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Section:	Prescription Drugs	**Effective Date:**	April 1, 2025
Subsection:	Cardiovascular Agents	**Original Policy Date:**	June 9, 2011
Subject:	Letairis	**Page:**	1 of 8

Last Review Date: March 7, 2025

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)

The diagnosis of WHO Group 1 PAH requires a right heart catheterization to demonstrate an mPAP ≥ 20mmHg at rest and a pulmonary vascular resistance (PVR) ≥ 3 Wood units, mean pulmonary capillary wedge pressure ≤ 15mmHg (to exclude pulmonary hypertension due to left heart disease, i.e., WHO Group 2 pulmonary hypertension) (4-6).

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 <CTEPHl

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).

Class I	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.
Class II	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.
Class III	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.
Class IV	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.

(3)

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, Opsynvi, Orenitram, PDE5 Inhibitor powders, Remodulin, Revatio, Tracleer, Tyvaso, Uptravi, Ventavis, Winrevair

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** if the conditions indicated below are met.

Letairis may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 18 years of age or older

Diagnosis

Patient must have the following:

1. Pulmonary Arterial Hypertension (PAH) - **WHO Group I**
    a. NYHA functional classification of physical activity – **Class II or III**
    b. Absence of clinically significant anemia
    c. Female patients **only**: must be enrolled in and meet all the conditions of the Letairis Risk Evaluation and Mitigation Strategy program
    d. Prescribed by or recommended by a cardiologist or pulmonologist
    e. Females of childbearing potential should have pregnancy excluded and agree to use acceptable method of contraception during therapy and for one month after stopping therapy
    f. Absence of a concurrent diagnosis of Idiopathic Pulmonary Fibrosis (IPF)

g. Prescriber agrees to monitor for pulmonary edema and discontinue if confirmed
h. **Brand Letairis only:** Patient **MUST** have tried the preferred product (generic Letairis: ambrisentan) unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

Prior – Approval *Renewal* Requirements

Age 18 years of age or older

Diagnosis

Patient must have the following:

1. Pulmonary Arterial Hypertension (PAH) - WHO Group I
    a. Symptoms have improved or stabilized
    b. Females of childbearing potential should have pregnancy excluded and agree to use acceptable method of contraception during therapy and for one month after stopping therapy
    c. Absence of a concurrent diagnosis of Idiopathic Pulmonary Fibrosis (IPF)
    d. Prescriber agrees to monitor for pulmonary edema and discontinue if confirmed
    e. **Brand Letairis only:** Patient **MUST** have tried the preferred product (generic Letairis: ambrisentan) unless the patient has a valid medical exception (e.g., inadequate treatment response, intolerance, contraindication)

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Quantity 30 tablets per 30 days

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. (1). 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

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4. Simonneau G, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1) Epub 2019 Jan 24.
5. Rose-Jones LJ and Mclaughlin V. Pulmonary Hypertension: Types and Treatments. Curr Cardiol Rev. 2015 Feb; 11(1): 73–79.
6. Rudolf KF, et al. Usefulness of pulmonary capillary wedge pressure as a correlate of left ventricular filling pressures in pulmonary arterial hypertension. The Journal of Heart and Lung Transplantation, Vol33, No2. February 2014.

Policy History

Date	Action

March 2011	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).
June 2012	Annual review
December 2012	Change to lifetime approval, to match other PAH drugs. Annual review
March 2013	Annual editorial and reference update
March 2014	Annual editorial and reference update
March 2015	Annual editorial and reference update
June 2016	Annual editorial review and reference update. Addition of age 18 and use of birth control if childbearing 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 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
March 2020	Annual review and reference update. Revised background section and added initial requirement of prescribed by or recommended by a cardiologist or pulmonologist per SME
June 2020	Annual editorial review. Addition of PA quantity limit per FEP
December 2020	Annual review. Added requirement that brand Letairis has to t/f the preferred product ambrisentan
June 2021	Annual review
December 2021	Annual review
June 2022	Annual review
September 2022	Annual review
December 2022	Annual review
June 2023	Annual review
September 2023	Annual review
March 2024	Annual review
September 2024	Annual review
March 2025	Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 7, 2025 and is effective on April 1, 2025.