Drug Coverage Policy

Effective Date.....8/15/2024
Coverage Policy Number.....IP0631
Policy Title.....Endothelin Receptor Antagonists

Pulmonary Arterial Hypertension – Endothelin Receptor Antagonists

- Letairis® (ambrisentan tablets – Gilead, generic)
- Opsumit® (macitentan tablets – Actelion/Janssen)
- Opsynvi® (macitentan/tadalafil tablets – Actelion/Janssen)
- Tracleer® (bosentan tablets and tablets for oral suspension - Actelion/Janssen, generic for tablets)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna Healthcare Coverage Policy

OVERVIEW

Ambrisentan (Letairis, generic), Opsumit, and bosentan (Tracleer, generic [generic for tablets only]), oral endothelin receptor antagonists, are indicated for the treatment of **pulmonary arterial hypertension** (PAH), World Health Organization (WHO) Group 1.[1-3]

- Ambrisentan is indicated to improve exercise ability and delay clinical worsening as well as for use in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.[2]
- Opsumit is noted to reduce the risks of disease progression and hospitalization for PAH.[3]
- Bosentan is indicated in adults to improve exercise ability and decrease the rate of clinical worsening and in pediatric patients ≥ 3 years of age with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability.[1]

Opsynvi is a combination of macitentan, an endothelin receptor antagonist (ERA), and tadalafil, a phosphodiesterase 5 (PDE5) inhibitor, indicated for the treatment of **pulmonary arterial hypertension** in adult patients of WHO functional class II to III.[20]

- Opsynvi may be initiated in PAH treatment-naïve patients or in those transitioning from an ERA, PDE5 inhibitor, or a combination of both agents. For treatment-naïve patients and those receiving an ERA only, Opsynvi is started at a low dose with subsequent increase to the maintenance dose once daily. For those transitioning from a PDE5 inhibitor monotherapy or combination ERA and PDE5 inhibitor, the maintenance dose of Opsynvi is initiated.

Clinical Efficacy

The BENEFiT (Bosentan Effects in iNopErable Forms of chronic Thromboembolic pulmonary hypertension) study was a double-blind trial involving patients with chronic thromboembolic pulmonary hypertension (CTEPH) who were randomized to Tracleer or placebo for 16 weeks (n = 156). Benefits were noted in some hemodynamic parameters (e.g., decreased PVR).[4] Adempas® (riociguat tablets), a soluble guanylate cyclase stimulator, is the only agent indicated for the treatment of adults with CTEPH (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.[5] The agent is also indicated for the treatment of adults with PAH (WHO Group 1). Adempas has a Boxed Warning regarding embryofetal toxicity and is contraindicated in patients using nitrates or nitric oxide donors in any forms, as well as in patients using phosphodiesterase inhibitors. The main adverse event associated with Adempas is symptomatic hypotension.

Tracleer has been used in patients with systemic sclerosis who have digital ulcers.[6-13] In a prospective, multicenter, placebo-controlled, double-blind study patients (n = 122) with limited or diffuse systemic sclerosis (scleroderma) were randomized in a 2:1 ratio to receive Tracleer or placebo for 16 weeks.[6] Patients receiving Tracleer had a 48% reduction in the mean number of new ulcerations (1.4 vs. 2.7 new ulcers; P = 0.0083), the primary efficacy endpoint. The effect was more substantial in patients with digital ulcers at study entry. However, no differences were noted in the healing of established ulcers.[6] Another trial showed a reduction in the occurrence of new digital ulcers in patients given Tracleer for 24 weeks.[10]

Disease Overview

PAH is a serious but rare condition impacting fewer than 20,000 patients in the US.[14,15] It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized. In this progressive disorder, the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment. Although the mean age of diagnosis is between 36 and 50 years, patients of any age may be affected, including pediatric patients. PAH is defined as a mean pulmonary artery pressure (mPAP) > 20 mmHg (at rest) with a pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and a pulmonary vascular resistance > 2 Wood units measured by cardiac

catheterization.[19] The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved.

CTEPH is a persistent obstruction of pulmonary arteries and is often a complication of pulmonary embolism.[16,17] It is classified within Group 4 pulmonary hypertension. Symptoms include progressive dyspnea on exertion, as well as fatigue, syncope, hemoptysis, and signs of right heart failure. Pulmonary endarterectomy is the treatment of choice for most patients with CTEPH. However, around 40% of patients are deemed inoperable for various reasons. Medication therapy may also be recommended. Anticoagulant therapy is also given.

Guidelines

Various guidelines address endothelin receptor antagonists.

- **Pulmonary Arterial Hypertension (PAH):** The CHEST guideline and Expert Panel Report regarding therapy for PAH (2019) in adults details many medications. It was noted that ERAs and PDE5 inhibitors play a vital role and have various benefits in the management of PAH.[15] The European Society of Cardiology and the European Respiratory Society guidelines regarding the treatment of pulmonary hypertension (2022) also recognize PDE5 inhibitors and ERAs as having a prominent role in the management of this condition, as monotherapy or in use as combination with other agents.[18]
- **Systemic Sclerosis:** In 2017, the European League Against Rheumatism (EULAR) updated recommendations for the treatment of systemic sclerosis.[12] Tracleer should be considered to reduce the number of new digital ulcers in systemic sclerosis, especially in patients who have multiple digital ulcers despite use of calcium channel blockers, phosphodiesterase type 5 inhibitors or iloprost therapy.

Medical Necessity Criteria

I. <u>Ambrisentan (Letairis, generic), Opsumit, Opsynvi, and bosentan (Tracleer, generic)</u> are considered medically necessary when the following criteria are met:

FDA-Approved Indication

1. Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1]. Approve for the duration noted if the patient meets ONE of the following (A <u>or</u> B):

A) <u>Initial Therapy</u>. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, <u>and</u> iv).

- **i.** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
- **ii.** Patient meets BOTH of the following (a <u>and</u> b):
  - **a)** Patient has had a right heart catheterization; AND
  - **b)** Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
- **iii.** The medication is prescribed by or in consultation with a cardiologist or a pulmonologist; AND
- **iv.** Preferred product criteria is met for the product(s) as listed in the below table(s).

B) <u>Patient is Currently Receiving the Requested Endothelin Receptor Antagonist (i.e., ambrisentan [Letairis, generic], Opsumit, or bosentan [Tracleer, generic]) or Opsynvi</u>. Approve for 1 year if the patient meets ALL of the following (i, ii, <u>and</u> iii):

- **i.** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
- **ii.** Patient meets BOTH of the following (a <u>and</u> b):

a) Patient has had a right heart catheterization; AND
Note: This refers to prior to starting therapy with a medication for WHO Group 1 PAH
b) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

iii. The medication is prescribed by or in consultation with a cardiologist or a pulmonologist.

Other Uses with Supportive Evidence

II. Bosentan (Tracleer, generic) is also considered medically necessary when the following criteria are met:

2. **Chronic Thromboembolic Pulmonary Hypertension (CTEPH).** Approve bosentan (Tracleer, generic) for 1 year if the patient meets ALL of the following (A, B, and C):
   A) Patient meets ONE of the following (i, ii, or iii):
      i. Patient has tried Adempas; OR
      ii. According to the prescriber, use of Adempas is contraindicated; OR
      Note: Examples of contraindications to use of Adempas include that the patient is receiving nitrates or nitric oxide donors, the patient is receiving a phosphodiesterase inhibitor such as sildenafil or tadalafil, or that the patient is hypotensive or is at risk for hypotension.
      iii. Patient is currently receiving bosentan (Tracleer, generic); AND
   B) The medication is prescribed by or in consultation with a cardiologist or a pulmonologist; AND
   C) Preferred product criteria is met for the product(s) as listed in the below table(s).

3. **Digital Ulcers in a Patient with Systemic Sclerosis.** Approve bosentan (Tracleer, generic) for 1 year if the patient meets the following (A or B and C):
   A) Patient has tried one calcium channel blocker; OR
   Note: Examples include amlodipine, felodipine and nifedipine.
   B) Patient has tried one phosphodiesterase type 5 (PDE5) inhibitor.
   Note: Examples include sildenafil, tadalafil and vardenafil; AND
   C) Preferred product criteria is met for the product(s) as listed in the below table(s).

Employer Plans:

Product	Criteria
Letairis (ambrisentan tablets)	**1.** The patient has tried the bioequivalent generic product, **ambrisentan tablets**, AND cannot take 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, per the prescriber, in a significant allergy or serious adverse reaction.
Tracleer (bosentan tablets) applies to Tracleer 62.5 mg and 125 mg tablets only	**1.** The patient has tried the bioequivalent generic product, **bosentan tablets**, AND cannot take 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, per the prescriber, in a significant allergy or serious adverse reaction.

Product	Criteria

Individual and Family Plans:

Product	Criteria
Letairis (ambrisentan tablets)	**1.** The patient has tried the bioequivalent generic product, **ambrisentan tablets**, AND cannot take 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, per the prescriber, in a significant allergy or serious adverse reaction.
Tracleer (bosentan) applies to Tracleer 62.5 mg and 125 mg tablets only	**1.** The patient has tried the bioequivalent generic product, **bosentan tablets**, AND cannot take 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, per the prescriber, in a significant allergy or serious adverse reaction.
Opsynvi (macitentan/tadalafil tablets)	**1.** The patient meets one of the following (A or B): **A)** Patient has concomitantly used BOTH of the following: 1) one endothelin receptor antagonist (Opsumit or ambrisentan [Letairis, generics]); AND 2) one phosphodiesterase-5 inhibitor (tadalafil [Adcirca, generics] or sildenafil [Revatio, generics]); [may require prior authorization] OR **B)** Patient has already been started on therapy with Opsynvi.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

I. Any other use of ambrisentan (Letairis, generic) , Opsumit, and bosentan (Tracleer, generic) is considered experimental, investigational, or unproven (criteria will be updated as new published data are available).

II. Any other use of Opsynvi is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Concurrent Use With Guanylate Cyclase Stimulators.** Use of Opsynvi with guanylate cyclase stimulators is contraindicated.[1]
   Note: An example of a guanylate cyclase stimulator is Adempas (riociguat tablets).

References

1. Tracleer® tablets and tablets for oral suspension [prescribing information]. South San Francisco, CA: Actelion/Janssen; July 2022.
2. Letairis® tablets [prescribing information]. Foster City, CA: Gilead; August 2019.
3. Opsumit® tablets [prescribing information]. Titusville, NJ: Actelion/Janssen; June 2023.
4. 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.
5. Adempas® tablets [prescribing information]. Wayne, NJ: Bayer; September 2021.
6. 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.
7. Chung L, Fiorentino D. Digital ulcers in patients with systemic sclerosis. *Autoimmun Rev*. 2006;5(2):125-128.
8. Pope JE. The diagnosis and treatment of Raynaud's phenomenon. A practical approach. *Drugs*. 2007;67(4):517-525.
9. Hinze AM, Wigley FM. Pharmacotherapy options in the management of Raynaud's phenomenon. *Curr Treatm Opt Rheumatol*. 2018;4(3):235-254.
10. 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.
11. Fernandez-Codina A, Canas-Ruano E, Pope JE. Management of Raynaud's phenomenon in systemic sclerosis-a practical approach. *J Scleroderma Relat Dis*. 2019;4(2):102-110.
12. 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.
13. 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.
14. Ruopp NF, Cockrill BA. Diagnosis and treatment of pulmonary arterial hypertension. A review. *JAMA*. 2022;327(4):1379-1391.
15. Klinger JR, Elliott CG, Levine DJ, et al. Therapy for pulmonary arterial hypertension in adults. Update of the CHEST guideline and Expert Panel Report. *CHEST*. 2019;155(3):565-586.
16. Kim NH, Delcroix M, Jais X, et al. Chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2019;53(1):1801915.
17. Papametheakis DG, Poch SD, Fernandes TM, et al. Chronic thromboembolic pulmonary hypertension: JACC focus seminar. *J Am Coll Cardiol*. 2020;76(180):2155-2169.
18. Humbert M, Kovacs G, Hoeper MM, et al, for the ESC/ERS Scientific Document Group. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43(38):3618-3731.
19. Maron B. Revised definition of pulmonary hypertension and approach to management: a clinical primer. *J Am Heart Assoc*. 2023 April 7. [epub ahead of print].
20. Opsynvi® tablets [prescribing information]. Titusville, NJ: Actelion/Janssen; March 2024.

Revision Details

Type of Revision	Summary of Changes	Date
New	New stand-alone policy created. The criteria were previously housed in the Pulmonary Hypertension Therapy class policy.	8/15/2024

	Pulmonary Arterial Hypertension (PAH): Updated criteria to include clarification for "Initial Therapy" versus "Patient is Currently Receiving the Requested Endothelin Receptor Antagonist (i.e., ambrisentan [Letairis, generic], Opsumit, or bosentan [Tracleer, generic]) or Opsynvi". Updated confirmation of PAH diagnosis to remove echocardiogram as an option. Added Opsynvi to the Policy, including additional preferred product criteria requirements for Individual and Family Plans. **Chronic Thromboembolic Pulmonary Hypertension (CTEPH):** Added new criteria for Other Uses with Supportive Evidence for bosentan (Tracleer, generic) including preferred product criteria requirements for the brand name, Tracleer tablets. **Digital Ulcers in a Patient with Systemic Sclerosis:** Added new criteria for Other Uses with Supportive Evidence for bosentan (Tracleer, generic) including preferred product criteria requirements for the brand name, Tracleer tablets. **Conditions Not Covered:** Added the following statement for Opsynvi, "Concurrent Use with Guanylate Cyclase Stimulators." An example of a guanylate cyclase stimulator was listed in a Note.	

The policy effective date is in force until updated or retired.