CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Pulmonary Arterial Hypertension – Epoprostenol Products Utilization Management Medical Policy
- Flolan® (epoprostenol intravenous infusion – GlaxoSmithKline, generic)
- Veletri® (epoprostenol intravenous infusion – Actelion)

REVIEW DATE: 03/04/2026

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 intravenous infusion 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] 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. Although the mean age of diagnosis is between 36 and 50 years, patients of any age may be affected, including pediatric patients. 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.

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. 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] A simplified treatment algorithm that utilizes risk classifications was introduced in these guidelines and reaffirmed in the 2024 World Symposium on Pulmonary Hypertension.[14] An initial risk assessment is recommended at baseline, 3-4 months, and periodically thereafter; it is based on functional class, 6-minute walk distance, and natriuretic peptides. Hemodynamics and right ventricle imaging can be used to supplement this assessment. For initial risk assessments patient are classified as not high risk or high risk. Patients who are not high risk are recommended to receive a combination of ERAs and PDE-5 inhibitors, whereas those who are high risk may require intravenous or subcutaneous therapies. For follow-up risk assessments, patients are classified into four categories: low-risk, intermediate-low risk, intermediate-high risk, and high risk. Recommendations are made for the addition of an activin-signaling inhibitor (Winrevair [sotatercept-csrk subcutaneous injection]), oral or inhaled prostacyclin therapies, or the switch to a soluble guanylyl cyclase stimulator (sGCS) [Adempas {riociguat tablets]. Patients who are classified as persistent intermediate-high or high-risk may need maximal four-drug therapies and a lung transplant evaluation.

- **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 medical benefit coverage of epoprostenol injection. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. 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 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 Utilization Management Medical 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. All documentation must include patient-specific identifying information. 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 Utilization Management Medical 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)** According to the prescriber, patient is intermediate-high risk or high-risk
       - **b)** According to the prescriber, patient is low-risk or intermediate-low risk and has tried or is currently receiving one or more agents for PAH from the following different categories (either alone or in combination with another therapy) for ≥ 60 days ([1], [2], [3]. [4], or [5]):
         - **(1)** Phosphodiesterase type 5 (PDE5) inhibitors; OR
         - **(2)** Endothelin receptor antagonists (ERAs); OR
         - **(3)** Adempas (riociguat tablets); OR
         - **(4)** Winrevair (sotatercept-csrk subcutaneous injection); OR
         - **(5)** Prostacyclin analogs/mimetics; AND

           Note: Examples of phosphodiesterase type 5 (PDE5) inhibitors include sildenafil and tadalafil. Endothelin receptor antagonists (ERAs) include bosentan, ambrisentan, Opsumit {macitentan tablets. Prostacyclin analogs/mimetics include Tyvaso (treprostinil inhalation solution), Tyvaso DPI (treprostinil oral inhalation powder), treprostinil injection, epoprostenol injection, Uptravi (selexipag tablets) and Yutrepia (treprostinil inhalation powder).
     - **iv.** Patient with idiopathic PAH must meet ONE of the following (a, b, c, d, or e):
       - **a)** Patient meets 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 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.

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

Other Use with Supportive Evidence

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

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

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), and treprostinil injection (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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11. Humbert M, Kovacs G, Hoeper MM, et al, for the ESC/ERS Scientific Document Group. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022 Aug 26. [Online ahead of print].
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HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Pulmonary Arterial Hypertension (PAH) World Health Organization (WHO) Group 1:** For a patient currently receiving epoprostenol, added a Note to indicate that requirement of a right heart catheterization (RHC) refers to a RHC prior to starting therapy with a medication for WHO Group 1 PAH.	10/09/2024
Annual Revision	**Pulmonary Arterial Hypertension (PAH) World Health Organization (WHO) Group 1:** For initial therapy, Orenitram (treprostinil extended-release tablets), and Uptravi (selexipag tablets) were removed from the Note of examples of oral medications that the patient has tried or is currently receiving for the condition in Functional Class II.	10/08/2025
Early Annual Revision	**Pulmonary Arterial Hypertension (PAH) World Health Organization (WHO) Group 1:** The requirement that the patient is in Functional Class II, III, or IV was removed. A requirement that, according to the prescriber, the patient is intermediate or high-risk or is low-risk or intermediate-low risk was added. For a patient with low-risk or intermediate-low risk, a requirement and associated Note was added that the patient has tried or is currently receiving one or more agents from the following different categories (either alone or in combination with another therapy) for ≥ 60 days: phosphodiesterase type 5 (PDE5) inhibitors, endothelin receptor antagonists (ERAs), Adempas, Winrevair, or prostacyclin analogs/mimetics. The previous requirement for systemic therapy that applied to all patients with Class II disease was removed. **Conditions Not Recommended for Approval:** Ventavis was removed from the Note that lists examples of medications that should not be taken in combination with epoprostenol products.	03/04/2026