Tracleer

Description

Tracleer (bosentan)

Background
Pulmonary arterial hypertension is a rare disorder of the pulmonary arteries in which the pulmonary arterial pressure rises above normal levels in the absence of left ventricular failure. This condition can progress to cause right-sided heart failure and death (1-2). Tracleer is indicated for treatment of pulmonary arterial hypertension (PAH) which is classified by WHO as Group 1. Tracleer is used to treat pulmonary arterial hypertension (PAH, high blood pressure in the lungs) to improve exercise ability (1).

The World Health Organization (WHO) has classified pulmonary hypertension into five different groups: (2)

WHO Group 1: Pulmonary Arterial Hypertension (PAH)
1.1 Idiopathic (IPAH)
1.2 Heritable PAH
   1.2.1 Germline mutations in the bone morphogenetic protein receptor type 2 (BMPR2)
   1.2.2 Activin receptor-like kinase type 1 (ALK1), endoglin (with or without hereditary hemorrhagic telangiectasia), Smad 9, caveolin-1 (CAV1), potassium channel super family K member-3 (KCNK3)
   1.2.3 Unknown
1.3 Drug-and toxin-induced
1.4 Associated with:
   1.4.1 Connective tissue diseases
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases (e.g. pulmonary artresia)
1.4.5 Schistosomiasis
1'. Pulmonary vena-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
1". Persistent pulmonary hypertension of the newborn (PPHN)

**WHO Group 2: Pulmonary Hypertension Owing to Left Heart Disease**

2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

**WHO Group 3: Pulmonary Hypertension Owing to Lung Disease and/or Hypoxia**

3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental abnormalities

**WHO Group 4: Chronic Thromboembolic Pulmonary Hypertension <CTEPH>**

**WHO Group 5: Pulmonary Hypertension with Unclear Multifactorial Mechanisms**

5.1 Hematologic disorders: Chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3 Metabolic disorders: glycogen storage disease, Gaucher's disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis, segmental PH

The American College of Chest Physicians (ACCP) has published an updated clinical practice guideline for treating PAH. These guidelines use the New York Heart Association (NYHA) functional classification of physical activity scale to classify PAH patients in classes I-IV based
on the severity of their symptoms. Tracleer is indicated for patients with NYHA Functional Class II, III or IV (2).

**NYHA CLASSIFICATION OF ADULTS**

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
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<tbody>
<tr>
<td>Class I</td>
<td>Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.</td>
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<tr>
<td>Class II</td>
<td>Patients with pulmonary hypertension resulting in slight limitation of physical activity. These patients are comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.</td>
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<tr>
<td>Class III</td>
<td>Patients with pulmonary hypertension resulting in marked limitation of physical activity. These patients are comfortable at rest, but less than ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.</td>
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<tr>
<td>Class IV</td>
<td>Patients with pulmonary hypertension resulting in inability to perform any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present at rest, and discomfort is increased by any physical activity.</td>
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**Regulatory status**
FDA Approved Indications: Tracleer is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (WHO Group I): (1)

1. In adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with 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%)

2. 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

Tracleer has a boxed warning due to the risks of elevations of liver aminotransferases (ALT, AST) and liver failure. Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly and therapy adjusted accordingly. Discontinue Tracleer if liver aminotransferase elevations are accompanied by clinical symptoms of hepatotoxicity (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin (1).
Tracleer is in pregnancy category X. Females of childbearing potential should have pregnancy excluded before the start of treatment with Tracleer, prevented during therapy, and for one month after treatment cessation (1).

Co-administration with cyclosporine A is contraindicated due to the markedly increased plasma concentrations of Tracleer. An increased risk of elevated liver aminotransferases was observed in patients receiving concomitant therapy with glyburide. Therefore, the concomitant administration of Tracleer and glyburide is contraindicated, and alternative hypoglycemic agents should be considered (1).

Should signs of pulmonary edema occur, consider the possibility of associated pulmonary veno-occlusive disease and consider whether Tracleer should be discontinued. Treatment with Tracleer can cause a dose-related decrease in hemoglobin and hematocrit. There have been postmarketing reports of decreases in hemoglobin concentration and hematocrit that have resulted in anemia requiring transfusion. It is recommended that hemoglobin concentrations be checked after 1 and 3 months, and every 3 months thereafter (1).

Due to the serious side effects associated with Tracleer, the FDA requires the manufacturer to provide a Risk Evaluation and Mitigation Strategy (REMS) program in which the patient, physician, and pharmacy must enroll and meet criteria for the prescribing, dispensing, and administration of the drug (1).

**Related policies**
Adcirca, Adempas, Flolan/Veletri, Letairis, Opsumit, Orenitram, Remodulin, Revatio, Tyvaso, Uptravi, Ventavis

**Policy**
This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Tracleer may be considered **medically necessary** for treatment of pulmonary arterial hypertension, WHO Group I, and if the conditions indicated below are met.

Tracleer may be considered **investigational** for all other indications.

**Prior-Approval Requirements**
Diagnosis

Patient must have the following:

Pulmonary Arterial Hypertension (PAH) – **WHO Group I**

**AND ALL** of the following for **18 years of age or older**:

1. NYHA functional classification of physical activity - Class II, III, or IV
2. **NOT** receiving treatment with cyclosporine A or glyburide (Diabeta, Micronase, Glynase or Glucovance)
3. Enrolled in and meet all the conditions of the Tracleer Access Program (TAP)
4. Females of childbearing potential should have pregnancy excluded before the start of treatment with Tracleer, prevented during therapy and for one month after treatment cessation
5. Prescriber agrees to monitor for pulmonary edema and discontinue if confirmed

Prior – Approval **Renewal Requirements**

**Diagnosis**

Patient must have the following:

Pulmonary Arterial Hypertension (PAH) – **WHO Group I**

**AND ALL** of the following for **18 years of age or older**:

1. Symptoms have improved or stabilized
2. **NOT** receiving treatment with cyclosporine A or glyburide (Diabeta, Micronase, Glynase or Glucovance)
3. Females of childbearing potential should have pregnancy excluded before the start of treatment with Tracleer, prevented during therapy and for one month after treatment cessation
4. Prescriber agrees to monitor for pulmonary edema and discontinue if confirmed

**Policy Guidelines**

**Pre - PA Allowance**

None
Prior - Approval Limits
Duration 2 years

Prior – Approval Renewal Limits
Same as above

Rationale

Summary
Pulmonary arterial hypertension is a rare disorder of the pulmonary arteries in which the pulmonary arterial pressure rises above normal levels in the absence of left ventricular failure. This condition can progress to cause right-sided heart failure and death (1,2). Tracleer is a endothelin receptor antagonist indicated for treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA class II, III, or IV to improve exercise ability and to decrease clinical worsening. Due to the serious side effects associated with Tracleer, the FDA requires the manufacturer to provide a Risk Evaluation and Mitigation Strategy (REMS) program in which the patient, physician, and pharmacy must enroll and meet criteria for the prescribing, dispensing, and administration of the drug (1).

Prior authorization is required to ensure the safe, clinically appropriate and cost effective use of Tracleer while maintaining optimal therapeutic outcomes.

References

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
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<tbody>
<tr>
<td>June 2012</td>
<td>Annual editorial and reference update</td>
<td></td>
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March 2013  Annual editorial and reference update
March 2014  Annual review
March 2015  Annual editorial and reference update
June 2016  Annual editorial review and reference update
Addition of age 18 and the prescriber agrees to monitor for pulmonary edema and discontinue if confirmed
Policy number change from 5.06.07 to 5.40.18
September 2017  Annual editorial review and reference update
November 2017  Change in age of approval from 18 years of age and older to no age restrictions
March 2018  Annual review
September 2019  Annual editorial review and reference update. Changed approval duration from lifetime to 2 years

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on September 13, 2019 and is effective on October 1, 2019.