MEDICAL MUTUAL®

Drug Policy

Policy:	**201806**	**Initial Effective Date:**	**04/28/2014**
Code(s):	**HCPCS J1325**	**Annual Review Date:**	**02/15/2018**
SUBJECT:	**Pulmonary Arterial Hypertension (PAH) – Epoprostenol for intravenous injection (Flolan®, Veletri®, generics)**	**Last Reviewed Date:**	**08/16/2018**

Prior approval is required for some or all procedure codes listed in this Corporate Drug Policy.

OVERVIEW

Epoprostenol injection is a prostacyclin vasodilator. It is indicated for the treatment of pulmonary arterial hypertension (PAH) World Health Organization (WHO) Group 1 to improve exercise capacity. Studies establishing the effectiveness predominately included patients with New York Heart Association (NYHA) Functional Class III to IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.[1-3] Several studies have noted beneficial effects with epoprostenol therapy.[1-8] Epoprostenol is given by intravenous infusion through a central venous catheter.[1-3]

The Site of Care Medical Necessity Criteria applies to initial therapy and reauthorizations.

POLICY STATEMENT

This policy involves the use of epoprostenol. Prior authorization is recommended for medical benefit coverage of epoprostenol. Coverage is recommended for those who meet the conditions of coverage in the **Criteria, Dosing, Initial or Extended Approval, Duration of Therapy, and Labs/Diagnostics** for the diagnosis provided. **Waste Management** applies for all covered conditions. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria and Waste Management section.

Because of the of the specialized skills required for evaluation and diagnosis of patients treated with epoprostenol as 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. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is required, a response to therapy is required for continuation of therapy.

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RECOMMENDED AUTHORIZATION CRITERIA
Coverage of epoprostenol therapy is recommended in those who meet the following criteria:

FDA-Approved Indications

Criteria for PAH is divided into patients initiating therapy (1A) and those who have already been started on epoprostenol therapy (1B).

1A. Pulmonary Arterial Hypertension (PAH) (World Health Organization [WHO] Group 1) for Patients not Currently Receiving Epoprostenol Therapy.

Criteria. *The patient must meet the following criteria (A, B, C, D, E and F):*

A) The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND

B) The patient has had a right heart catheterization to confirm the diagnosis of PAH and the results of the right heart catheterization are as follows: mean pulmonary arterial pressure (mPAP) > 25 mm Hg at rest; pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg; and pulmonary vascular resistance (PVR) > 3 Wood units; AND

C) The patient meets one of the following criteria (i or ii):

- **i.** The patient is in Functional Class III or IV; OR
- **ii.** 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 (e.g., Tracleer® [bosentan tablets], Letairis® [ambrisentan tablets], Opsumit® [macitentan tablets], Adempas® [riociguat tablets], Revatio®/Viagra® [sildenafil tablets or injection], Adcirca®/Cialis® [tadalafil tablets], Orenitram™ [treprostinil extended-release tablets]) or Uptravi™ [selexipag tablets]); OR
    The patient is unable to take any of the agents above (e.g., those with liver abnormalities [Tracleer], patient of childbearing potential [Tracleer, Letairis], concomitantly using nitrates [sildenafil, Adcirca/Cialis], hypotension, drug-drug interactions); OR
  - **(2)** The patient has tried one inhaled or parenteral prostacyclin product for PAH (e.g., Ventavis® [iloprost inhalation solution], Tyvaso® [treprostinil inhalation solution], Remodulin® [treprostinil injection]); AND

D) The patient has WHO Group 1 PAH; AND

E) Patients with idiopathic PAH must meet ONE of the following criteria (i, ii, iii, iv or v):

- **i.** 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 (e.g., amlodipine, nifedipine extended-release tablets); OR
- **ii.** The patient did not have an acute response to vasodilator testing; OR
- **iii.** The patient cannot undergo a vasodilator test; OR
- **iv.** The patient cannot take CCB therapy (e.g., right heart failure, decreased cardiac output); OR
- **v.** The patient has tried one CCB (e.g., amlodipine, nifedipine extended-release tablets); AND

F) Site of care medical necessity is met*.

1B.Pulmonary Arterial Hypertension (WHO Group 1) for Patients Currently Receiving Epoprostenol Therapy.

Criteria. *The patient must meet the following criteria (A OR B)*:

A) The patient meets all of the following conditions (i, ii, iii, iv and v):

- **i.** Currently receiving epoprostenol and receiving beneficial response; AND
- **ii.** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
- **iii.** The patient has had a right heart catheterization to confirm the diagnosis of PAH and the results of the right heart catheterization are as follows: mPAP > 25 mm Hg at rest; PCWP ≤ 15 mm Hg; and PVR > 3 Wood units; AND
- **iv.** The patient has WHO Group 1 PAH; AND
- **v.** Site of care medical necessity is met*; OR

B) Approve a short-term supply of epoprostenol for up to 14 days if the patient does not meet the criteria in 1Ba above or if there is insufficient information available and site of care medical necessity is met*. 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, up to 2 short-term approvals are allowed if a coverage determination cannot be made. Abrupt discontinuation of epoprostenol therapy may have severe adverse consequences.

Abrupt discontinuation or withdrawal of epoprostenol therapy should be avoided as patients may have symptoms associated with rebound hypertension (e.g., dyspnea, dizziness) or other adverse consequences.[1] In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

Epoprostenol injection is indicated for the treatment of PAH (WHO Group 1) to improve exercise capacity. Studies establishing effectiveness included mainly patients with NYHA Functional Class III to IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue disorders.[1-3] The World Symposium on Pulmonary Hypertension (WSPH) updated treatment algorithm of PAH recommend intravenous epoprostenol for patients in WHO Functional Class III or Class IV.[16] Of note, continuous intravenous epoprostenol is recommended first-line for patients in Functional Class IV because of the survival benefit in this subset.[16] Patients in Functional Class II should be treated with an oral agent for PAH (e.g., Tracleer, Opsumit, Letairis, Adempas, sildenafil, Adcirca). The American College of Chest Physicians (ACCP) guidelines for the screening, early detection, and diagnosis of PAH, established in 2004, recommend to perform a right heart catheterization in patients with suspected pulmonary hypertension to confirm the presence of pulmonary hypertension, establish the diagnosis, and to determine disease severity.[5] An American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) 2009 consensus document on pulmonary hypertension, developed in collaboration with the ACCP, the American Thoracic Society (ATS) and the Pulmonary Hypertension Association, notes all patients suspected of having PAH after noninvasive evaluation should undergo right heart catheterization prior to initiation of therapy.[4] The current hemodynamic definition of PAH is a mPAP greater than 25 mm Hg; a PCWP, left atrial pressure, or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mm Hg; and a PVR greater than 3 Wood units. Acute vasodilator testing should be done in all idiopathic PAH patients who might be considered potential candidates for long-term calcium channel blocker therapy. Those with overt right heart failure or hemodynamic instability should not undergo acute vasodilator testing. The definition of an acute responder is a reduction in mPAP to at least 10 mm Hg or an absolute mPAP of less than 40 mmHg without a decrease in cardiac output.[4] Abrupt discontinuation or withdrawal of epoprostenol therapy should be avoided as patients may have symptoms associated with rebound

pulmonary hypertension (e.g., dyspnea, dizziness) or other adverse consequences.[1] In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

Dosing in Pulmonary Arterial Hypertension (PAH). *Dosing must meet ONE of the following (a OR b)*:

a) In adults, epoprostenol is given intravenously as a continuous infusion. Therapy is initiated at 2 ng per kg per min and adjusted according to response (PAH symptom relief) or adverse effects. Patients are carefully monitored as the dose is adjusted. Per the prescribing information, the mean dose at the end of one 12-week study was 11.2 ng per kg per min. The mean incremental increase was 2 to 3 ng per kg per min every 3 weeks but the titration schedule is highly individualized. Higher doses have been utilized in clinical practice. In one guideline most experts believed that the optimal dose range for chronic therapy is between 25 and 40 ng per kg per min for most adult patients, when used as monotherapy. An absolute maximum dosage has not been established. With chronic use, it is expected that the dose will be increased if PAH symptoms persist, recur, or worsen; OR

b) In children and adolescents, dosing is similar to adults. In clinical practice the final doses utilized in children/adolescents are frequently higher than those utilized in adults on a ng per kg per min basis. The mean dose in children, especially young children, is usually 50 to 80 ng per kg per min or higher with significant patient variability regarding the optimal dose. An absolute maximum dosage has not been established.

Initial Approval/Extended Approval.

a) *Initial Approval:* Approve for 6 months.

b) *Extended Approval:* Approve at 6-month intervals if the patient is benefiting from the agent as determined by the prescribing physician (e.g., improving in functional class or quality of life, or in other hemodynamic or clinical parameters).

Since PAH is a progressive disease, patients will deteriorate despite therapy.

Duration of Therapy in PAH. Indefinite in patients who are responding or benefiting as defined by the prescribing physician.

Labs/Diagnostics. The patient has had a right heart catheterization (with documented results) to confirm the proper diagnosis of WHO Group 1 PAH.

Waste Management for All Indications.

The dose is weight-based and is titrated to efficacy and tolerability. The number of vials should be calculated based on the dose.

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.[15]

2. **Acute Respiratory Distress Syndrome (ARDS).** A number of potential therapies were once regarded as promising in patients with ARDS, but have since proven to be either ineffective or harmful. These therapies include intravenous prostaglandin such as epoprostenol.[21]

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

Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the drug provided or services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

REFERENCES

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†Revised World Health Organization Classification of Pulmonary Hypertension

Group 1: Pulmonary Arterial Hypertension
Idiopathic
Heritable
BMPR2

ALK-1, ENG, SMAD9, CAV1, KCNK3 Unknown Drug and toxin-induced Associated with Connective tissue disease Human immunodeficiency virus (HIV) infection Portal hypertension Congenital heart diseases Schistosomiasis Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis Persistent pulmonary hypertension of the newborn
Group 2: Pulmonary hypertension due to left heart disease Left ventricular systolic dysfunction Left ventricular diastolic dysfunction Valvular disease Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
Group 3: Pulmonary hypertension due to lung diseases and/or hypoxemia Chronic obstructive lung disease Interstitial lung disease Other pulmonary diseases with mixed restrictive and obstructive pattern Sleep-disordered breathing Alveolar hypoventilation disorders Chronic exposure to high altitude Developmental lung diseases
Group 4: Chronic thromboembolic pulmonary hypertension (CTEPH)
Group 5: Pulmonary hypertension with unclear multifactorial mechanisms Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangiomyomatosis Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental pulmonary hypertension.

BMPR2 – Bone morphogenic protein receptor type 2; ALK-1 – Activin-like receptor kinase-1; ENG – Endoglin; Smad 9 – Mothers against decapentaplegic; CAV1 – Caveolin-1; KCNK3 – Potassium channel super family K member-3.

Pulmonary Hypertension

Class	Description
I	Patients in whom there is no limitation of usual physical activity. Ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope.
II	Patients who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope.
III	Patients who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope.
IV	Patients who are unable to perform any physical activity at rest and who may have signs of right

††**World Health Organization (WHO) Functional Classification for**

	ventricular failure. Dyspnea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

FOR MEDICAL BENEFIT COVERAGE REQUESTS:

***MMO Site of Care Medical Necessity Criteria:**

- Medications in this policy will be administered in a place of service that identifies the location to be a non-hospital facility based location (i.e., home infusion provider, provider's office, free-standing ambulatory infusion center) unless *at least one* of the following are met[†]:

    1. Age less than 21 years; or
    2. Clinically unstable based upon documented medical history (e.g., patient is hemodynamically unstable); or
    3. History of a severe adverse event from previous administration of the prescribed medication; or
    4. Requested medication is being administered as follows:
        - part of a chemotherapy regimen (e.g., anti-neoplastic agent, colony stimulating factor, erythropoiesis-stimulating agent, anti-emetic) for treatment of cancer; or
        - administered with dialysis; or
    5. Physical or cognitive impairment and caregiver is not available to assist with safe administration of prescribed medication in the home; or
    6. Up to 1 dose of medication or re-initiation after at least 12 months; or
    7. Experiencing adverse events that are not managed by premedication or resources available at a non-hospital facility based location.

[†]**This criterion does not apply to Medicare or Medicare Advantage members.**

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Prior approval is required for HCPCS Codes J1325

HCPCS Code(s):	
J1325	Injection, epoprostenol, 0.5 mg