MEDICAL MUTUAL®

Drug Policy

Policy:	Endothelin Receptor Antagonists (ERAs) Tracleer (bosentan) Letairis (ambrisentan) Opsumit (macitentan)	Annual Review Date: 02/20/2024 Last Revised Date: 02/20/2024

OVERVIEW

Tracleer, Letairis and Opsumit are oral endothelin receptor antagonists (ERAs) that are used for the treatment of pulmonary arterial hypertension (PAH). Tracleer, which is given twice daily (BID), is indicated for the treatment of PAH (World Health Organization [WHO] Group 1) to improve exercise ability and decrease the rate of clinical worsening. Studies establishing the effectiveness included predominantly those with New York Heart Association (NYHA) Functional Class II to IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%). Patients with WHO Class II symptoms demonstrated reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider if these benefits are sufficient to offset the risk of liver injury in WHO Class II patients, which may preclude future use as disease progression occurs. Letairis, which is given once daily (QD), is indicated for the treatment of PAH (WHO Group 1) to improve exercise ability and delay clinical worsening; it is also indicated for use in combination with Adcirca (tadalafil tablets) to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability. Studies establishing effectiveness included predominantly those with WHO Functional Class II to III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%). Opsumit, which is given QD, is indicated for the treatment of PAH (WHO Group 1) to delay disease progression. Disease progression included: death, initiation of intravenous or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsening PAH symptoms, and need for additional PAH treatment). Opsumit also reduced hospitalizations for PAH. All agents are in Pregnancy Category X and have a Boxed Warning regarding teratogenicity. Tracleer has a Boxed Warning regarding hepatotoxicity. All agents have a Boxed Warning regarding embryofetal toxicity.

POLICY STATEMENT

This policy involves the use of ERAs. Prior authorization is recommended for pharmacy benefit coverage of ERAs. Approval is recommended for those who meet the conditions of coverage in the **Criteria and Initial/Extended Approval** for the diagnosis provided. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria. Requests for uses not listed in this policy will be reviewed for evidence of efficacy and for medical necessity on a case-by-case basis.

Because of the specialized skills required for evaluation and diagnosis of patients treated with ERAs as well as the monitoring required for adverse events and long-term efficacy, initial approval requires ERAs be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy unless otherwise noted below.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of ERAs is recommended in those who meet the following criteria:

1. **Pulmonary Arterial Hypertension (World Health Organization [WHO] Group 1), Initial Therapy**
   Criteria. *Patient must meet the following criteria*
   - **A.** The patient has a diagnosis of PAH (WHO Group 1); AND
   - **B.** The patient has had a right heart catheterization to confirm the diagnosis of PAH (WHO Group 1) and results confirm all of the following [documentation required]:
     - **a.** Mean pulmonary arterial pressure (mPAP) greater than or equal to 25 mmHg at rest; AND
     - **b.** Pulmonary capillary wedge pressure (PCWP) less than or equal to 15 mmHg; AND
     - **c.** Pulmonary vascular resistance (PVR) greater than 3 Wood units; AND
   - **C.** The agent is prescribed by or in consultation with a cardiologist or pulmonologist; AND
   - **D.** Medication will not be used in combination with another advanced therapy pulmonary hypertension agent, unless under ONE of the following conditions:
     - **a.** Inadequate control of PAH; OR
     - **b.** The requested medication is Letairis for use in combination with Adcirca (tadalafil); AND
   - **E.** Patient is NOT pregnant and complies with the pregnancy and contraception requirements in the REMS program; AND
   - **F.** The prescriber has fulfilled the REMS requirements for certification; AND
   - **G.** If the request is for brand Letairis or Tracleer, the patient has failed a trial of the respective generic product and/or the patient cannot take the respective generic product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the generic product which would result in a significant allergy or serious adverse reaction per the prescribing physician [documentation required].

2. **Pulmonary Arterial Hypertension (World Health Organization [WHO] Group 1), Patients Currently Receiving the Requested ERA**
   Criteria. *Patient must meet the following criteria*
   - **A.** The patient has a diagnosis of PAH (WHO Group 1); AND
   - **B.** The patient has had a right heart catheterization to confirm the diagnosis of PAH (WHO Group 1) [documentation required]; AND
   - **C.** The patient is currently experiencing a beneficial response as determined by the physician (e.g. improvement in functional class or quality of life, or in other hemodynamic or clinical parameters); AND
   - **D.** The requested agent is prescribed by or in consultation with a cardiologist or pulmonologist; AND
   - **E.** Medication will NOT be used in combination with another advanced therapy pulmonary hypertension agent, unless under ONE of the following conditions:
     - **a.** Inadequate control of PAH; OR
     - **b.** The requested medication is Letairis for use in combination with Adcirca (tadalafil); AND
   - **F.** Patient is NOT pregnant and complies with the pregnancy and contraception requirements in the REMS program; AND
   - **G.** The prescriber has fulfilled the REMS requirements for certification; AND

H. If the request is for brand Letairis or Tracleer, the patient has failed a trial of the respective generic product and/or the patient cannot take the respective generic product due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product which would result in a significant allergy or serious adverse reaction per the prescribing physician [documentation required].

3. Chronic Thromboembolic Pulmonary Hypertension (CTEPH), WHO Group 4

Criteria. *Patient must meet the following criteria*

A. The request is for Tracleer (brand or generic); AND
B. Tracleer is prescribed by or in consultation with a cardiologist or pulmonologist; AND
C. The patient meets ONE of the following:
  a. The patient has tried Adempas; OR
  b. The patient has a specific contraindication to use of Adempas according to the prescribing physician (e.g. the patient is receiving nitrates or nitric oxide donors, the patient is receiving a phosphodiesterase inhibitor [e.g. Revatio, Adcirca, sildenafil], the patient is hypotensive or at risk for hypotension); OR
  c. The patient is currently receiving Tracleer for CTEPH; AND
D. The patient has been treated surgically or CTEPH is inoperable
E. For brand Tracleer, the patient has failed a trial of generic bosentan and/or the patient cannot take generic bosentan due to a formulation difference in the inactive ingredient(s) [e.g., difference in dyes, fillers, preservatives] between the brand and the bioequivalent generic product which would result in a significant allergy or serious adverse reaction per the prescribing physician [documentation required].

4. Digital Ulcers in Systemic Sclerosis

Criteria. *Patient must meet the following criteria*

A. The request is for Tracleer (brand or generic); AND
B. The patient meets one of the following:
  a. The patient has tried one vasodilator/prostanoid therapy [examples include epoprostenol injection and alprostadil injection]; OR
  b. The patient has tried two other therapies for this condition such as calcium channel blockers (CCBs) [examples include amlodipine, felodipine, and nifedipine], phosphodiesterase type 5 (PDE5) inhibitors [examples include sildenafil and Levitra (vardenafil)], alpha-adrenergic blockers [example: prazosin], nitroglycerin, or angiotensin converting enzyme (ACE) inhibitors; AND
C. For brand Tracleer, the patient has failed a trial of generic bosentan and/or the patient cannot take generic bosentan due to a formulation difference in the inactive ingredient(s) [e.g. differences in dyes, fillers, preservatives] between the brand and the bioequivalent generic product which would result in a significant allergy or serious adverse reaction per the prescribing physician [documentation required]

Initial Approval/ Extended Approval.
A) *Initial Approval:* 1 year
B) *Extended Approval:* 1 year

CONDITIONS NOT RECOMMENDED FOR APPROVAL

ERAs have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

REFERENCES

1. Tracleer® tablets [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals, Inc; July 2022.
2. Letairis® tablets [prescribing information]. Foster City, CA: Gilead Sciences; August 2019.
3. Opsumit® tablets [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals; June 2023.
4. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *CHEST*. 2004;126:14-34.
5. 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.
6. Badesch DB, Abman SH, Simonneau G, et al. Medical therapy for pulmonary arterial hypertension. Updated ACCP evidence-based clinical practice guidelines. *CHEST*. 2007;131:1917-1928.
7. Korn JH, Mayes M, Cerinic MM, et al, for the RAPIDS-1 study group. Digital ulcers in systemic sclerosis. *Arthritis Rheum*. 2004;50(12):3985-3993.
8. Jain M, Varga J. Bosentan for the treatment of systemic sclerosis-associated pulmonary arterial hypertension, pulmonary fibrosis and digital ulcers. *Expert Opin Pharmacother*. 2006;7(11):1487-1501.
9. Chung L, Fiorentino D. Digital ulcers in patients with systemic sclerosis. *Autoimmun Rev*. 2006;5(2):125-128.
10. Pope JE. The diagnosis and treatment of Raynaud's phenomenon. A practical approach. *Drugs*. 2007;67(4):517-525.
11. Steen V, Denton CP, Pope JE, Matucci-Cerinic M. Digital ulcers: overt vascular disease in systemic sclerosis. *Rheumatology* (*Oxford*). 2009;48(Suppl 3):iii19-iii24.
12. Matucci-Cerinic M, Denton CP, Furst DE, et al. Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomized, double-blind, placebo-controlled trial. *Ann Rheum Dis*. 2011;70:32-38.
13. Dhillon S. Bosentan. A review of its use in the management of digital ulcers associated with systemic sclerosis. *Drugs*. 2009;69(14):2005-2024.

14. Kowal-Bielecka O, Fransen J, Avouac J, et al, for the EUSTAR Coauthors. Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis*. 2017;76:1327-1339.
15. Walker KM, Pope J, on behalf of participating members of the Scleroderma Clinical Trials Consortium (SCTC) and Canadian Scleroderma Research Group (CSRG). Treatment of systemic sclerosis complications: what to use when first-line treatment fails-a consensus of systemic sclerosis experts. *Semin Arthritis Rheum*. 2012;42(1):42-55.
16. Adempas™ tablets [prescribing information]. Wayne, NJ: Bayer; September 2021.
17. Jais W, D'Armini AM, Jansa P, et al, for the BENEFiT Study Group. Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension. BENEFiT (Bosentan Effects in iNopErable Forms of chronic Thromboembolic pulmonary hypertension), a Randomized, Placebo-Controlled Trial. *J Am Coll Cardiol*. 2008;52:2127-2134.
18. Jaff MR, McMurtry S, Archer SL, on behalf of the American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, Council on Peripheral Vascular Disease, and Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation*. 2011;123:1788-1830.
19. Hoeper MM, Mandani MM, Nakanishi N, et al. Chronic thromboembolic pulmonary hypertension. *Lancet Respir Med*. 2014;2(7):573-582.
20. Kim NH. Group 4 pulmonary hypertension. Chronic thromboembolic pulmonary hypertension: epidemiology, pathophysiology, and treatment. *Cardiol Clin*. 2016;34:435-441.
21. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D34-D41.
22. Wigley FM, Flavahan NA. Raynaud's phenomenon. *N Engl J Med*. 2016;375(6):556-565.
23. Cruz JE, Ward A, Anthony S, et al. Evidence for the use of epoprostenol to treat Raynaud's phenomenon with or without digital ulcers: a review of the literature. *Ann Pharmacother*. 2016;50(12):1060-1067.
24. Bosentan. In: DRUGDEX [online database]. Truven Health Analytics; Greenwood Village, CO. Last updated 24 January 2024. Accessed on 20 February 2024.
25. Macitentan. In: DRUGDEX [online database]. Truven Health Analytics; Greenwood Village, CO. Last updated 12 August 2023. Accessed 20 February 2024.
26. Ambrisentan. In: DRUGDEX [online database]. Truven Health Analytics; Greenwood Village, CO. Last updated 11 December 2023. Accessed 20 February 2024.
27. Bosentan. In: Lexi-Drugs. Lexicomp. Wolters Kluwer Clinical Drug Information, Inc.; Riverwoods, IL. Available at: http://www.online.lexi.com. Last updated 1 February 2024. Accessed on 20 February 2024.