

Clinical Policy: Ambrisentan (Letairis)

Reference Number: PA.CP.PHAR.190

Effective Date: 03/16

Last Review Date: 07/18

[Coding Implications](#)

[Revision Log](#)

Description

The intent of the criteria is to ensure that patients follow selection elements established by Pennsylvania Health and Wellness[®] clinical policy for ambrisentan (Letairis[®]).

FDA Approved Indication(s)

Letairis is indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1):

- to improve exercise ability and delay clinical worsening;
- 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 trials predominantly in patients with WHO Functional Class (FC) II-III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%).

Policy/Criteria

It is the policy of health plans affiliated with Pennsylvania Health and Wellness[®] that Letairis is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Pulmonary Hypertension (must meet all):

1. Diagnosis of PAH;
2. Prescribed by or in consultation with a cardiologist or pulmonologist;
3. Failure of a trial of a calcium channel blocker, unless member meets one of the following (a or b):
 - a. Inadequate response or contraindication to acute vasodilator testing;
 - b. Contraindication or clinically significant adverse effects to a calcium channel blocker are experienced;
4. Dose does not exceed 10 mg once daily.

Approval duration: 6 months

B. Other diagnoses/indications: Refer to PA.CP.PMN.53

II. Continued Approval

A. Pulmonary Hypertension (must meet all):

1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA.LTSS.PHAR.01) applies;

2. Member is responding positively to therapy;
3. Prescribed dose of Letairis does not exceed 10 mg once daily.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2):

1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy or the Continuity of Care Policy (PA.LTSS.PHAR.01) applies; or
2. Refer to PA.CP.PMN.53

Background

Description/Mechanism of Action:

Letairis is the brand name for ambrisentan, an endothelin receptor antagonist that is selective for the endothelin type-A (ET_A) receptor. Endothelin-1 (ET-1) is a potent autocrine and paracrine peptide. Two receptor subtypes, ET_A and ET_B, mediate the effects of ET-1 in the vascular smooth muscle and endothelium. The primary actions of ET_A are vasoconstriction and cell proliferation, while the predominant actions of ET_B are vasodilation, antiproliferation, and ET-1 clearance. In patients with PAH, plasma ET-1 concentrations are increased as much as 10-fold and correlate with increased mean right atrial pressure and disease severity. ET-1 and ET-1 mRNA concentrations are increased as much as 9-fold in the lung tissue of patients with PAH, primarily in the endothelium of pulmonary arteries. These findings suggest that ET-1 may play a critical role in the pathogenesis and progression of PAH. Ambrisentan is a high-affinity ET_A receptor antagonist with a high selectivity for the ET_A versus ET_B receptor. The clinical impact of high selectivity for ET_A is not known.

Formulations:

Letairis oral tablets: 5 mg, 10 mg

Appendices

Appendix A: Abbreviation Key

- FC: functional classification
- NYHA: New York Heart Association
- PAH: pulmonary arterial hypertension
- PH: pulmonary hypertension
- WHO: World Health Organization

Appendix B: Pulmonary Hypertension: WHO Classification

- Group 1: PAH (pulmonary arterial hypertension)
- Group 2: PH due to left heart disease
- Group 3: PH due to lung disease and/or hypoxemia
- Group 4: CTEPH (chronic thromboembolic pulmonary hypertension)
- Group 5: PH due to unclear multifactorial mechanisms

Appendix C: Pulmonary Hypertension: WHO/NYHA Functional Classes (FC)

Treatment Approach*	FC	Status at Rest	Tolerance of Physical Activity (PA)	PA Limitations	Heart Failure
Monitoring for progression of PH and treatment of co-existing conditions	I	Comfortable at rest	No limitation	Ordinary PA does not cause undue dyspnea or fatigue, chest pain, or near syncope.	
Advanced treatment of PH with PH-targeted therapy - see Appendix D**	II	Comfortable at rest	Slight limitation	Ordinary PA causes undue dyspnea or fatigue, chest pain, or near syncope.	
	III	Comfortable at rest	Marked limitation	Less than ordinary PA causes undue dyspnea or fatigue, chest pain, or near syncope.	
	IV	Dyspnea or fatigue may be present at rest	Inability to carry out any PA without symptoms	Discomfort is increased by any PA.	Signs of right heart failure

*PH supportive measures may include diuretics, oxygen therapy, anticoagulation, digoxin, exercise, pneumococcal vaccination. **Advanced treatment options also include calcium channel blockers.

Appendix D: Pulmonary Hypertension: Targeted Therapies

Mechanism of Action	Drug Class	Drug Subclass	Drug	Brand/Generic Formulations
Reduction of pulmonary arterial pressure through vasodilation	Prostacyclin* pathway agonist <i>*Member of the prostanoid class of fatty acid derivatives.</i>	Prostacyclin	Epoprostenol	Velettri (IV) Flolan (IV) Flolan generic (IV)
		Synthetic prostacyclin analog	Treprostinil	Orenitram (oral tablet) Remodulin (IV) Tyvasco (inhalation)
			Iloprost	Ventavis (inhalation)
		Non-prostanoid prostacyclin receptor (IP receptor) agonist	Selexipag	Upravi (oral tablet)
	Endothelin receptor antagonist (ETRA)	Selective receptor antagonist	Ambrisentan	Letairis (oral tablet)
		Nonselective dual action receptor antagonist	Bosentan	Tracleer (oral tablet)
	Macitentan		Opsummit (oral tablet)	
	Nitric oxide-cyclic guanosine monophosphate enhancer	Phosphodiesterase type 5 (PDE5) inhibitor	Sildenafil	Revatio (IV, oral tablet, oral suspension)
			Tadalafil	Adcirca (oral tablet)
	Guanylate cyclase stimulant (sGC)	Riociguat	Adempas (oral tablet)	

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-

date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
N/A	

Reviews, Revisions, and Approvals	Date	Approval Date
Removed WHO/NYHA classifications from initial criteria since specialist is involved in care. References reviewed and updated.	02/18	

References

1. Letairis Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; October 2015. Available at http://www.gilead.com/~media/Files/pdfs/medicines/cardiovascular/letairis/letairis_pi.pdf. Accessed November 20, 2017.
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3. Taichman D, Ornelas J, Chung L, et al. CHEST guideline and expert panel report: Pharmacologic therapy for pulmonary arterial hypertension in adults. *Chest.* 2014; 146 (2): 449-475.
4. Abman SH, Hansmann G, Archer SL, et al. Pediatric pulmonary hypertension: Guidelines from the American Heart Association and American Thoracic Society. *Circulation.* 2015 Nov 24; 132(21): 2037-99.
5. Kim NH, Delcroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension. *J Am Coll Cardiol* 2013; 62(25): Suppl D92-99.
6. Galiè N, Humbert M, Vachiary JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of Pulmonary Hypertension. *European Heart Journal.* Doi:10.1093/eurheartj/ehv317.