Department:	Pharmacy Management	**Original Approval:**	12/24/2015
Policy #:	PM114	**Last Approval:**	05/20/2019
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 Members	***Step-utilization of Part D drugs not required.***

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

Food and Drug Administration (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]) 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]); AND

v. Patients with idiopathic PAH must meet the following criteria (a, b, c, d, and 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

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, and c):

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; 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 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.

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. 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 HEALTH PROGRAM	http://chpw.org/our-plans/apple-health/
INTEGRATED MANAGED CARE	http://chpw.org/our-plans/apple-health/

Citations & References

References

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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
04/02/2019	Annual review. Addition of appendices for PAH classification.	Jennifer Farley, PharmD
05/20/2019	Approval	UM Pharmacy Subcommitee

APPENDIX

Guidelines from the ACCP for the screening, early detection, and diagnosis of PAH, established in 2004, recommend a right heart catheterization to confirm the presence of pulmonary hypertension, establish the diagnosis, and determine PAH severity.[5] An ACCF/AHA 2009 consensus document on pulmonary hypertension, developed in collaboration with the American Thoracic Society 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] Also, the guidelines state that acute vasodilator testing should be done in all patients with idiopathic PAH who may be considered potential candidates for long-term therapy with oral calcium channel blockers. Idiopathic PAH patients in whom chronic calcium channel blocker therapy would not be considered, such as patients with overt right heart failure or hemodynamic instability, need not have acute vasodilator testing performed. The definition of an acute response that may suggest initiation with oral calcium channel blockers is 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. Although this definition may misclassify a few patients who could be effectively treated with long-term oral calcium channel blockers, it will reliably identify those who are least likely to benefit from oral calcium channel blocker therapy and, therefore, provides the greatest degree of safety. Those with PAH due to conditions other than idiopathic PAH have a very low rate of long-term responsiveness to oral calcium channel blocker therapy and therefore, the decision to perform acute testing in these patients should be determined on an individual basis. Acute vasodilator testing is not indicated, and may be harmful, in those with significantly elevated left heart filling pressures. The WHO categorizes PAH into stages. A summary of the stages (functional status) of PAH are provided in Table 1.

Table 1. WHO Classification of Functional Status of Patients with Pulmonary Hypertension.[5]

Class	Description
I	Patients with pulmonary hypertension 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 with pulmonary hypertension who have mild limitation of physical activity. There is not discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope.
III	Patients with pulmonary hypertension 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 with pulmonary hypertension 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.

WHO – World Health Organization.

Table 2 lists the updated clinical classification of pulmonary hypertension by the World Symposium on PulmonaryHypertension.[17]

Table 2. Updated Classification of Pulmonary Hypertension.[17]

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 Hypoxia Chronic obstructive pulmonary 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.