PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Endothelin Receptor Antagonists
- Letairis® (ambrisentan tablets – Gilead, generic)
- Opsumit® (macitentan tablets – Actelion/Janssen)
- Opsynvi® (macitentan/tadalafil tablets – Actelion/Janssen)
- Tracleer® (bosentan tablets and tablets for oral suspension – Actelion/Janssen, generic for tablets)

REVIEW DATE: 10/02/2024

OVERVIEW

Ambrisentan (Letairis, generic), Opsumit, and bosentan (Tracleer, generic [generic for tablets only]), oral endothelin receptor antagonists, are indicated for the treatment of **pulmonary arterial hypertension** (PAH), World Health Organization (WHO) Group 1.[1-3]

- Ambrisentan 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]
- Bosentan 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]

Opsynvi is a combination of macitentan, an endothelin receptor antagonist (ERA), and tadalafil, a phosphodiesterase 5 (PDE5) inhibitor, indicated for the treatment of **pulmonary arterial hypertension** in adult patients of WHO functional class II to III.[20]

- Opsynvi may be initiated in PAH treatment-naïve patients or in those transitioning from an ERA, PDE5 inhibitor, or a combination of both agents. For treatment-naïve patients and those receiving an ERA only, Opsynvi is started at a low dose with subsequent increase to the maintenance dose once daily. For those transitioning from a PDE5 inhibitor monotherapy or combination ERA and PDE5 inhibitor, the maintenance dose of Opsynvi is initiated.

Clinical Efficacy

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 phosphodiesterase 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]

Disease Overview

PAH is a serious but rare condition impacting fewer than 20,000 patients in the US.[14,15] 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. Although the mean age of diagnosis is between 36 and 50 years, patients of any age may be affected, including pediatric patients. PAH is defined as a mean pulmonary artery pressure (mPAP) > 20 mmHg (at rest) with a pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and a pulmonary vascular resistance > 2 Wood units measured by cardiac catheterization.[19] 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.

CTEPH is a persistent obstruction of pulmonary arteries and is often a complication of pulmonary embolism.[16,17] 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 (PAH):** The CHEST guideline and Expert Panel Report regarding therapy for PAH (2019) in adults details many medications. It was noted that ERAs and PDE5 inhibitors play a vital role and have various benefits in the management of PAH.[15] The European Society of Cardiology and the European Respiratory Society guidelines regarding the treatment of pulmonary hypertension (2022) also recognize PDE5 inhibitors and ERAs as having a prominent role in the management of this condition, as monotherapy or in use as combination with other agents.[18]
- **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 ambrisentan, Opsumit, Opsynvi, and bosentan. 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: Documentation is required for initiation of therapy as 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

I. Coverage of ambrisentan (Letairis, generic), Opsumit, Opsynvi, and bosentan (Tracleer, generic) 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 1 year if the patient meets ALL of the following (i, ii, and iii).
     - **i.** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
     - **ii.** Patient meets BOTH of the following (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., ambrisentan [Letairis, generic], Opsumit, or bosentan [Tracleer, generic]) or Opsynvi. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
     - **ii.** Patient meets BOTH of the following (a and b):
       - **a)** Patient has had a right heart catheterization; AND
         Note: This refers to prior to starting therapy with a medication for WHO Group 1 PAH
       - **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

II. Coverage of bosentan (Tracleer, generic) is also recommended in those who meet the following criteria:

2. **Chronic Thromboembolic Pulmonary Hypertension (CTEPH).** Approve bosentan (Tracleer, generic) for 1 year if the patient meets BOTH of the following (A and B):
   - **A)** Patient meets ONE of the following (i, ii, or iii):
     - **i.** Patient has tried Adempas; OR
     - **ii.** According to the prescriber, use of Adempas is contraindicated; 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 bosentan (Tracleer, generic)
   - **B)** The medication is prescribed by or in consultation with a cardiologist or a pulmonologist.

3. **Digital Ulcers in a Patient with Systemic Sclerosis.** Approve bosentan (Tracleer, generic) for 1 year if the patient meets ONE of the following (A or B):
   A) Patient has tried one calcium channel blocker; OR
   Note: Examples include amlodipine, felodipine and nifedipine.
   B) Patient has tried one phosphodiesterase type 5 (PDE5) inhibitor.
   Note: Examples include sildenafil, tadalafil and vardenafil.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

I. Coverage of ambrisentan (Letairis, generic), Opsumit, and bosentan (Tracleer, generic) 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.

II. Coverage of Opsynvi is not recommended in the following situations:

2. **Concurrent Use With Guanylate Cyclase Stimulators.** Use of Opsynvi with guanylate cyclase stimulators is contraindicated.[1]
   Note: An example of a guanylate cyclase stimulator is Adempas (riociguat tablets).

3. 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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