EXPRESS SCRIPTS®

PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Endothelin Receptor Antagonists
- Tracleer® (bosentan tablets and oral suspension – Actelion)
- Letairis® (ambrisentan tablets – Gilead)
- Opsumit® (macitentan tablets – Actelion)

TAC APPROVAL DATE: 08/22/2018

OVERVIEW

Tracleer, Letairis and Opsumit are oral endothelin receptor antagonists (ERAs) that are used for the treatment of pulmonary arterial hypertension (PAH).[1-3] Tracleer, which is given twice daily (BID), is indicated for the treatment of PAH (World Health Organization [WHO] Group 1) 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] 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.[2] 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%).[2] Opsumit, which is given QD, is indicated for the treatment of PAH (WHO Group 1) to delay disease progression.[3] 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.[1-3] Tracleer has a Boxed Warning regarding hepatotoxicity.[1] All agents have a Boxed Warning regarding embryofetal toxicity.[1-3]

Guidelines

The WHO classification of functional capacity, which is an adaptation of the NYHA system, is in Table 1. This provides a qualitative assessment of activity tolerance and is useful in monitoring disease progression and response to therapy.[4]

Table 1. WHO Classification of Functional Status of Patients with Pulmonary Hypertension.[4]

Class	Description
I	Patients in whom there is no limitation of usual physical activity. Ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope.
II	Patients who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope.
III	Patients who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope.
IV	Patients who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

WHO – World Health Organization.

Pulmonary hypertension can be classified into five different groups.[21] Tracleer, Opsumit, and Letairis are indicated in Group 1 PAH.[1-3] The five major categories of pulmonary hypertension are cited in Table 2.[21]

Table 2. Updated Classification of Pulmonary Hypertension.[21]

Group 1: Pulmonary Arterial Hypertension
Idiopathic
Heritable
BMPR2
ALK-1, ENG, SMAD9, CAV1, KCNK3
Unknown
Drug and toxin-induced
Associated with
Connective tissue disease
Human immunodeficiency virus infection
Portal hypertension
Congenital heart diseases
Schistosomiasis
Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
Persistent pulmonary hypertension of the newborn
Group 2: Pulmonary Hypertension Due to Left Heart Disease
Left ventricular systolic dysfunction
Left ventricular diastolic dysfunction
Valvular disease
Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
Group 3: Pulmonary Hypertension Due to Lung Diseases and/or Hypoxia
Chronic obstructive pulmonary disease
Interstitial lung disease
Other pulmonary diseases with mixed restrictive and obstructive pattern
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental lung diseases
Group 4: Chronic Thromboembolic Pulmonary Hypertension
Group 5: Pulmonary Hypertension with Unclear Multifactorial Mechanisms
Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangiomyomatosis
Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension.

BMPR2 – Bone morphogenic protein receptor type 2; ALK-1 – Activin-like receptor kinase-1; ENG – Endoglin; SMAD9 – Mothers against decapentaplegic; CAV1 – Caveolin-1; KCNK3 – Potassium channel super family K member-3.

In 2004, the American College of Chest Physicians (ACCP) developed evidence-based clinical practice guidelines regarding the screening, early detection, and diagnosis of PAH.[4] In patients with suspected pulmonary hypertension, right heart catheterization is required to confirm the presence of pulmonary hypertension, establish the specific diagnosis, and determine disease severity (grade A recommendation). In patients with suspected pulmonary hypertension, right heart catheterization is required to guide therapy (grade B recommendation).[4] The 2007 ACCP guidelines for medical therapy for PAH also restate these recommendations.[6]

In 2009, the American College of Cardiology Foundation (ACCF) Task Force on Expert Consensus Documents and the American Heart Association (AHA), developed in collaboration with the ACCP, American Thoracic Society (ATS) and the Pulmonary Hypertension Association, published an expert consensus document on pulmonary hypertension.[5] The guidelines state that the diagnosis of PAH requires confirmation with a complete right heart catheterization. The hemodynamic definition of PAH is a mean pulmonary artery pressure (mPAP) greater than 25 mmHg; a pulmonary capillary wedge pressure (PCWP), left atrial pressure (LAP) or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mmHg; and a pulmonary vascular resistance (PVR) greater than 3 Wood units.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Tracleer, Letairis, and Opsumit. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tracleer, Letairis, and Opsumit, as well as the monitoring required for adverse events and long-term efficacy, approval requires the agents to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 years in duration unless otherwise noted below.

Documentation: In the *Pulmonary Arterial Hypertension – Endothelin Receptor Antagonists Prior Authorization Policy*, documentation is required for initiation of therapy where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory reports. For a patient case in which the documentation requirement of the right heart catheterization upon prior authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension – Endothelin Receptor Antagonist Prior Authorization Policy* is considered to be met.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tracleer, Opsumit, and Letairis is recommended in those who meet the following criteria:

FDA-Approved Indications

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 or B):
   - **A)** Initial Therapy. Approve for 3 years if the patient meets all of the following criteria (i, ii, and iii).
     - **i.** The patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
     - **ii.** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
     - **iii.** The patient meets the following criteria (a and b):
       - **a)** The patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND
       - **b)** The results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; OR
   - **B)** Patients Currently Receiving the Requested Endothelin Receptor Antagonist (i.e., Tracleer, Letairis or Opsumit). Approve for 3 years if the patient meets the following criteria (i, ii, and iii):
     - **i.** The patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
     - **ii.** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
     - **iii.** The patient meets the following criteria (a and b):
       - **a)** The patient has had a right heart catheterization; AND
       - **b)** The results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH.

   Tracleer is indicated for the treatment of PAH (WHO Group 1) 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, which is expected to result in an improvement in exercise ability.[1] Letairis is indicated for the treatment of PAH (WHO Group 1) to

improve exercise ability and delay clinical worsening.[2] Opsumit is indicated for the treatment of PAH (WHO Group 1) to delay disease progression.[3] ACCP guidelines for the screening, early detection, and diagnosis of PAH, established in 2004, recommend to perform a right heart catheterization in patients with suspected pulmonary hypertension to confirm the presence of pulmonary hypertension, establish the diagnosis, and to determine disease severity.[4,6] An ACCF/AHA 2009 consensus document on pulmonary hypertension, developed in collaboration with the ACCP, ATS and Pulmonary Hypertension Association, notes all patients suspected of having PAH after noninvasive evaluation should undergo right heart catheterization prior to initiation of therapy.[5]

Other Uses with Supportive Evidence

Coverage of Tracleer is also recommended in those who meet the following criteria:

2. **Digital Ulcers/Systemic Sclerosis.** Approve Tracleer for 3 years if the patient meets the following criteria (A or B):
   - **A)** The patient has tried two other therapies for this condition such as calcium channel blockers (CCBs) [e.g., amlodipine, felodipine, nifedipine], alpha-adrenergic blockers (e.g., prazosin), nitroglycerin, phosphodiesterase type 5 (PDE5) inhibitors (e.g., sildenafil tablets, Levitra® [vardenafil tablets]), or angiotensin converting enzyme (ACE) inhibitors; OR
   - **B)** The patient has tried one vasodilator/prostanoid therapy (e.g., epoprostenol injection, alprostadil injection).

   Tracleer has been used in patients with systemic sclerosis who have digital ulcers.[7-14] In a randomized, 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.[7] Tracleer was administered as 62.5 mg BID for 4 weeks and then 125 mg BID for 12 weeks. 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.[7] Another trial showed a reduction in the occurrence of new digital ulcers in patients given Tracleer for 24 weeks.[12] Many other agents are utilized in digital ulcers.[10,14] In 2017 EULAR updated recommendations for the treatment of systemic sclerosis.[14] Tracleer has efficacy from two high-quality randomized controlled trials to reduce the number of new digital ulcers in patients with systemic sclerosis. 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, PDE5 inhibitors or iloprost therapy.[14] A consensus of systemic sclerosis experts published an article that discusses therapy for digital ulcers.[15] The algorithm for digital ulcer prevention lists the following as first-line, second-line, third-line, and fourth-line treatment respectively: CCBs, PDE5 inhibitors, ERAs, and prostanoids. For the prevention of severe digital ulcers, selective sympathetecomy may occasionally be recommended. For active treatment CCBs are used first line, followed by PDE5 inhibitors.[15] A review on Raynaud's phenomenon and its manifestations (e.g., digital ulcers) also mentions similar medications. Other data describing use of epoprostenol are available.[22-23]

3. **Chronic Thromboembolic Pulmonary Hypertension (CTEPH).** Approve Tracleer for 3 years if the patient meets the following criteria (A and B):
   - **A)** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
   - **B)** The patient meets ONE of the following conditions (i, ii, or iii):

i. The patient has tried Adempas; OR
ii. 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], the patient is hypotensive or is at risk for hypotension); OR
iii. The patient is currently receiving Tracleer for CTEPH.

Adempas, 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. Adempas has a Boxed Warning regarding embryo-fetal toxicity and is contraindicated in patients using nitrates or nitric oxide donors in any forms, as well as in patients using PDE inhibitors. The main adverse effects of Adempas are symptomatic hypotension.[16] The BENEFiT (Bosentan Effects in iNopErable Forms of chronic Thromboembolic pulmonary hypertension) study was a double-blind trial[17] involving 156 patients with CTEPH who were randomized to placebo or Tracleer therapy (target dose of 125 mg BID) for 16 weeks. Benefits were noted in some hemodynamic parameters (e.g., decreased pulmonary vascular resistance).[17] In 2011, the American Heart Association published a scientific statement on the management of a variety of thromboembolic conditions, including CTEPH.[18] Pulmonary endarterectomy (PEA) is the treatment of choice for CTEPH, which is potentially curative and leads to nearly normalized pulmonary hemodynamics and substantial clinical improvement. It was stated that the BENEFiT trial utilizing Tracleer was the only randomized, multicenter, placebo-controlled trial in PAH-specific therapy for CTEPH. In a 16-week trial, a modest reduction in PVR was observed and no improvement was noted in either exercise capacity or the six-minute walk distance.[18] Two more recent reviews note the benefits of Adempas in patients with CTEPH.[19-20]

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Letairis, Tracleer and Opsumit have has 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.

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

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HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Annual revision	For patients with pulmonary arterial hypertension (PAH) World Health Organization (WHO) Group 1, for patients currently receiving therapy, Uptravi was added to the list of other PAH medications.	08/10/2016
Annual revision	No criteria changes.	08/30/2017
Selected revision	Selected revision to add Tracleer oral suspension to the policy. No criteria changes were made.	02/07/2018
Annual revision	For initial review, documentation is required for the right heart catheterization. For patients who are currently receiving the requested endothelin receptor antagonist, the wording "or who are receiving another medication for WHO Group 1 PAH" was removed, along with the cited alternatives. Also, the requirement was added that the patient has had a right heart catheterization and that the results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH. A note was added in the documentation section that for a patient case in which the documentation requirement of the right heart catheterization upon prior authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement is considered to be met.	08/22/2018

TAC – Therapeutic Assessment Committee; * For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx; PAH – Pulmonary arterial hypertension; WHO – World Health Organization.