

## **Clinical Policy: Ambrisentan (Letairis)**

Reference Number: CP.PHAR.190

Effective Date: 03.16

Last Review Date: 02.19

Line of Business: Commercial, HIM, Medicaid

[Revision Log](#)

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

### **Description**

Ambrisentan (Letairis<sup>®</sup>) is an endothelin receptor antagonist.

### **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**

*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

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

#### **I. Initial Approval Criteria**

##### **A. Pulmonary Arterial Hypertension** (must meet all):

1. Diagnosis of PAH;
2. Prescribed by or in consultation with a cardiologist or pulmonologist;
3. Failure of a calcium channel blocker (*see Appendix B*), 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 calcium channel blockers are experienced;
4. Dose does not exceed 10 mg per day.

##### **Approval duration:**

**Medicaid/HIM** – 6 months

**Commercial** – Length of Benefit

**B. Other diagnoses/indications**

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

**II. Continued Therapy**

**A. Pulmonary Arterial 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. If request is for a dose increase, new dose does not exceed 10 mg per day.

**Approval duration:**

**Medicaid/HIM** – 12 months

**Commercial** – Length of Benefit

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

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.

**Approval duration: Duration of request or 6 months (whichever is less);** or

2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid

**III. Diagnoses/Indications for which coverage is NOT authorized:**

- A.** Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

**IV. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*

FC: functional class

FDA: Food and Drug Administration

NYHA: New York Heart Association

PAH: pulmonary arterial hypertension

PH: pulmonary hypertension

WHO: World Health Organization

*Appendix B: Therapeutic Alternatives*

*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.*

| <b>Drug Name</b>   | <b>Dosing Regimen</b>                          | <b>Dose Limit/<br/>Maximum Dose</b> |
|--|--|-------------------------------------|
| nifedipine (Adalat <sup>®</sup> CC, Afeditab <sup>®</sup> CR, Procardia <sup>®</sup> , Procardia XL <sup>®</sup> ) | 60 mg PO QD; may increase to 120 to 240 mg/day | 240 mg/day                          |

| Drug Name   | Dosing Regimen      | Dose Limit/<br>Maximum Dose |
|---|---------------------|-----------------------------|
| diltiazem (Dilacor XR <sup>®</sup> , Dilt-XR <sup>®</sup> , Cardizem <sup>®</sup> CD, Cartia XT <sup>®</sup> , Tiazac <sup>®</sup> , Taztia XT <sup>®</sup> , Cardizem <sup>®</sup> LA, Matzim <sup>®</sup> LA) | 720 to 960 mg PO QD | 960 mg/day                  |
| amlodipine (Norvasc <sup>®</sup> )  | 20 to 30 mg PO QD   | 30 mg/day                   |

*Therapeutic alternatives are listed as Brand name<sup>®</sup> (generic) when the drug is available by brand name only and generic (Brand name<sup>®</sup>) when the drug is available by both brand and generic.*

*Appendix C: Contraindications/Boxed Warnings*

- Contraindication(s):
  - Pregnancy
  - Idiopathic pulmonary fibrosis
- Boxed warning(s): embryo-fetal toxicity

*Appendix D: 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 E: 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 F**     | 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 F: 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<br><br><i>*Member of the prostanoid class of fatty acid derivatives.</i> | Prostacyclin                                 | Epoprostenol          | Velettri (IV)<br>Flolan (IV)<br>Flolan generic (IV)              |
|   |  | Synthetic prostacyclin analog                | Treprostinil          | Orenitram (oral tablet)<br>Remodulin (IV)<br>Tyvaso (inhalation) |
|   |  |  | Iloprost              | Ventavis (inhalation)  |
|   | Non-prostanoid prostacyclin receptor (IP receptor) agonist   | Selexipag                                    | Uptravi (oral tablet) |  |
|   | Endothelin receptor antagonist (ETRA)  | Selective receptor antagonist                | Ambrisentan           | Letairis (oral tablet)   |
|   |  | Nonselective dual action receptor antagonist | Bosentan              | Tracleer (oral tablet)   |
|   | Macitentan   |  | Opsumit (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)  |

**V. Dosage and Administration**

| Indication | Dosing Regimen | Maximum Dose |
|------------|----------------|--------------|
| PAH        | 5 mg PO QD     | 10 mg/day    |

**VI. Product Availability**

Tablets: 5 mg, 10 mg

**VII. 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](http://www.gilead.com/~media/Files/pdfs/medicines/cardiovascular/letairis/letairis_pi.pdf).  
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2. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association - developed in collaboration with the American College of Chest Physicians, American Thoracic Society, Inc., and the Pulmonary Hypertension Association. *J Am Coll Cardiol*. 2009; 53(17): 1573-1619.
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.

| Reviews, Revisions, and Approvals  | Date     | P&T Approval Date |
|--|----------|-------------------|
| <p>Policy split from CP.PHAR.33.PAH and converted to new template.<br/>Criteria: added specialist requirement; removed echocardiogram as an option for confirming a PH diagnosis; removed hard stop after 3 months of therapy.<br/>Appendices removed: 1) examples of calcium channel blocker contraindications; 2) nitrate therapy examples; 3) PAH definition.</p>   | 02.16    | 03.16             |
| <p>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.<br/>Appendices covering PH group, functional class and therapy reorganized.</p> | 02.17    | 03.17             |
| <p>1Q18 annual review: Policies combined for HIM and Medicaid; Converted to new template; Removed WHO/NYHA classifications from initial criteria since specialist is involved in care; References reviewed and updated.</p>  | 11.20.17 | 02.18             |
| <p>1Q 2019 annual review: added Commercial line of business; no significant changes; references reviewed and updated.</p>  | 11.20.18 | 02.19             |

**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.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

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This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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**Note:**

**For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

**For Health Insurance Marketplace members**, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the formulary exception policy.

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