MEDICAL MUTUAL®

Drug Policy

Policy:	**201806**	**Initial Effective Date:**	**04/28/2014**
Code(s):	**HCPCS J1325**	**Annual Review Date:**	**02/20/2024**
SUBJECT:	**Pulmonary Arterial Hypertension (PAH) – Epoprostenol for intravenous injection (Flolan®, Veletri®, generics)**	**Last Reviewed Date:**	**02/20/2024**

☒Subject to Site of Care

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

Initial and renewal requests for the medication(s) listed in this policy are subject to site of care management. When billed under the medical benefit, administration of the medication will be restricted to a non-hospital facility-based location (i.e., home infusion provider, provider's office, free-standing ambulatory infusion center) unless the member meets the site of care exception criteria. To view the exception criteria and a list of medications subject to site of care management please click here.

Policy Statement

This policy involves the use of epoprostenol. Prior authorization is recommended for pharmacy and medical benefit coverage of epoprostenol. Approval is recommended for those who meet the conditions of coverage in the **Criteria, Dosing, Initial/Extended Approval, Duration of Therapy**, and **Labs/Diagnostics** for the diagnosis provided. **Waste Management** applies for all covered conditions that are administered by a healthcare professional. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria and Waste Management section. Requests for uses not listed in this policy will be reviewed for evidence of efficacy and for medical necessity on a case-by-case basis.

Because of the specialized skills required for evaluation and diagnosis of patients treated with epoprostenol as well as the monitoring required for AEs and long-term efficacy, initial approval requires epoprostenol 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 allowed, a response to therapy is required for continuation of therapy unless otherwise noted below.

Documentation: 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 policy is considered to be met.

Recommended Authorization Criteria
Coverage of epoprostenol therapy is recommended in those who meet the following criteria:

The requested medication will not be used in patients with 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] AND;

The requested medication will not be used in patients with 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] AND;

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 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 (e.g., Tracleer® [bosentan tablets], Letairis® [ambrisentan tablets], Opsumit® [macitentan tablets], Adempas® [riociguat tablets], Revatio® [sildenafil tablets {generic} and suspension], Adcirca® [tadalafil tablets {generic}], Orenitram™ [treprostinil extended-release tablets]), Alyq (tadalafil tablets), Tadliq (tadalafil oral suspension) or Uptravi™ [selexipag tablets]); 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]), Tyvaso DPI (treprostinil oral inhalation powder), and epoprostenol injection; AND
     - **v.** Patients with idiopathic PAH must meet the following criteria (a, b, c, d, or 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 (e.g., amlodipine, 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 (e.g., amlodipine, nifedipine extended-release tablets); OR
f) If brand Veletri or Flolan is prescribed, the patient must meet the following criteria (a, OR b):
   a. The patient has previously failed or is intolerant to generic epoprostenol; OR
   b. Brand Veletri or Flolan is being requested due to a formulation difference in the inactive ingredient(s) [e.g., preservatives] between the brand and the bioequivalent generic product which, per the prescribing physician, has or would result in a significant allergy or serious adverse reaction. [documentation required].

B) Patients Currently Receiving Epoprostenol. Approve for the duration noted below if the patient meets the following criteria (i or ii):
   i. Approve if the patient meets ALL of the following conditions (a, b, c, and d:
      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; AND
      d) If brand Veletri or Flolan is prescribed, the patient must meet the following criteria (a, OR b):
         (1) The patient has previously failed or is intolerant to generic epoprostenol; OR
         (2) Brand Veletri or Flolan is being requested due to a formulation difference in the inactive ingredient(s) [e.g., preservatives] between the brand and the bioequivalent generic product which, per the prescribing physician, has or would result in a significant allergy or serious adverse reaction. [documentation required]; 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 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. Alter the infusion by 1 to 2 ng per kg per minute in increments in at least 15 minute intervals per tolerability and clinical response. 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 Pulmonary Arterial Hypertension (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 documentation for initial therapy) to confirm the proper diagnosis of WHO Group 1 PAH.

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.

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.

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

1. Flolan® intravenous infusion [prescribing information]: Research Triangle Park: NC; GlaxoSmithKline; August 2021.
2. Epoprostenol sodium intravenous infusion [prescribing information]. North Wales, PA: Teva; January 2021.
3. Veletri® intravenous infusion [prescribing information]. South San Francisco, CA: Actelion/Janssen; July 2022.
4. 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.
5. Bresser P, Fedullo PF, Auger WR, et al. Continuous epoprostenol for chronic thromboembolic pulmonary hypertension. *Eur Respir J.* 2004; 23:595-600.
6. 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.
7. Ruopp NF, Cockrill BA. Diagnosis and treatment of pulmonary arterial hypertension. A review. *JAMA*. 2022;327(14):1379-1391.
8. 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.
9. Kim NH, Delcroix M, Jais X, et al. Chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2019;53(1):1801915.
10. Papamatheakis DG, Poch DS, Fernandes TM, et al. Chronic thromboembolic pulmonary hypertension: JACC focus seminar. *J Am Coll Cardiol*. 2020;76(180):2155-2169.
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].
12. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2023 report). © 2023 Global Initiative for Chronic Obstructive Lung Disease. Available at: https://goldcopd.org/2023-gold-report-2/. Accessed on September 6, 2023.
13. Maron B. Revised definition of pulmonary hypertension and approach to management: a clinical primer. *J Am Heart Assoc*. 2023 April 7. [epub ahead of print].

_†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 – End decapentaplegic; CAV1 – Caveolin-1; KCNK3 – Potassium channel super family K member-3.oglin; Smad 9 – Mothers against decapentaplegic; CAV1 – Caveolin-1; KCNK3 – Potassium channel super family K member-3.

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

Prior approval is required for HCPCS Codes J1325
Edits and Denials:

Prior approval: Prior approval is required for epoprostenol **(HCPCS Code J1325)**, Requests for prior approval will be authorized by a nurse reviewer if submitted documentation meets criteria outlined within the Corporate Medical Policy.

Requests for prior approval will be forwarded to a qualified physician reviewer if submitted documentation does not meet criteria outlined within the Corporate Medical Policy.

TOPPS: Claims received with **HCPCS Codes J1325** will edit with **Remark Code M3M or M4M** and will be adjudicated in accordance with the Corporate Medical Policy.

Liability: A participating provider will be required to write off charges denied as not medically necessary.

Revised:

04/28/2014: Policy enacted.
09/09/2015: Annual review, added FDA approved dosing, approval duration and updated tables. Revised policy effective
10/30/2015.
06/13/2016: SOC added.
02/15/2018: Annual Review. No clinical changes. Epoprostenol moved from PAH policy to individual policy. Reformatting of criteria.
08/16/2018: Select revision to add ARDS to conditions not recommended for approval.
02/21/2019: Annual Review. Moved to CC/ESI standard criteria with addition of ARDS to conditions not recommended for approval. Also, removed criteria for CTEPH as this was not in the MMO original criteria.
08/15/2019: Annual Review. No changes to clinical criteria.

02/20/2020:	Annual Review. No changes to clinical criteria. Formatting changes, re-arranged placement of criteria not recommended for approval.
02/18/2021:	Annual Review. No changes to clinical criteria.
03/18/2021:	Select revision. Generic trial requirement added to initial and continuation criteria. Request mainframe coding.
02/17/2022:	Annual Review. No changes to clinical criteria
02/16/2023:	Annual Review: No changes to clinical criteria
02/20/2024	Annual Review**: Pulmonary Arterial Hypertension** (World Health Organization Group 1): Tyvaso /DPI and Tadliq was added as examples was added as agents used for pulmonary arterial hypertension. **Conditions Not Recommended for Approval:** It was added that concurrent use with parenteral treprostinil products, oral prostacyclin products, or inhaled prostacyclin agents used for pulmonary hypertension is not permitted.

Reviewed:

03/13/2014:	Chief Medical Officer, Clinical Pharmacist, PharmD, Director, Pharmacy Services and Vice President Pharmacy, Quality & Strategic Initiatives.
09/09/2015:	Chief Medical Officer; Clinical Pharmacist, PharmD, Director, Pharmacy Services; Clinical Pharmacist, PharmD; and Vice President Pharmacy & Care Management.
06/13/2016:	Chief Medical Officer; Clinical Pharmacist, PharmD, Manager, Pharmacy Services; Clinical Pharmacist, PharmD; and Vice President Pharmacy & Care Management.
02/15/2018:	Senior Medical Officer, Clinical Operations; Vice President, Pharmacy Management; Clinical Pharmacist, PharmD, Manager, Clinical Pharmacy Programs; and Clinical Pharmacist, PharmD.
08/16/2018:	Senior Medical Officer, Clinical Operations; Vice President, Pharmacy Management; Clinical Pharmacist, PharmD, Director, Clinical Pharmacy Programs; and Clinical Pharmacist, PharmD.
02/21/2019:	Senior Medical Officer, Clinical Operations; Vice President, Pharmacy Management; Clinical Pharmacist, PharmD, Director, Clinical Pharmacy Programs; and Clinical Pharmacist, PharmD.
08/15/2019:	Senior Medical Officer, Clinical Operations; Vice President, Pharmacy Management; Clinical Pharmacist, PharmD, Director, Clinical Pharmacy Programs; Supervisor, Clinical Pharmacy Programs; and Clinical Pharmacist, PharmD.
02/20/2020:	Senior Medical Officer, Clinical Operations; Vice President, Pharmacy Management; Clinical Pharmacist, PharmD, Director, Clinical Pharmacy Programs; Supervisor, Clinical Pharmacy Programs; and Clinical Pharmacist, PharmD.
02/18/2021:	Senior Medical Officer, Clinical Operations; Vice President, Pharmacy Management; Clinical Pharmacist, PharmD, Director, Clinical
03/18/2021:	Senior Medical Officer, Clinical Operations; Vice President, Pharmacy Management; Clinical Pharmacist, PharmD, Director, Clinical Pharmacy Programs; and Clinical Pharmacist, RPh, Supervisor, Clinical Pharmacy Programs.
02/17/2022:	TJ
02/16/2023:	TJ
02/20/2024:	John K. Porch, PharmD.

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