Clinical Policy Title:	ambrisentan
Policy Number:	RxA.203
Drug(s) Applied:	Letairis®
Original Policy Date:	02/07/2020
Last Review Date:	06/10/2021
Line of Business Policy Applies to:	All lines of business

Background

Ambrisentan (Letairis®) is an endothelin receptor antagonist.

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%).

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
ambrisentan (Letairis®)	Pulmonary arterial hypertension	5 mg PO once daily	10 mg/day

Dosage Forms

- Tablets: 5 mg, 10 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

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. Age 18 years of age or older;
4. Member does not have moderate or severer hepatic impairment;
5. 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;
6. Dose does not exceed 10 mg per day.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. Pulmonary arterial hypertension (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
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
Commercial: 12 months
Medicaid: 12 months

III. Appendices

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
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
nifedipine (Adalat CC®, Procardia®, Procardia XL®)	60 mg PO once daily; may increase to 120 to 240 mg/day	240 mg/day
diltiazem (, Dilt-XR®, Cardizem CD®, Cartia XT®, Tiazac®, Taztia XT®, Cardizem LA®, Matzim LA®)	720 to 960 mg PO once daily	960 mg/day
amlodipine (Norvasc®)	20 to 30 mg PO once daily	30 mg/day

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

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Pregnancy
  - Idiopathic pulmonary fibrosis with pulmonary hypertension (WHO Group 3)
- Boxed Warning(s):
  - Embryo-fetal toxicity

APPENDIX D: General Information

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

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 **	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.	

Treatment Approach*	FC	Status at Rest	Tolerance of Physical Activity (PA)	PA Limitations	Heart Failure
	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.

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 **Member of the prostanoid class of fatty acid derivatives.*	Prostacyclin	Epoprostenol	Veletri® (IV) Flolan (IV) Flolan generic (IV)
		Synthetic prostacyclin analog	Treprostinil	Orenitram® (oral tablet) Remodulin® (IV) 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	Phosphodiesterase type 5	Sildenafil	Revatio® (IV, oral tablet, oral suspension)

Mechanism of Action	Drug Class	Drug Subclass	Drug	Brand/Generic Formulations
	monophosphate enhancer	(PDE5) inhibitor	Tadalafil	Adcirca® (oral tablet)
		Guanylate cyclase stimulant (sGC)	Riociguat	Adempas® (oral tablet)

References

1. Letairis Prescribing Information. Foster City, CA: Gilead Sciences, Inc.; August 2019. Available at: http://www.gilead.com/~/media/Files/pdfs/medicines/cardiovascular/letairis/letairis_pi.pdf. Accessed March 03, 2021.
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. Accessed March 03, 2021.
3. 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. Accessed March 03, 2021.
4. 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. Accessed March 03, 2021.
5. 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. Accessed March 03, 2021.
6. Kim NH, Delcroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension.J Am Coll Cardiol 2013; 62(25): Suppl D92-99. Accessed March 03, 2021.
7. 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. Accessed March 03, 2021.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Policy description table was updated 2. Continuation therapy criteria II.A.1. was rephrased to “Member is currently receiving medication that has been authorized by RxAdvance…” 3. Appendix C, contraindications was updated 4. Initial therapy and continued therapy approval duration for “commercial” was updated from length of benefit to 6 months and 12 months respectively 5. References were updated	06/15/2020	09/14/2020

Policy was reviewed: 1. Statement about provider sample, ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy. 2. Age criteria was added to Initial approval criteria I.A.3. 3. Safety criteria about hepatic impairment was added to initial approval criteria I.A.4. 4. Therapeutic alternative verbiage was updated to “Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements”. 5. References were reviewed and updated.	03/04/2021	06/10/2021