PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Epoprostenol Products Prior Authorization Policy
- Flolan® (epoprostenol intravenous infusion – GlaxoSmithKline, generic)
- Veletri® (epoprostenol intravenous infusion – Actelion/Janssen)

REVIEW DATE: 10/09/2024

OVERVIEW

Epoprostenol intravenous infusion, 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]

Epoprostenol injection has been used with varying results in patients with chronic thromboembolic pulmonary hypertension (CTEPH).[4-6] It is sometimes used as a bridge prior to surgery. Limited options are available for patients with CTEPH.

Disease Overview

PAH is a serious but rare condition impacting fewer than 20,000 patients in the US.[7,8] The estimated incidence of PAH is 2 cases per 1 million per year with a prevalence of 10.6 cases per 1 million adults.[7] It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized.[7,8] 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. 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 (e.g., connective tissue disease, HIV) 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) > 20 mmHg (at rest) with a pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and a pulmonary vascular resistance > 2 Wood units measured by cardiac catheterization.[13] 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 system to evaluate activity tolerance.

CTEPH is a persistent obstruction of pulmonary arteries and is often a complication of pulmonary embolism.[9,10] 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

Several guidelines address intravenous epoprostenol products in the management of pulmonary hypertension.[8,11]

- **Pulmonary Arterial Hypertension:** The CHEST guidelines and Expert Panel Report regarding therapy for PAH in adults (2019) cites the many medications that have utility for this condition.[8] In the absence of contraindications, patients with PAH should undergo acute vasoreactivity testing utilizing a short-acting agent (e.g., calcium channel blockers). For patients in Functional Class II,

oral therapies are recommended such as endothelin receptor antagonists (ambrisentan, bosentan, Opsumit® [macitentan tablets]), phosphodiesterase type 5 inhibitors (tadalafil, sildenafil), and Adempas® (riociguat tablets). It is suggested 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.[8] The European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines regarding the treatment of pulmonary hypertension (2022) also recognize intravenous epoprostenol as having a prominent role in the management of this condition, usually in later therapy stages and after other therapies.[11]

- **Chronic Thromboembolic Pulmonary Hypertension:** Guidelines from the ESC/ERS regarding the treatment of pulmonary hypertension (2022) recommended to consider parenteral prostacyclin analogs for patients with inoperable CTEPH.[11]

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 prescription benefit coverage of epoprostenol injection. All approvals are provided for 1 year in duration unless otherwise noted below. Specifically, approvals will remain up to 14 days for patients currently receiving the agent for the indication of PAH (WHO Group 1) with inadequate information or if the criteria are not met. These cases are reviewed by a nurse or pharmacist. Because of the specialized skills required for evaluation and diagnosis of patients treated with epoprostenol injection as well as the monitoring required for adverse events and long-term efficacy, approval requires epoprostenol injection to be prescribed by or in consultation with a physician who specializes in the condition being treated.

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

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of epoprostenol injection is recommended in those who meet one of the following criteria:

FDA-Approved Indication

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 (i, ii, iii, iv, and v):
     - **i.** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
     - **ii.** Patient meets BOTH of the following (a and b):
       - **a)** Patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND
       - **b)** Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
     - **iii.** Patient meets ONE of the following (a or b):
       - **a)** Patient is in Functional Class III or IV; OR
       - **b)** Patient is in Functional Class II and meets ONE of the following [(1) or (2)]:
         - **(1)** Patient has tried or is currently receiving one oral agent for PAH; OR
           Note: Examples of oral agents for PAH include bosentan, ambrisentan, Opsumit (macitentan tablets), Opsynvi (macitentan/tadalafil tablets), Adempas (riociguat tablets), sildenafil, tadalafil, Orenitram (treprostinil extended-release tablets), Alyq (tadalafil tablets), Tadliq (tadalafil oral suspension), and Uptravi (selexipag tablets).
         - **(2)** Patient has tried one inhaled or parenteral prostacyclin product for PAH; AND
           Note: Examples of inhaled and parenteral prostacyclin products for PAH include Tyvaso (treprostinil inhalation solution), Tyvaso DPI (treprostinil oral inhalation powder), Ventavis (iloprost inhalation solution), treprostinil injection, and epoprostenol injection.
     - **iv.** Patient with idiopathic PAH must meet ONE of the following (a, b, c, d, or e):
       - **a)** Patient must meet BOTH of the following [(1) and (2)]:
         - **(1)** According to the prescriber, the patient has had an acute response to vasodilator testing that occurred during the right heart catheterization; AND
           Note: An example of a response can be defined as a decrease in mean pulmonary artery pressure of at least 10 mm Hg to an absolute mean pulmonary artery pressure of less than 40 mm Hg without a decrease in cardiac output.
         - **(2)** Patient has tried one oral calcium channel blocker (CCB) therapy; OR
           Note: Examples of CCBs include amlodipine and nifedipine extended-release tablets.
       - **b)** According to the prescriber, the patient did not have an acute response to vasodilator testing; OR
       - **c)** According to the prescriber, the patient cannot undergo a vasodilator test; OR
       - **d)** Patient cannot take CCB therapy; OR
         Note: Examples of reasons a patient cannot take CCB therapy include right heart failure or decreased cardiac output.
       - **e)** Patient has tried one CCB; AND
         Note: Examples of CCBs include amlodipine and nifedipine extended-release tablets.
     - **v.** Medication is prescribed by or in consultation with a cardiologist or a pulmonologist; OR
   - **B)** Patient Currently Receiving Epoprostenol. Approve for the duration noted below if the patient meets ONE of the following (i or ii):
     - **i.** Approve for 1 year if the patient meets ALL of the following (a, b, and c):
       - **a)** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
       - **b)** Patient meets BOTH of the following [(1) and (2)]:
         - **(1)** Patient has had a right heart catheterization; AND

Note: This refers to prior to starting therapy with a medication for WHO Group 1 PAH.

(2) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

c) Medication is prescribed by or in consultation with a cardiologist or a pulmonologist; 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. All approvals are reviewed by a nurse or pharmacist.

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.

Other Uses with Supportive Evidence

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

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of epoprostenol injection is not recommended in the following situations:

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.[12]

2. **Concurrent Use with Parenteral Treprostinil Products, Oral Prostacyclin Products, or Inhaled Prostacyclin Agents Used for Pulmonary Hypertension.**
   Note: Examples of medications include Orenitram (treprostinil extended-release tablets), Uptravi (selexipag tablets and intravenous infusion), Tyvaso (treprostinil inhalation solution), Tyvaso DPI (treprostinil oral inhalation powder), Ventavis (iloprost inhalation solution), and treprostinil subcutaneous injection and intravenous infusion (Remodulin, generic).

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

REFERENCES

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