicated for the treatment of pulmonary arterial hypertension (PAH) World Health Organization (WHO) Group 1.[1-3] Letairis is indicated to improve exercise ability and delay clinical worsening as well as for use in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.[2] Opsumit is noted to reduce the risks of disease progression and hospitalization for PAH.[3] Tracleer is indicated 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]

The BENEFiT (Bosentan Effects in iNopErable Forms of chronic Thromboembolic pulmonary hypertension) study was a double-blind trial involving patients with chronic thromboembolic pulmonary hypertension (CTEPH) who were randomized to Tracleer or placebo for 16 weeks (n = 156). Benefits were noted in some hemodynamic parameters (e.g., decreased PVR).[4] Adempas® (riociguat tablets), 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.[5] The agent is also indicated for the treatment of adults with PAH (WHO Group 1). Adempas has a Boxed Warning regarding embryofetal toxicity and is contraindicated in patients using nitrates or nitric oxide donors in any forms, as well as in patients using phosphodiestase inhibitors. The main adverse event associated with Adempas is symptomatic hypotension.

Tracleer has been used in patients with systemic sclerosis who have digital ulcers.[6-13] In a 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.[6] 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.[6] Another trial showed a reduction in the occurrence of new digital ulcers in patients given Tracleer for 24 weeks.[10] Many other agents are utilized in digital ulcers.[8,14,15]

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.[16,17] 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.

CTEPH is a persistent obstruction of pulmonary arteries and is often a complication of pulmonary embolism.[18,19] 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

Various guidelines address endothelin receptor antagonists.

- **Pulmonary Arterial Hypertension:** In 2019, an updated CHEST guideline and Expert Panel Report regarding therapy for pulmonary arterial hypertension in adults details many medications. It was noted that endothelin receptor antagonists play a vital role and have various benefits in the management of PAH.[17]
- **Systemic Sclerosis:** In 2017 the European League Against Rheumatism (EULAR) updated recommendations for the treatment of systemic sclerosis.[12] 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 inhibitors or iloprost therapy.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Letairis, Opsumit, and Tracleer. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with these agents, 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.

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 Letairis, Opsumit, and Tracleer is recommended in those who meet the following criteria:

FDA-Approved Indication

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.** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
     - **ii.** Patient meets the following criteria (a and b):
       - **a)** Patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND
       - **b)** Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
     - **iii.** The medication is prescribed by or in consultation with a cardiologist or a pulmonologist.
   - **B)** Patient is Currently Receiving the Requested Endothelin Receptor Antagonist (i.e., Letairis, Opsumit, or Tracleer). Approve for 3 years if the patient meets the following criteria (i, ii, and iii):
     - **i.** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
     - **ii.** Patient meets the following criteria (a and b):
       - **a)** Patient has had a right heart catheterization; AND
       - **b)** Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
     - **iii.** The medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist.

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)** Patient meets one of the following criteria (i, ii, or iii):
     - **i.** Patient has tried Adempas; OR
     - **ii.** Patient has a specific contraindication to use of Adempas according to the prescriber; OR
       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.
     - **iii.** Patient is currently receiving Tracleer.
   - **B)** The medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist.

3. **Digital Ulcers/Systemic Sclerosis.** Approve Tracleer for 3 years if the patient meets the following criteria (A or B):
   - **A)** 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; OR
     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).

B) Patient has tried one vasodilator/prostanoid therapy.
Note: Examples of vasodilator/prostanoid therapies include epoprostenol injection and alprostadil injection.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Letairis, Opsumit, and Tracleer is not recommended in the following situations:

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

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