BlueCross BlueShield Federal Employee Program

LETAIRIS
(ambrisentan)

RATIONALE FOR INCLUSION IN PA PROGRAM

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 <CTEPHI

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) in adult patients 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).

Letairis carries a boxed warning of the contraindication in pregnancy. Letairis should only be administered to females of reproductive potential after a negative pregnancy test. Advise use of effective contraception before initiation, during treatment and for one month after treatment with Letairis (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).

The safety and effectiveness of Letairis in pediatric patients have not been established (1).

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 females of reproductive potential. 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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