Department:	Pharmacy Management	**Original Approval:**	12/24/2015
Policy #:	PM114	**Last Approval:**	06/14/2018
Title:	Epoprostenol (Flolan®, Veletri®, generics)		
Approved By:	Medical Management Leadership Team		

REQUIRED CLINICAL DOCUMENTATION FOR REVIEW

Documentation required to determine medical necessity for Epoprostenol (Flolan,Veletri, generics): History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Diagnosis -Prescribed by or in consultation with a cardiologist or pulmonologist -Labs/Diagnostics -Medication list (current and past) to include start and end dates of previous trials for all pulmonary arterial hypertension agents -Weight -Dosing and duration requested -Age -Initial/Extended approval.

BACKGROUND

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 (generic) and Flolan are supplied as sterile freeze-dried powder in glass vials.[1-2] Of note, Flolan and epoprostenol (generic) must be reconstituted only with specific Sterile Diluent for epoprostenol, Flolan or with pH 12 for Flolan.[1-2] Veletri is supplied as a sterile lyophilized material in vials.[3] Veletri may be stored at room temperature. There are different storage requirements for Flolan based on the diluent utilized. Refer to the respective prescribing information for details.

Epoprostenol is given by continuous intravenous infusion via a central venous catheter using an ambulatory infusion pump. During initiation of treatment, epoprostenol may be given using a peripheral vein.[1-3]

DEFINITIONS

None.

INDICATIONS/CRITERIA

Medicaid Members	***Continue to criteria for approval below.***
Medicare	***Step-utilization of Part D drugs not required.***

Members	

Coverage of Epoprostenol is recommended in those who meet the following criteria:

Food and Drug Administration (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 AND E):*

- **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).

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, and iii):
  - **i.** The agent is prescribed by, or in consultation with, a cardiologist or a pulmonologist; AND
  - **ii.** 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
  - **iii.** The patient has WHO Group 1 PAH; 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. 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.

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. The 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 documented results) to confirm the proper diagnosis of WHO Group 1 PAH.

Other Uses with Supportive Evidence

2. Chronic Thromboembolic Pulmonary Hypertension (CTEPH).

Criteria. *The patient must meet the following criteria:* The agent is prescribed by, or in consultation with, a pulmonologist or a cardiologist.

Although surgical pulmonary thromboendarterectomy (PTE) is the treatment of choice in symptomatic CTEPH, epoprostenol therapy has been used with varying results to achieve hemodynamic stabilization prior to PTE.[10-14,18-19] Epoprostenol injection has been studied (retrospectively) as a therapeutic bridge between CTEPH diagnosis and surgical intervention. The 4th World Symposium on Pulmonary Hypertension published a paper that focused on non-PAH forms of pulmonary hypertension.[10] Final recommendations include that in severely compromised patients with surgically accessible disease but for whom surgery must be delayed, pre-operative medical therapy (e.g., prostanoids, endothelin

receptor antagonists [ERAs] or phosphodiesterase type 5 [PDE5] inhibitors) may be used to improve hemodynamics and clinical performance before surgery. Preliminary data suggest that medications currently approved for PAH may have beneficial effects in patients with CTEPH, but as long as there are no robust data from randomized controlled trials, the decision of whether or not to treat CTEPH patients with these medications should be restricted to centers experienced in the management of the disease.[10] If surgery is not possible, only limited options are available for patients with CTEPH. The guidelines have not been updated since the approval of Adempas for CTEPH.[20] In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

Dosing in CTEPH. *Dosing must meet the following:* The doses are titrated to efficacy and tolerability. The mean epoprostenol dose is 20 ng per kg per minute IV. Dose ranges have been between 6 to 41 ng per kg per minute IV.[11-14] 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, improvement in the 6-minute walk distance, or in other hemodynamic or clinical parameters).

Duration of Therapy in CTEPH. Use is chronic, unless the patient undergoes pulmonary thromboendarterectomy or undergoes a lung transplantation.

Labs/Diagnostics. None required.

3. Patients who are Currently Receiving Epoprostenol Therapy (for any Indication). Approve a short-term supply for up to 14 days if the patient does not meet any of the criteria above or if there is insufficient information available. These cases should 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.

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.

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]

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

SPECIAL CONSIDERATIONS

None.

LIMITATIONS/EXCLUSIONS

Please refer to a product line's certificate of coverage for benefit limitations and exclusions for these services:

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
WASHINGTON APPLE HEALTH	http://chpw.org/our-plans/apple-health/
INTEGRATED MANAGED CARE	http://chpw.org/our-plans/apple-health/

Citations & References

References	1. Flolan® injection [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; June 2016. 2. Epoprostenol injection [prescribing information]. Sellersville, PA: Teva; October 2011. 3. Veletri® injection [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals; July 2016. 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.
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CFR		
WAC	WAC 284-43-2050	
RCW		
Contract Citation	☒ WAH	
	☒ IMC	
	☒ MA	
Other Requirements		
NCQA Elements		

Revision History

Revision Date	Revision Description	Revision Made By
12/23/2015	New	Kelly Force; Yusuf Rashid, RPh
12/24/2015	Approval	MMLT
01/11/2017	No revisions	Fran McGaugh
01/12/2017	Approval	MMLT
06/16/2017	Revision reviewed	Sonya Ou, Pharm.D.
07/24/2017	Formatted to currently approved template	Sophia Yun, PharmD
07/25/2017	Approved	MMLT
03/09/2018	Reassigned from UM to PM	Cindy Bush
04/25/2018	Transferred to new template	Cindy Bush
06/11/2018	No revisions	Jennifer Farley, PharmD
06/14/2018	Approval	UM Committee