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Subject: Pulmonary Hypertension Medications
Effective Date: January 10, 2012

Clinical Documentation and Prior Authorization Required	√	Type of Review - Case Management	
Not Covered		Type of Review – Clinical Review	√
Pharmacy (RX) or Medical (MED) Benefit	RX and MED	Administrative Process (Internal Use Only)	RN

Note: This pharmacy medical necessity guideline applies to commercial products. For Tufts Health Plan Medicare Preferred members, please refer to the Tufts Medicare Preferred Prior Authorization Criteria. Background, applicable product and disclaimer information can be found on the last page.

Overview

Adcirca™ (tadalafil) is an inhibitor of phosphodiesterase type 5 (PDE5), the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP). Pulmonary hypertension is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations in the pulmonary vascular smooth muscle. PDE5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 by tadalafil increases the concentrations of cGMP resulting in relaxation of pulmonary vascular smooth muscle cells and vasodilation of the pulmonary vascular bed.

Flofan® / Veletri® (epoprostenol sodium) is both a vasodilator and inhibitor of platelet aggregation used for the treatment of Primary Pulmonary Hypertension (PPH) and Pulmonary Hypertension secondary to connective tissue diseases, thromboembolic disease of the pulmonary arteries, portal hypertension, HIV infection, diet drug therapy, and congenital heart disease. PPH is defined as a mean pulmonary artery pressure (PAP) of greater than 25 mmHg at rest, or greater than 30 mmHg with exercise. Flofan was approved by the FDA in 1995 and became available January 1996 for use in symptomatic PPH. Flofan is effective in reducing pulmonary vascular resistance, increasing exercise capacity, and improving symptoms related to the disease. Because Flofan only lasts for several minutes (3-5) in the circulation, it requires uninterrupted IV infusion and should be considered a lifetime therapy unless a lung/heart and lung transplant is performed. This requires implantation of a permanent central venous catheter, the use of an external portable infusion pump, careful training of the patient in preparing the medication daily, and comprehensive follow-up by fully trained medical staff. The drug is often used as a bridge to help those patients waiting for a transplant. The dosage is dependent on relief of PPH symptoms and tolerance of drug related side effects. Because each individual responds differently to the drug there is no set dosage.

Letairis™ (ambrisentan) is used in the management of pulmonary arterial hypertension (PAH; World Health Organization [WHO] group 1) in patients with WHO class II or III symptoms to improve exercise capacity and to slow the rate of clinical worsening. Ambrisentan, a selective endothelin-1 (ET-1) type A receptor antagonist, is a vasodilator. Although pharmacologically related to other ET-1 receptor antagonists (e.g., bosentan), ambrisentan differs structurally from bosentan and also exhibits greater selectivity for ET-1 type A receptors than does bosentan. Ambrisentan is approximately 4000-fold more selective for the type A receptor compared with the type B receptor, whereas bosentan exhibits only slightly greater affinity for ET-1 type A receptors compared with ET-1 type B receptors. However, the clinical implications of this selectivity remain to be established.

Remodulin[®] (treprostinil sodium) is a prostacyclin analog that acts as both a vasodilator and inhibitor of platelet aggregation. Treprostinil sodium is similar to endogenous prostacyclin that is produced by the cells lining blood vessels and is effective in reducing pulmonary vascular resistance, increasing exercise capacity, and improving symptoms related to the disease. Remodulin is administered as a continuous subcutaneous infusion that has been shown to improve hemodynamics, symptoms and survival time in patients with pulmonary hypertension unresponsive to conventional therapies, typically Calcium Channel Blocking agents.

Revatio[™] and **Viagra**[®] (sildenafil) are inhibitors of PDE5, a hormone produced by the body that causes blood vessel to constrict by inactivating the vasodilator, nitric oxide. Because of the high concentrations of PDE5 in the lungs, sildenafil may function by prolonging the effects of nitric oxide and causing vasodilation.

Tracleer[®] (bosentan) is an oral medication indicated for the treatment of Pulmonary Arterial Hypertension. Pulmonary arterial hypertension (PAH) is defined as abnormally high blood pressure in the arteries between the heart and lungs. PAH significantly reduces the ability of patients to exert themselves physically without becoming short of breath. PAH significantly shortens the life span of patients because it leads to heart failure. Tracleer blocks the action of endothelin, a substance made by the body. Endothelin narrows blood vessels and elevates blood pressure. Endothelin exists in higher levels in people with pulmonary hypertension and is harmful to the lung and pulmonary arteries. The damaged lung and pulmonary arteries create the blood flow resistance that results in hypertension. Bosentan antagonizes or “blocks” the effects of endothelin, lowering endothelin levels and reversing its effects, resulting in lower artery pressure.

Tyvaso[®] (treprostinil) inhalation solution is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III symptoms, to increase walk distance. This medication must be administered via a special nebulizer four times daily.

Ventavis[®] (iloprost) is a synthetic molecule structurally similar to prostacyclin. This medication must be administered via a special nebulizer six to nine times per day.

Pharmacy Coverage Guidelines

Tufts Health Plan may authorize coverage of Adcirca, generic epoprostenol, Flolan/Veletri (**please see additional guidelines “*Coverage for Flolan/Veletri” below**), Letairis, Remodulin, Tracleer, Tyvaso, Ventavis, or sildenafil tablets for Members when the following criteria are met:

1. The Member must have a definitive diagnosis of pulmonary artery hypertension (WHO group I; see below) from a cardiologist or pulmonologist and confirmed by right heart catheterization

World Health Organization Classification of Pulmonary Hypertension
Group I:

- Idiopathic PAH (primary pulmonary hypertension)
- Heritable PAH
- Drug- and toxin-induced PAH
- PAH associated with other diseases and conditions (APAH)
 - Connective tissue diseases
 - HIV infection
 - Portal hypertension
 - Congenital heart disease
 - Schistosomiasis

- Chronic hemolytic anemia
- Persistent pulmonary hypertension of the newborn

AND

2. The pulmonary hypertension has progressed despite surgical treatment and/or maximal medical treatment of the underlying condition

AND

3. The medication used for treatment is consistent with its FDA approved functional class (See corresponding chart below)

Drug	FDA Approved Functional Class of Symptoms
Adcirca	WHO Class II and III
epoprostenol (Flolan/Veletri)	NYHA Class III and IV
Letairis	WHO Class II and III
Remodulin	NYHA Class II, III, and IV
sildenafil	WHO Class II, III, and IV
Tracleer	WHO Class II, III, and IV
Tyvaso	NYHA Class III
Ventavis	NYHA Class III and IV

Note: Please refer to References Section for a description of NYHA and WHO Functional Class descriptions.

***Coverage for Flolan / Veletri (epoprostenol)**

Tufts Health Plan requires Members initiating treatment with epoprostenol to utilize the generic version (provided that he/she meets the pharmacy coverage guidelines described above) prior to authorization of brand name Flolan or Veletri. Coverage of Flolan / Veletri will be considered for Members who have failed an adequate trial of or are unable to tolerate generic epoprostenol.

Limitations

1. Tufts Health Plan will not authorize coverage of **generic epoprostenol, Flolan/Veletri, Letairis, Remodulin, Tracleer, Tyvaso, Ventavis, Adcirca and sildenafil tablets** for pulmonary hypertension secondary to the following conditions:
 - Diseases of the left atrium and ventricle such as congestive heart failure (CHF) or cardiomyopathy
 - Diseases of the mitral and aortic valves
 - Chronic lung diseases such as COPD (chronic obstructive pulmonary disease), restrictive pulmonary disease or interstitial pulmonary disease
 - Obstructive sleep apnea or other sleep disorders involving breathing or alveolar hyperventilation disorders
2. The following quantity limitations apply:
 - Adcirca tablets - 60 tablets per 30 days
 - Revatio tablets - 90 tablets per 30 days
3. Tufts Health Plan may authorize coverage of Viagra tablets for pulmonary hypertension when the dosage for sildenafil exceeds 20mg three times a day.

Codes

The following HCPCS/CPT code(s) are:

Code	Description
J1325	Injection, epoprostenol, 0.5mg
J3285	Injection, treprostinil
J7686	Treprostinil, inhalation solution, FDA-approved final product, noncompounded, administered through DME, unit dose form, 1.74 mg
Q4074	Iloprost, inhalation solution, administered through DME, up to 20mcg

References

NYHA Pulmonary Arterial Hypertension Functional Classification of Symptoms

Class I	No limitation	Ordinary physical activity does not cause symptoms
Class II	Slight limitation	Comfortable at rest Ordinary physical activity causes symptoms
Class III	Marked limitation	Comfortable at rest Less than ordinary activity causes symptoms
Class IV	Inability to carry on any physical activity	Symptoms present at rest

WHO Pulmonary Arterial Hypertension Functional Classification of Symptoms

Class I	No limitation	Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II	Slight limitation	Comfortable at rest Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III	Marked limitation	Comfortable at rest Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV	Inability to carry on any physical activity	Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

1. Adcirca (tadalafil) [package insert]. Indianapolis, IN: Eli Lilly and Company; February 2011.
2. AHFS Drug information 2007. *Ambrisentan*. Copyright ©1997-2005, American Society of Health-System Pharmacists, Inc. All rights reserved.
3. Ambrisentan (*Letairis*) For Pulmonary Arterial Hypertension, Medical Letter, October 22, 2007, Vol. 49 Issue 1272.
4. Barst RJ, Gibbs JS, Ghofrani HA, et al. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; 54: S78–S84.
5. Bosentan (*Tracleer*) For Pulmonary Arterial Hypertension, Medical Letter, April 1, 2002, Vol. 44 Issue 1127.
6. Daly, Richard C., MD., “Lung transplantation for Pulmonary Hypertension”, Mayo Foundation for Medical Education and Research, August 1997.
7. Diagnosis and Functional Assessment of PAH. Available at: www.actelion.com. Accessed 2002, March.
8. FDA Talk Paper, FDA Approves First Oral Medication for Pulmonary Arterial Hypertension, November 20, 2001.
9. Fishman, Alfred P. MD. “Pulmonary Hypertension -Beyond Vasodilator Therapy,” *New England Journal of Medicine*, Volume 338, Number 5, January 29, 1998.

10. Flolan (epoprostenol sodium) for Injection [package insert]. Research Triangle Park, NC: GlaxoSmithKline; March 2011.
11. Ghofrani, "Combination Therapy with Oral Sildenafil and Inhaled Iloprost for Severe Pulmonary Hypertension", *Annals of Internal Medicine*, April 2002, volume 136, Pages 515-522.
12. Letairis (ambrisentan) [package insert]. Foster City, CA: Gilead Sciences, Inc. July 2011.
13. Mayo Pulmonary Hypertension Clinic, "What is Pulmonary Hypertension?" Available at: <http://www.mayoclinic.org/pulmonary-hypertension/>. Accessed 1997, March.
14. McGoon, Michael D., "Primary Pulmonary Hypertension: Medical Treatment," Mayo Foundation for Medical Education and Research, August 1997.
15. National Heart, Lung, and Blood Institute, National Institute of Health: "Primary Pulmonary Hypertension," November 1996, NIH Publication No. 96-3291 Pages 1-11.
16. Remodulin (treprostinil) Injection [package insert]. Research Triangle Park, NC: United Therapeutics Corp.; February 2011.
17. Revatio (sildenafil) [package insert]. New York, NY: Pfizer Labs; November 2010.
18. Tracleer (bosentan) [package insert]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc.; February 2011.
19. Tyvaso (treprostinil) [package insert]. Research Triangle Park, NC: United Therapeutics Corp.; January 2011.
20. Veletri (epoprostenol for injection) [package insert]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc.; March 2011.

Approval History

Reviewed by the Pharmacy and Therapeutics Committee in May 2003.

Subsequent Endorsement Date(s) and Changes Made:

1. May 10, 2005: No changes
2. September 13, 2005:
 - Add **Ventavis** (iloprost) to the TOPIC, CLINICAL COVERAGE CRITERIA and LIMITATIONS.
 - Change criteria #1 **from** "The Member must have the definitive diagnosis of either Primary or Secondary symptomatic Pulmonary Hypertension (PH) from a cardiologist or pulmonologist confirmed by the two diagnostic tests, *Right-heart cardiac catheterization* and *Echocardiogram* showing right atrial and ventricular enlargement" **to** "The Member must have a definitive diagnosis of pulmonary artery hypertension (WHO group I) from a cardiologist or pulmonologist and confirmed by right heart catheterization".
 - Add criteria #3, "The Member's symptoms are New York Heart Association (NYHA) class III to IV" (see table above).
3. November 8, 2005:
 - Change the brand name "Viagra" in the Topic, Coverage Criteria and Coverage Limitations to sildenafil.
 - Add the coverage limitations: "Tufts Health Plan may authorize coverage of Viagra for pulmonary hypertension when the dosage for sildenafil exceeds 20mg three times a day".
4. October 10, 2006: No changes.
5. November 13, 2007:
 - Add **Letairis** (ambrisentan) to the **Overview, Pharmacy Coverage Guidelines, and Limitations**.
 - Add description of WHO Pulmonary Arterial Hypertension Functional Classes
6. November 11, 2008: No changes.

7. September 8, 2009:
For effective date December 1, 2009:
 - Added guidelines for “*Coverage for Flolan”
 - Added WHO class II to FDA approved functional class for Tracleer
8. November 10, 2009:
 - Added Adcirca to Pharmacy Coverage Guidelines.
 - Added dispensing limitation for Adcirca and Revatio to Pharmacy Medical Necessity Guidelines.
 - Updated FDA Approved Functional Class of Symptoms for sildenafil.
 - Revised WHO Classification of Pulmonary Hypertension Group I
9. January 1, 2010:
 - Removal of Tufts Medicare Preferred language (separate criteria have been created specifically for Tufts Medicare Preferred).
10. January 12, 2010:
 - Added Tyvaso (treprostinil) inhalation solution to Medical Necessity Guidelines.
11. May 11, 2010:
 - Clarified dosage form of sildenafil and Revatio as tablets.
12. January 1, 2011:
 - Administrative Update: Added reimbursement code J7686. Removed discontinued code Q4080.
13. January 11, 2011:
 - Added Veletri (epoprostenol for injection) to Medical Necessity Guidelines.
14. January 10, 2012: No changes.

Background, Product and Disclaimer Information

Pharmacy Medical Necessity Guidelines have been developed for determining coverage for Tufts Health Plan benefits and are published to provide a better understanding of the basis upon which coverage decisions are made. They are used in conjunction with a Member’s benefit document and in coordination with the Member’s physician(s). Tufts Health Plan makes coverage decisions on a case-by-case basis considering the individual Member’s health care needs. Pharmacy Medical Necessity Guidelines are developed for selected therapeutic classes or drugs found to be safe, but proven to be effective in a limited, defined population of patients or clinical circumstances. They include concise clinical coverage criteria based on current literature review, consultation with practicing physicians in the Tufts Health Plan service area who are medical experts in the particular field, FDA and other government agency policies, and standards adopted by national accreditation organizations. Tufts Health Plan revises and updates Pharmacy Medical Necessity Guidelines annually, or more frequently if new evidence becomes available that suggests needed revisions.

Pharmacy Medical Necessity Guidelines apply to all fully insured Tufts Health Plan offerings unless otherwise noted in this policy or the Member’s benefit document. Check the applicable formulary in the Pharmacy section of our Web site at <http://www.tuftshealthplan.com/providers> to determine if the drug requires you to get prior authorization. This Pharmacy Medical Necessity Guideline does not apply to Uniformed Services Family Health Plan Members or to certain delegated service arrangements. Unless otherwise noted in the Member’s benefit document or applicable Pharmacy Medical Necessity Guideline, Pharmacy Medical Necessity Guidelines do not apply to CareLinkSM Members. For self-insured plans, drug coverage may vary depending on the terms of the benefit document. If a discrepancy exists between a coverage guideline and a self-insured Member’s benefit document, the provisions of the benefit document will govern. Applicable state or federal mandates will take precedence.

For Tufts Medicare Preferred, please refer to Tufts Medicare Preferred Prior Authorization Criteria.

Treating providers are solely responsible for the medical advice and treatment of Members. The use of this policy is not a guarantee of payment or a final prediction of how specific claim(s) will be adjudicated. Claims payment is subject to Member eligibility and benefits on the date of service, coordination of benefits, referral/authorization and utilization management guidelines when applicable, and adherence to plan policies and procedures and claims editing logic.