Clinical Policy: Endothelin Receptor Antagonists-ETRA (Letairis, Opsumit, Tracleer)

Reference Number: AZ.CP.PHAR.1012
Effective Date: 08.18.19
Last Review Date: 02.22
Line of Business: Arizona Medicaid (AzCH-CCP and Care1st) Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
The following are endothelin receptor antagonists (ETRAs) requiring prior authorization: ambrisentan (Letairis®), bosentan (Tracleer®), and macitentan (Opsumit®).

AHCCCS preferred drugs in this class include Letairis (brand only) and Tracleer (brand only).

AHCCCS non-preferred drugs in this class include ambrisentan (generic), bosentan (generic), and Opsumit.

FDA approved indications
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%).

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

- In adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with New York Heart Association (NYHA) Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%)
- In pediatric patients aged 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability

Opsumit is indicated for treatment of pulmonary arterial hypertension (PAH) (World Health Organization (WHO) Group I) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH

treatment). Opsumit also reduced hospitalization for PAH.
Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients were treated with Opsumit monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

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 Arizona Complete Health-Complete Care Plan and Care1st that endothelin receptor antagonists (ETRAs) are **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. Right heart catheterization (RHC) results with a mean pulmonary arterial pressure (PAP) $\geq$ 25 mm Hg;
4. For Letairis and Tracleer requests: brand only;
5. For Opsumit requests: failure of Letairis AND Tracleer, unless contraindicated or clinically significant adverse effects are experienced;
6. 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 blocker;
7. Dose does not exceed the FDA approved maximum recommended dose (*see Section V*).

Approval duration: 6 months

B. Other diagnoses/indication

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): AZ.CP.PMN.53 for Arizona 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 the FDA approved maximum recommended dose (*see Section V*).

Approval duration: 12 months

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 – AZ.CP.PMN.53 for Arizona Medicaid.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FC: functional class
FDA: Food and Drug Administration
NYHA: New York Heart Association
RHC: right heart catheterization
PAH: pulmonary arterial hypertension
PH: pulmonary hypertension
WHO: World Health Organization
PAP: pulmonary arterial pressure

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.

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

Drug Name	Contraindication(s)	Boxed Warning(s)
Letairis (ambrisentan)	• Pregnancy • Idiopathic Pulmonary Fibrosis	• Embryo-fetal toxicity
Tracleer (bosentan)	• Pregnancy • Use with cyclosporine	• Risk of hepatotoxicity • Embryo-fetal toxicity

Drug Name	Contraindication(s)	Boxed Warning(s)
	• Use with glyburide • Hypersensitivity	
Opsumit (macitentan)	• Pregnancy	• 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

CLINICAL POLICY
Endothelin Receptor Antagonists (ETRA)

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 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

Drug Name	Dosing Regimen	Maximum Dose
Letairis (ambrisentan)	5 mg PO QD	10 mg/day
Tracleer (bosentan)	Initially 62.5 mg PO BID for 4 weeks, then increased to 125 mg PO BID	250 mg/day
Opsumit (macitentan)	10 mg PO QD	10 mg/day

VI. Product Availability

Drug Name	Availability
Letairis (ambrisentan)	Tablets: 5 mg, 10 mg
Tracleer (bosentan)	Tablets: 62.5 mg, 125 mg Tablet for oral suspension: 32 mg

Drug Name	Availability
Opsumit (macitentan)	Tablets: 10 mg

VII. References

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CLINICAL POLICY
Endothelin Receptor Antagonists (ETRA)

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	08.18.19	10.19
1Q 2020 annual review: no significant changes; added max quantity per day; references reviewed and updated.	01.14.2020	01.2020
1Q 2021 annual review: no significant changes; references reviewed and updated.	02.11.21	02.12.21
Added Care1st logo. Added verbiage to specify that criteria also applies to Care1st.	5.10.21	04.21
1Q 2022 annual review: no significant changes; references reviewed and updated.	12.23.21	02.22

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.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

CLINICAL POLICY
Endothelin Receptor Antagonists (ETRA)

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.

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