POLICY: Pulmonary Arterial Hypertension (PAH) – Epoprostenol (epoprostenol injection for intravenous use, Flolan®, Veletri®, generics)

APPROVAL DATE: 09/11/2019

OVERVIEW

Epoprostenol injection, a prostacyclin vasodilator, is indicated for the treatment of pulmonary arterial hypertension (PAH) [World Health Organization {WHO} Group 1] to improve exercise capacity.[1-3] Studies establishing effectiveness included predominantly patients with New York Heart Association (NYHA) Functional Class III to IV symptoms and etiologies of idiopathic or heritable PAH (49%) or PAH associated with connective tissue diseases (51%). It is administered as a continuous intravenous infusion.[1-3]

Disease Overview

PAH is a serious but rare condition impacting approximately fewer than 20,000 patients in the US. It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized. In this progressive disorder the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment.[4,5] In time, right-sided heart failure and/or death may occur. Common PAH symptoms include shortness of breath, fatigue, chest pain, dizziness and fainting, along with impairment in activity tolerance. It is more prevalent in women. Patients of all ages may develop the disease; however, the mean age of diagnosis typically happens between 36 to 50 years. Children may also have PAH. The condition may occur due to various underlying medical conditions or as a disease that uniquely impacts the pulmonary circulation; both genetic and environmental factors may be involved. PAH is defined as a mean pulmonary artery pressure (mPAP) $\geq$ 25 mmHg with a pulmonary capillary wedge pressure (PCWP) $\leq$ 15 mmHg measured by cardiac catheterization. The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved. Lung transplantation may be recommended if pharmacological or medical therapies fail, based upon patient status. The WHO categorizes PAH into stages, which is also referred to as the functional class (Class I to IV) and is an adaptation of the New York Heart Association (NYHA) system to evaluate activity tolerance.

CTEPH is a persistent obstruction of pulmonary arteries and is often a complication of pulmonary embolism.[6,7] It is classified within Group 4 pulmonary hypertension. Symptoms include progressive dyspnea on exertion, as well as fatigue, syncope, hemoptysis, and signs of right heart failure. Pulmonary endarterectomy is the treatment of choice for most patients with CTEPH. However, around 40% of patients are deemed inoperable for various reasons. Medication therapy may also be recommended. Anticoagulant therapy is also given.

Guidelines

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.[4] 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. Many different medications from varying therapies classes and different routes of administration are recognized.

In 2019, and updated CHEST guideline and Expert Panel Report regarding therapy for pulmonary arterial hypertension in adults was released.[5] Evidence for use of the many medications available is also detailed. In the absence of contraindications, patients with PAH should undergo acute vasoreactivity testing utilizing a short-acting agent (e.g., calcium channel blockers [CCBs]). For patients in Functional Class II, oral therapies are recommended such as endothelin receptor antagonists (Letairis® [ambrisentan tablets], Tracleer® [bosentan tablets], Opsumit® [macitentan tablets]), phosphodiesterase type 5 [PDE 5] inhibitors (tadalafil, sildenafil), and Adempas® (riociguat tablets). It is suggest that parenteral or inhaled prostanoids not be chosen as initial therapy for treatment naïve patients with PAH with WHO Functional Class II symptoms or as second-line agents for patients with PAH with WHO Functional Class II who have not met their treatment goals. Parenteral prostanoids are recommended for patients with PAH in Functional Class III and IV.

Other Uses with Supportive Evidence

Epoprostenol injection has been used with varying results in patients with CTEPH.[8-10] It is sometimes used as a bridge prior to surgery. Limited options are available for patients with CTEPH.

Safety

Epoprostenol should not be abruptly discontinued or have the dose rapidly decreased as rebound pulmonary hypertension may occur.[1-3]

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of epoprostenol. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with epoprostenol well as the monitoring required for adverse events and long-term efficacy, approval requires epoprostenol to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: In the *Pulmonary Arterial Hypertension – Epoprostenol Care Continuum 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 – Epoprostenol Care Continuum Policy* is considered to be met.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of epoprostenol therapy 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 1 year if the patient meets ALL of the following criteria (i, ii, iii, iv, and v):
     - **i.** The patient has 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; AND
     - **iv.** The patient meets ONE of the following criteria (a or b):
       - **a)** The patient is in Functional Class III or IV; OR
       - **b)** The patient is in Functional Class II and meets ONE of the following criteria [(1) or (2)]:
         - **(1)** The patient has tried or is currently receiving one oral agent for PAH
           Note: Examples of oral agents for PAH include Tracleer® (bosentan tablets), Letairis® (ambrisentan tablets [generic]), Opsumit® (macitentan tablets), Adempas® (riociguat tablets), Revatio® (sildenafil tablets and suspension [generics]), Adcirca® (tadalafil tablets [generic]), Orenitram® (treprostinil extended-release tablets) and Uptravi® (selexipag tablets); OR
         - **(2)** The patient has tried one inhaled or parenteral prostacyclin product for PAH
           Note: Examples of inhaled and parenteral prostacyclin products for PAH include Remodulin® (treprostinil injection [generics]), Ventavis® (iloprost inhalation solution), and Tyvaso® (treprostinil inhalation solution); AND
     - **v.** Patients with idiopathic PAH must meet the following criteria (a, b, c, d, and e):
       - **a)** The patient had an acute response to vasodilator testing that occurred during the right heart catheterization (defined as a decrease in mPAP of at least 10 mm Hg to an absolute mPAP of less than 40 mm Hg without a decrease in cardiac output) AND has tried one oral calcium channel blocker (CCB) therapy
         Note: Examples of CCBs include amlodipine and nifedipine extended-release tablets; OR
       - **b)** The patient did not have an acute response to vasodilator testing; OR
       - **c)** The patient cannot undergo a vasodilator test; OR
       - **d)** The patient cannot take CCB therapy (e.g., right heart failure, decreased cardiac output); OR
       - **e)** The patient has tried one CCB
         Note: Examples of CCBs include amlodipine and nifedipine extended-release tablets; OR
   - **B)** Patients Currently Receiving Epoprostenol. Approve for the duration noted below if the patient meets the following criteria (i or ii):
     - **i.** Approve for 1 year if the patient meets ALL of the following conditions (a, b, and c):
       - **a)** The patient has World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
       - **b)** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
       - **c)** The patient meets the following criteria [(1) and (2)]:

(1) The patient has had a right heart catheterization; AND
(2) The results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; OR

ii. Approve a short-term supply of epoprostenol for up to 14 days if the patient does not meet the criteria in 1Bi above or if there is insufficient information available. These cases must be forwarded immediately to the medical director for review.
Note: A 14-day supply should be sufficient to address coverage issues. However, multiple short-term approvals are allowed if a coverage determination cannot be made. Abrupt discontinuation of epoprostenol therapy may have severe adverse consequences.

Dosing. Approve up to 100 ng per kg per minute intravenously.

Other Uses with Supportive Evidence

2. Chronic Thromboembolic Pulmonary Hypertension (CTEPH). Approve for 1 year if the agent is prescribed by or in consultation with a pulmonologist or a cardiologist.

Dosing. Approve up to 45 ng per kg per minute intravenously.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Epoprostenol injection (Flolan, Veletri generics) 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. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

1. Chronic Obstructive Pulmonary Disease (COPD) in a Patient Without PAH (WHO Group 1). COPD is classified as Group 3 Pulmonary Hypertension (pulmonary hypertension associated with lung diseases and/or hypoxia). Pulmonary hypertension may develop late in the course of COPD, but medications used for the treatment of PAH (WHO Group 1) are not recommended therapies.[11]

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

REFERENCES

1. Flolan® injection for intravenous use [prescribing information]: Research Triangle Park: NC; GlaxoSmithKline; December 2018.
2. Epoprostenol sodium for injection [prescribing information]. North Wales, PA: Teva; March 2019.
3. Veletri® injection [prescribing information]. South San Francisco, CA: Actelion; December 2018.
4. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension: A report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association Developed in Collaboration with the American College of Chest Physicians: American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol.* 2009;53:1573-1619.
5. Klinger JR, Elliott CG, Levine DJ, et al. Therapy for pulmonary arterial hypertension in adults. Update of the CHEST guideline and Expert Panel Report. *CHEST*. 2019;155(3):565-586.
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8. Condliffe R, Kiely DG, Gibbs SR, et al. Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med.* 2008;177:1122-1127.
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10. Cabrol S, Souza R, Jais X, et al. Intravenous epoprostenol in inoperable chronic thromboembolic pulmonary hypertension. *J Heart Lung Transplant*. 2007;26(4):357-362.
11. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. © 2019 Global Initiative for Chronic Obstructive Lung Disease, Inc. Available at: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-POCKET-GUIDE-DRAFT-v1.7-14Nov2018-WMS.pdf. Accessed on September 6, 2019.

HISTORY

Type of Revision	Summary of Changes	Approval Date
Annual revision	For initial review, documentation is required for the right heart catheterization and the result confirm the diagnosis of WHO Group 1 PAH. The specific values required from the heart catheterization test were removed. For patients currently receiving epoprostenol a right heart catheterization is required and the results should confirm the diagnosis of WHO Group 1 PAH, but documentation is not required. For patients in Functional Class II, the exceptions to use of other medications was removed as these can be handled on a case by case basis. Viagra and Cialis were removed from the listing of medications for WHO Group 1 PAH as Revatio and Adcirca are available generically. 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. Criteria that provided a 14 day approval for patients currently receiving epoprostenol for any indication were removed. The dosing section was slightly altered to reflect that the lower initial dose can be used (0.625 ng per kg per min) if systemic adverse events occur (not just due to mild or moderate hepatic insufficiency).	08/22/2018
Annual revision	For all conditions, the Dosing sections were revised to provide for the maximum range of dosing (see Policy). Additionally, the following sections were removed: initial/extended approval, duration of therapy, and labs/diagnostics. The waste management section was also deleted. Medications alternatives are now listed in notes. Additional changes per the specific indications were as follows: **PAH WHO Group 1:** The approval durations were changed from 6 months to 1 year. However, the short-term up to 14 day approval duration for PAH still remains for patients who are been receiving therapy but do not meet criteria or in those with insufficient information. **Chronic Thromboembolic Pulmonary Hypertension:** The approval duration was changed from 6 months to 1 year.	09/11/2019