**BENEFIT DESCRIPTION AND LIMITATIONS OF COVERAGE**

**ITEM:** Letairis® (ambrisentan tablets), Tracleer® (bosentan tablets)  
**PRODUCT LINES:** Commercial HMO/PPO/CDHP  
**COVERED UNDER:**  
   - HMO: Rx  
   - PPO/CDHP: Rx  

**DESCRIPTION:** Blocks endothelin receptor subtypes ET\(_A\) and ET\(_B\) on vascular endothelium and smooth muscle. Stimulation of these receptors in smooth muscle cells is associated with vasoconstriction. Simulation of ET\(_B\) receptors in endothelial cells is associated with vasodilation and antiproliferative effects. Although ambrisentan blocks both ET\(_A\) and ET\(_B\) receptors, the affinity is greater for the \(A\) subtype. Improvement in symptoms of pulmonary artery hypertension and a decrease in the rate of clinical deterioration have been demonstrated in clinical trials.

**CPT/HCPCS Code:** J8499  
**Company Supplying:** Gilead, Actelion  
**Setting:** Oral Rx  
**Coverage Criteria:** Express Scripts, Inc. monograph dated 07/27/2011  
**Approval Period:** up to 12 months

**Recommended Authorization Criteria**

Coverage of bosentan tablets and ambrisentan tablets are recommended in those who meet the following criteria:

**FDA-Approved Indications**

1. **Pulmonary arterial hypertension.** Approve if the patient has had a right-heart catheterization to confirm the diagnosis of PAH to ensure appropriate medical assessment, and if the agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist. Bosentan is FDA-approved for the treatment of PAH (WHO Group 1) in patients with WHO Class III or IV symptoms to improve exercise ability and decrease the rate of clinical worsening. Ambrisentan is indicated for the treatment of PAH (WHO Group 1) in patients with WHO Class II or III symptoms to improve exercise capacity and delay clinical worsening. ACCP guidelines for the screening, early detection, and diagnosis of PAH, established in 2004, recommend a right-heart catheterization to confirm the presence of pulmonary hypertension, establish the diagnosis, and determine PAH disease severity.

2. **Pulmonary arterial hypertension.** For patients who are currently receiving bosentan or ambrisentan therapy, approve if the patient has a diagnosis of PAH and the agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist. The purpose of this criteria is to allow for continuation of therapy in patients who have not had a right-heart catheterization or among those that do not have documentation of this procedure being performed.
Other Uses with Supportive Evidence

Coverage of bosentan tablets only are recommended in those who meet the following criteria:

3. **Digital ulcers.** Approve bosentan if the patient has tried two other therapies for this condition such as calcium channel blockers (e.g., amlodipine, felodipine, isradipine, nifedipine), alpha-adrenergic blockers (e.g., prazosin), nitroglycerin, PDE-5 inhibitors (e.g., sildenafil, vardenafil), or ACE inhibitors OR has tried one vasodilator (e.g., intravenous epoprostenol [Flolan®], intravenous alprostadil [Prostin VR Pediatric®, generic]). Bosentan 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 (Sc; scleroderma) were randomized in a 2:1 ratio to receive bosentan or placebo for 16 weeks. Bosentan was administered as 62.5 mg BID for 4 weeks and then 125 mg BID for 12 weeks. Patients receiving bosentan 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 bosentan at 24 weeks. Many other agents are utilized in digital ulcers.

4. **Chronic Thromboembolic Pulmonary Hypertension (CTEPH).** Approve bosentan. The BENEFIT study (Bosentan Effects in iNopErable Forms of chronic Thromboembolic pulmonary hypertension) was a double-blind trial involving 156 patients with CTEPH who were randomized to placebo or bosentan therapy (target dose of 125 mg BID) for 16 weeks. Benefits were noted in some hemodynamic parameters (e.g., decreased pulmonary vascular resistance), but there was no substantial improvement regarding exercise capacity (mean treatment effect was a 2.2 meter increase in the 6MWD). However, a better treatment effect regarding 6MWD was noted in patients who did not have previous pulmonary endarterectomy surgery. For CTEPH, pulmonary endarterectomy is the treatment of choice; however, this surgical procedure is not possible for 10% to 50% of patients. The 4^th^ World Symposium on Pulmonary Hypertension published a paper that focused on non-PAH-forms of pulmonary hypertension. The paper states that the BENEFIT trial with bosentan is the largest trial in patients with inoperable CTEPH and noted the hemodynamic improvement but lack of improvement regarding 6MWD and time to clinical worsening. Final recommendations include that in severely compromised patients with surgically accessible disease but for whom surgery must be delayed, pre-operative medical therapy (e.g., prostanoids, ERAs or PDE-5 inhibitors) may be used to improve hemodynamics and clinical performance before surgery. Preliminary data suggest that medications currently approved for PAH may have beneficial effects in patients with CTEPH, but as long as there are no robust data from randomized controlled trials, the decision of whether or not to treat CTEPH patients with these medications should be restricted to centers experienced in the management of the disease. If surgery is not possible, only limited options are available for patients with CTEPH.

**Exclusions**

Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.
Table 1. WHO Classification of Functional Status of Patients with Pulmonary Hypertension.

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Patients in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain or presyncope.</td>
</tr>
<tr>
<td>II</td>
<td>Patients who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope.</td>
</tr>
<tr>
<td>III</td>
<td>Patients who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope.</td>
</tr>
<tr>
<td>IV</td>
<td>Patients who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest and symptoms are increase by almost any physical activity.</td>
</tr>
</tbody>
</table>

Table 2. Five Major Categories of Pulmonary Hypertension.

**Group 1: PAH**
- Idiopathic
- Familial
- Associated with:
  - Collagen vascular disease
  - Congenital systemic-to-pulmonic shunt
  - Portal hypertension
  - Human immunodeficiency virus (HIV) infection
  - Drugs and toxins
  - Other: thyroid disorders, glycogen storage disease, Gaucher’s disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy.
- Associated with significant venous or capillary involvement
  - Pulmonary veno-occlusive disease
  - Pulmonary capillary hemangiomatosis
- Persistent pulmonary hypertension of the newborn

**Group 2: Pulmonary hypertension with left heart disease**
- Left-sided ventricular or atrial disease
- Left-sided valvular disease

**Group 3: Pulmonary hypertension associated with lung disease and/or hypoxemia**
- Chronic obstructive lung disease
- Interstitial lung disease
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

**Group 4: Pulmonary hypertension due to chronic thrombotic and/or embolic disease**
- Thromboembolic obstruction of proximal pulmonary arteries
- Thromboembolic obstruction of distal pulmonary arteries

**Group 5: Miscellaneous**
- Sarcoidosis, histiocytosis X, lymphangiomyomatosis, compression of pulmonary vessels.

*AS OF 7/2010*

**APPROVAL:**
**ENDORSED BY:** Pharmacy & Therapeutics Committee  **Original Date:** 1/21/2009
**APPROVED BY:**  **Date:** 7/21/2010