Letairis

Description

Letairis (ambrisentan)

Background
Pulmonary arterial hypertension is a rare disorder of the pulmonary arteries in which the pulmonary arterial pressure rises above normal levels in the absence of left ventricular failure. This condition can progress to cause right-sided heart failure and death (1). Letairis is indicated for treatment of pulmonary arterial hypertension (PAH) which is classified by WHO as Group 1. Letairis is used to treat pulmonary arterial hypertension (PAH, high blood pressure in the lungs) to improve the exercise ability (1).

The World Health Organization (WHO) has classified pulmonary hypertension into five different groups: (2)

**WHO Group 1: Pulmonary Arterial Hypertension (PAH)**
1.1 Idiopathic (IPAH)
1.2 Heritable PAH
   1.2.1 Germline mutations in the bone morphogenetic protein receptor type 2 (BMPR2)
   1.2.2 Activin receptor-like kinase type 1 (ALK1), endoglin (with or without hereditary hemorrhagic telangiectasia), Smad 9, caveolin-1 (CAV1), potassium channel super family K member-3 (KCNK3)
   1.2.3 Unknown
1.3 Drug-and toxin-induced
1.4 Associated with:
   1.4.1 Connective tissue diseases
   1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1'. Pulmonary vena-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
1". Persistent pulmonary hypertension of the newborn (PPHN)

**WHO Group 2: Pulmonary Hypertension Owing to Left Heart Disease**

2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

**WHO Group 3: Pulmonary Hypertension Owing to Lung Disease and/or Hypoxia**

3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental abnormalities

**WHO Group 4: Chronic Thromboembolic Pulmonary Hypertension <CTEPH**

**WHO Group 5: Pulmonary Hypertension with Unclear Multifactorial Mechanisms**

5.1 Hematologic disorders: Chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3 Metabolic disorders: glycogen storage disease, Gaucher’s disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis, segmental PH

The American College of Chest Physicians (ACCP) has published an updated clinical practice guideline for treating PAH. These guidelines use the New York Heart Association (NYHA) functional classification of physical activity scale to classify PAH patients in classes I-IV based on
the severity of their symptoms (3). Letairis is indicated for patients with NYHA Functional Class II or III (1).

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.</td>
</tr>
<tr>
<td>Class II</td>
<td>Patients with pulmonary hypertension resulting in slight limitation of physical activity. These patients are comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.</td>
</tr>
<tr>
<td>Class III</td>
<td>Patients with pulmonary hypertension resulting in marked limitation of physical activity. These patients are comfortable at rest, but less than ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.</td>
</tr>
<tr>
<td>Class IV</td>
<td>Patients with pulmonary hypertension resulting in inability to perform any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present at rest, and discomfort is increased by any physical activity.</td>
</tr>
</tbody>
</table>

**Regulatory Status**

**FDA Approved Indications:** Letairis 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 and in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%) (1).

The distribution of Letairis is limited for female patient through a restricted program called the Letairis Risk Evaluation and Mitigation Strategy. Letairis carries a boxed warning of the contraindication in pregnancy. Letairis should only be administered to women of child-bearing age after a negative pregnancy test (1).

Letairis is contraindicated in patients with idiopathic pulmonary fibrosis (IPF), including patients with IPF with pulmonary hypertension (WHO group 3). Letairis may be given with or without tadalafil (1).

There have been post-marketing reports of decreases in hemoglobin concentration and hematocrit that have resulted in anemia requiring transfusion. Measure hemoglobin prior to initiation of Letairis, at one month, and periodically thereafter. Initiation of Letairis therapy is not recommended for patients with clinically significant anemia. If a clinically significant decrease in hemoglobin is observed and other causes have been excluded, consider discontinuing Letairis (1).
Related policies
Adcirca, Adempas, Flolan/Veletri, Opsumit, Orenitram, Remodulin, Revatio, Tracleer, Tyvaso, Uptravi, Ventavis

Policy
This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Letairis may be considered medically necessary in patients 18 years of age or older for the treatment of pulmonary arterial hypertension, WHO Group 1 and if the conditions indicated below are met.

Letairis may be considered investigational in patients under the age of 18 and for all other indications.

Prior-Approval Requirements
Age 18 years of age or older

Diagnoses
Patient must have ALL the following:

1. Pulmonary Arterial Hypertension (PAH) - WHO Group I
2. NYHA functional classification of physical activity – Class II or III
3. Absence of clinically significant anemia
4. ALL female patients must be enrolled in and meet all the conditions of the Letairis Risk Evaluation and Mitigation Strategy program
5. Female patient must not be pregnant and, if of child bearing potential, use acceptable method of contraception during therapy and for one month after stopping therapy
6. Absence of a concurrent diagnosis of Idiopathic Pulmonary Fibrosis (IPF)
7. Prescriber agrees to monitor for pulmonary edema and discontinue if confirmed

Prior – Approval Renewal Requirements

Age 18 years of age or older

Diagnoses

Patient must have ALL the following:

1. Pulmonary Arterial Hypertension (PAH) - WHO Group I
2. Symptoms have improved or stabilized
3. Female patient must not be pregnant and, if of child bearing potential, use acceptable method of contraception during therapy and for one month after stopping therapy
4. Absence of a concurrent diagnosis of Idiopathic Pulmonary Fibrosis (IPF)
5. Prescriber agrees to monitor for pulmonary edema and discontinue if confirmed

Policy Guidelines

Pre - PA Allowance
None

Prior - Approval Limits
Duration 2 years

Prior – Approval Renewal Limits
Same as above

Rationale

Summary
Pulmonary arterial hypertension is a rare disorder of the pulmonary arteries in which the pulmonary arterial pressure rises above normal levels in the absence of left ventricular failure.
The FDA has approved Letairis (ambrisentan), an endothelin receptor antagonist, for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in patients with NYHA class II or III symptoms (1). Letairis has been shown to improve exercise capacity, symptoms, and hemodynamics in patients with PAH and maybe given with tadalafil. Letairis is a pregnancy category X. Pregnancy must be excluded prior to beginning therapy and monthly pregnancy tests should be obtained during treatment in women of childbearing age. Letairis is contraindicated in patients with a concurrent diagnosis of idiopathic pulmonary fibrosis (IPF) (1).

Prior authorization is required to ensure the safe, clinically appropriate and cost effective use of Letairis while maintaining optimal therapeutic outcomes.

References

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2011</td>
<td>The FDA removes the black box warning for hepatic impairment. Further evaluation of the clinical trial data and post-marketing safety information has led the FDA to conclude that the risk of liver injury in patients treated with this drug is low. Monthly liver function testing is no longer required; instead it should be done periodically based on clinical judgment (8,9).</td>
</tr>
<tr>
<td>June 2012</td>
<td>Annual review</td>
</tr>
<tr>
<td>December 2012</td>
<td>Change to lifetime approval, to match other PAH drugs.</td>
</tr>
<tr>
<td>March 2013</td>
<td>Annual editorial and reference update</td>
</tr>
<tr>
<td>March 2014</td>
<td>Annual editorial and reference update</td>
</tr>
<tr>
<td>March 2015</td>
<td>Annual editorial and reference update</td>
</tr>
<tr>
<td>June 2016</td>
<td>Annual editorial review and reference update.</td>
</tr>
<tr>
<td></td>
<td>Addition of age 18 and use of birth control if child bearing age. Change of name from LEAP to Letairis Risk Evaluation and Mitigation Strategy which is for ALL female patients. Addition of contraindication of concurrent diagnosis of idiopathic pulmonary fibrosis (IPF) and</td>
</tr>
</tbody>
</table>
prescriber agrees to monitor for pulmonary edema and discontinue if confirmed
Policy number change from 5.06.04 to 5.40.16

September 2017  Annual editorial review
September 2018  Annual review
September 2019  Annual editorial review and reference update. Changed approval duration from lifetime to 2 years

**Keywords**

This policy was approved by the FEP® Pharmacy and Therapeutics Committee on September 13, 2019 and is effective on October 1, 2019.