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TRACLEER **(bosentan)**
Preferred product: generic bosentan

## RATIONALE FOR INCLUSION IN PA PROGRAM

### 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)

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The diagnosis of WHO Group 1 PAH requires a right heart catheterization to demonstrate an mPAP ≥ 20mmHg at rest and a pulmonary vascular resistance (PVR) ≥ 3 Wood units, mean pulmonary capillary wedge pressure ≤ 15mmHg (to exclude pulmonary hypertension due to left heart disease, i.e. WHO Group 2 pulmonary hypertension) (5-7).

**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 <CTEPHl**

**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**

| | |
|---|---|
| Class I | 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. |
| Class II | 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. |
| Class III | 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. |
| Class IV | 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. |

(3)

**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 boxed warnings regarding elevations of liver aminotransferases (ALT, AST), liver failure and major birth defects if used during pregnancy. 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. Females of reproductive potential must have pregnancy excluded prior and during treatment. To prevent pregnancy, females of reproductive potential must use two reliable forms of contraception during treatment and for one month after stopping Tracleer (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).

**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**

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