ORAL ENDOTHELIN RECEPTOR ANTAGONISTS FOR PULMONARY ARTERIAL HYPERTENSION

UTILIZATION MANAGEMENT CRITERIA

<table>
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<th>DRUG CLASS: ENDOTHELIN RECEPTOR ANTAGONISTS FOR PULMONARY ARTERIAL HYPERTENSION (PAH)</th>
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<td>BRAND (generic) NAMES:</td>
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<td>Tracleer (bosentan) 62.5, 125 mg tablet</td>
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<tr>
<td>Letairis (ambrisentan) 5, 10 mg tablet</td>
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FDA-APPROVED INDICATIONS
Treatment of pulmonary arterial hypertension (WHO Group I) in patients with WHO class II or III symptoms (Letairis) or with WHO class II to IV symptoms (Tracleer) to improve exercise capacity and decrease clinical worsening.

COVERAGE AUTHORIZATION CRITERIA for Tracleer and Letairis for NEW USERS only:

- Patient has a confirmed diagnosis of pulmonary arterial hypertension (WHO Group I) which is symptomatic.
- Patient is under the care or referral of a cardiologist of pulmonologist.
- Bosentan and ambrisentan are only to be used in combination with other PAH therapies when treatment with one PAH agent failed to adequately control the patient’s symptoms.

WHO Group 1: PAH
Idiopathic
Heritable
BMPR2
ALK2, endoglin (with or without hereditary hemorrhagic telangiectasia)
Unknown
Drug- and toxin-induced
Associated with:
   Connective tissue diseases
   HIV infection
   Portal hypertension
   Congenital heart diseases
   Schistosomiasis
   Chronic hemolytic anemia
   Persistent pulmonary hypertension of the newborn.
   Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH).

Adapted from Simonneau et al, JACC 2009[3] (based on the 4th World Symposium, 2008)
BLACK BOX WARNINGS

WARNING: POTENTIAL LIVER INJURY AND CONTRAINDICATION IN PREGNANCY

- Elevations of liver aminotransferases (ALT, AST) and/or serious liver injury have been reported with these drugs.
- Monitor liver aminotransferases prior to initiation of therapy and then monthly. Modify the dose of Tracleer if liver aminotransferases are >3 and <5 ULN, and discontinue Tracleer or Letairis if >5 x ULN or if elevations are accompanied by bilirubin >2 x ULN or by signs or symptoms of liver dysfunction.
- May cause fetal harm if taken during pregnancy.
- Must exclude pregnancy before and during treatment.
- Prevent pregnancy during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNG 20 IUS, in which case no additional contraception is needed.

TRACLEER:
Because of the risk of liver injury and birth defects, Tracleer is available only through a special restricted distribution program called the Tracleer Access Program (T.A.P.), by calling 1 866 228 3546. Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute Tracleer. In addition, Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P.

LETAIRIS:
Because of the risks of liver injury and birth defects, LETAIRIS is available only through a special restricted distribution program called the LETAIRIS Education and Access Program (LEAP), by calling 1-866-664-LEAP (5327). Only prescribers and pharmacies registered with LEAP may prescribe and distribute LETAIRIS. In addition, LETAIRIS may be dispensed only to patients who are enrolled in and meet all conditions of LEAP.

CONTRAINDICATIONS:
In women who are or may become pregnant (see also Black Box Warning). Bosentan: concomitant use of bosentan and cyclosporine A or glyburide.

DOSAGE AND ADMINISTRATION:

Tracleer: Initiate at 62.5 mg twice daily with or without food for 4 weeks, and then increase to 125 mg twice daily. Patients with low body weight (<40 kg) and >12 years old: Initial and maintenance dose is 62.5 mg twice daily.

Letairis: Initiate treatment at 5 mg once daily with or without food, and consider increasing the dose to 10 mg once daily if 5 mg is tolerated.

REFERENCES:

