Reference number(s)
4820-A

STANDARD MEDICARE PART B MANAGEMENT

Flolan (epoprostenol injection)
Veletri (epoprostenol injection)
epoprostenol injection

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication
Flolan/Veletri/epoprostenol is indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group I) to improve exercise capacity. Studies establishing effectiveness included predominantly patients with New York Heart Association (NYHA) Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

Compendial Uses
1. Angina pectoris
2. Peripheral vascular disease (e.g., Raynaud's disease, thrombotic angiopathy)

All other indications will be assessed on an individual basis. Submissions for indications other than those enumerated in this policy should be accompanied by supporting evidence from Medicare approved compendia.

II. CRITERIA FOR INITIAL APPROVAL

A. Pulmonary Hypertension (PH)
Indefinite authorization may be granted for treatment of pulmonary hypertension when ALL of the following criteria are met:
1. The pulmonary hypertension is not secondary to pulmonary venous hypertension (e.g., left-sided atrial or ventricular disease, left-sided valvular heart disease, etc.) or disorders of the respiratory system (e.g., chronic obstructive pulmonary disease, interstitial lung disease, obstructive sleep apnea, or other sleep disordered breathing, alveolar hypoventilation disorders, etc.)
2. The member has primary pulmonary hypertension or pulmonary hypertension, which is secondary to one of the following conditions: connective tissue disease, thromboembolic disease of pulmonary arteries, human immunodeficiency virus (HIV) infection, cirrhosis, diet drugs, congenital left to right shunts, etc. If these conditions are present, then all of the following criteria must be met:
   i. The pulmonary hypertension has progressed despite maximal medical and/or surgical treatment of the identified condition.
   ii. The mean pulmonary artery pressure is greater than 25 mmHg at rest or greater than 30 mmHg with exertion.
   iii. The member has significant symptoms from the pulmonary hypertension (i.e., severe dyspnea on exertion, and either fatigability, angina, or syncope).

iv. Treatment with oral calcium channel blocking agents has been tried and failed or has been considered and ruled out.

B. Angina Pectoris
Authorization of 3 months may be granted for treatment of angina pectoris.

C. Peripheral vascular disease (e.g., Raynaud's disease, thrombotic angiopathy)
Authorization of 12 months may be granted for treatment of peripheral vascular disease (e.g., Raynaud's disease, thrombotic angiopathy).

III. CONTINUATION OF THERAPY

All members (including new members) requesting authorization for continuation of therapy must be currently receiving therapy with the requested medication through a paid pharmacy or medical benefit.

A. Pulmonary Arterial Hypertension (PAH)
Authorization for members who are requesting authorization for continuation of therapy must meet all initial authorization criteria.

B. Angina pectoris
Authorization of 3 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat angina pectoris.
3. The member is receiving benefit from therapy. Benefit is defined as either:
   a. Disease stability
   b. Disease improvement

C. Peripheral vascular disease (e.g., Raynaud's disease, thrombotic angiopathy)
Authorization of 12 months may be granted when all of the following criteria are met:
1. The member is currently receiving therapy with the requested medication.
2. The requested medication is being used to treat peripheral vascular disease (e.g., Raynaud's disease, thrombotic angiopathy).
3. The member is receiving benefit from therapy. Benefit is defined as either:
   a. Disease stability
   b. Disease improvement

IV. APPENDIX

WHO Classification of Pulmonary Hypertension
1 PAH
1.1 Idiopathic (PAH)
1.2 Heritable PAH
1.3 Drug- and toxin-induced PAH
1.4. PAH associated with:
   1.4.1 Connective tissue diseases
   1.4.2 HIV infection
   1.4.3 Portal hypertension
   1.4.4 Congenital heart diseases
   1.4.5 Schistosomiasis
1.5 PAH long-term responders to calcium channel blockers

1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
1.7 Persistent PH of the newborn syndrome

2 PH due to left heart disease
2.1 PH due to heart failure with preserved LVEF
2.2 PH due to heart failure with reduced LVEF
2.3 Valvular heart disease
2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3 PH due to lung diseases and/or hypoxia
3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders

4 PH due to pulmonary artery obstruction
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
- 4.2.1 Sarcoma (high or intermediate grade) or angiosarcoma
- 4.2.2 Other malignant tumors
  - Renal carcinoma
  - Uterine carcinoma
  - Germ cell tumours of the testis
  - Other tumours
- 4.2.3 Non-malignant tumours
  - Uterine leiomyoma
- 4.2.4 Arteritis without connective tissue disease
- 4.2.5 Congenital pulmonary artery stenosis
- 4.2.6 Parasites
  - Hydatidosis

5 PH with unclear and/or multifactorial mechanisms
5.1 Hematologic disorders: Chronic hemolytic anemia, myeloproliferative disorders
5.2 Systemic and metabolic disorders: Pulmonary Langerhans cell histiocytosis, Gaucher disease, glycogen storage disease, neurofibromatosis, sarcoidosis
5.3 Others: chronic renal failure with or without hemodialysis, fibrosing mediastinitis
5.4 Complex congenital heart disease

V. SUMMARY OF EVIDENCE

The contents of this policy were created after examining the following resources:
1. The prescribing information for Flolan, Veletri and generic epoprostenol.
2. The available compendium
   a. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   b. Micromedex DrugDex
   c. American Hospital Formulary Service- Drug Information (AHFS-DI)
   d. Lexi-Drugs
   e. Clinical Pharmacology
3. External Infusion Pumps Local Coverage Determination (L33794)

After reviewing the information in the above resources, the FDA-approved indications listed in the prescribing information for Flolan, Veletri and generic epoprostenol are covered in addition to the following:

A. Angina pectoris
B. Peripheral vascular disease (e.g., Raynaud's disease, thrombotic angiopathy)

VI. EXPLANATION OF RATIONALE

Support for FDA-approved indications can be found in the manufacturer's prescribing information and the external infusion pump Local Coverage Determination (L33794).

Support for using Flolan, Veletri and generic epoprostenol to treat angina pectoris can be found in studies cited in Micromedex. Epoprostenol infusions have been relatively ineffective in patients with exertional angina and unstable angina. In Prinzmetal angina, limited studies suggest lack of beneficial effects in most patients. Support for using epoprostenol for Prinzmetal angina (also known as variant angina) can be found in a small study by Chierchia et al (1982). The study evaluated the effects of IV epoprostenol (PGI2) in nine patients with variant angina and six normal volunteers. In normal subjects, PGI2 (2.5, 5, 10 and 20 nanograms/kg/min) had significant antiplatelet effects, caused a dose-dependent decrease in both systolic and diastolic arterial pressure and a decrease in pulmonary resistance. Heart rate increased in a dose-dependent manner, but no consistent effects on myocardial contractility (evaluated by ultrasound) were observed. Side effects were negligible and readily reversible. Although producing obvious antiplatelet and vasodilatory effects, PGI2 did not affect the number, severity and duration of spontaneous ischemic episodes due to coronary vasospasm in five patients and ergonovine-induced spasm in three. However, the number of ischemic episodes was consistently reduced in one patient during four consecutive periods of PGI2 infusion alternated with placebo. A severe, prolonged ischemic episode with ST elevation and pain was consistently observed in this patient every time PGI2 was discontinued. In the appropriate environment, PGI2 can be administered safely to patients with ischemic heart disease. Occasionally, PGI2 may result in a complete disappearance of ischemic episodes due to coronary vasospasm, but usually it is ineffective. These conflicting results could be related to different etiologies of coronary spasm.

Support for using Flolan, Veletri and generic epoprostenol to treat peripheral vascular disease can be found in small studies. Belch et al (1983) conducted a study of two groups of outpatients with Raynaud's syndrome. The patients were randomly allocated to receive at weekly intervals for three weeks either a 5 h intravenous infusion of buffer or epoprostenol (prostacyclin, PGI2) in buffer (7.5 ng/kg/min after the first hour). PGI2 reduced the frequency and duration of ischemic attacks (both p less than 0.01). Hand temperature measurements with a thermocouple were significantly improved at 1 week; 6 weeks after the last infusion hand temperatures had returned to baseline. There was a corresponding loss of clinical response 8-10 weeks after the last infusion.
Additionally, Bellucci et al (1986) studied infused prostacyclin (PGI2) given IV (7.5 ng/kg/min) three times at weekly intervals in 8 patients with Raynaud's phenomenon (RP). In 4 patients, improvement was long-term, more than 90 days after the last infusion (good responders); in 3 patients, improvement was mild, less than 15 days, and in one patient no improvement was observed (poor responders). Clinical response was always accompanied by improvement, although less prolonged, of capillary appearance and/or function, as judged by microscopy and/or hemodynamic tests (pulse volume index; radial artery blood flow). Lastly, increased catabolism of PGI2 seemed to be excluded in poor responders, since no statistical difference in PGI2 metabolism could be observed between the two groups.

VII. REFERENCES

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