

Clinical Policy: Ambrisentan (Letairis)

Reference Number: CP.PHAR.190

Effective Date: 03/16

Last Review Date: 03/17

[Coding Implications](#)

[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

Description

The intent of the criteria is to ensure that patients follow selection elements established by Centene® clinical policy for ambrisentan (Letairis®).

Policy/Criteria

It is the policy of health plans affiliated with Centene Corporation® that Letairis is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Pulmonary Hypertension (must meet all):

1. Prescribed by or in consultation with a cardiologist or pulmonologist experienced in the diagnosis and treatment of pulmonary hypertension (PH);
2. Diagnosis of PH confirmed by right heart catheterization and classified as (a and b):
 - a. WHO Group 1: PAH (pulmonary arterial hypertension; Appendix B) and (i or ii):
 - i. Inadequate response or contraindication to acute vasodilator testing;
 - ii. Trial and failure of, or contraindication to, at least one calcium channel blocker;
 - b. WHO/NYHA Functional Class II, III or IV (Appendix C);
3. Prescribed dose of Letairis does not exceed 10 mg once daily.

Approval duration: 6 months

B. Other diagnoses/indications: Refer to CP.PHAR.57 - Global Biopharm Policy.

II. Continued Approval

A. Pulmonary Hypertension (must meet all):

1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
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 Centene benefit and documentation supports positive response to therapy; or
2. Refer to CP.PHAR.57 - Global Biopharm Policy.

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

FDA Approved Indications:

Letairis is an endothelin receptor antagonist/oral tablet formulation indicated for:

- Treatment of PAH (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 predominantly patients with WHO Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

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	Veletri (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 Macitentan	Tracleer (oral tablet) 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
Policy split from CP.PHAR.33.PAH and converted to new template. Criteria: added specialist requirement; removed echocardiogram as an option for confirming a PH diagnosis; removed hard stop after 3 months of therapy. Appendices removed: 1) examples of calcium channel blocker contraindications; 2) nitrate therapy examples; 3) PAH definition.	02/16	03/16
FC II is added to the prostanoid class of PH drugs. Safety criteria were removed unless they represent contraindications or black box warnings not covered by a REMS program, and 2) provide specific lab/imaging parameters that must be met prior to initiation of therapy. An efficacy statement is added to the continuation criteria. Initial and continuation criteria durations increased to 6 and 12 months respectively. Appendices covering PH group, functional class and therapy reorganized.	02/17	03/17

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

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Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at <http://www.cms.gov> for additional information.

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