Reference number(s)
4821-A

STANDARD MEDICARE PART B MANAGEMENT

Remodulin (treprostinil injection)
treprostinil 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 Indications

1. Pulmonary Arterial Hypertension
   Indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with New York Heart Association (NYHA) Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH, PAH associated with congenital systemic-to-pulmonary shunts, or PAH associated with connective tissue diseases.
2. Pulmonary Arterial Hypertension in Patients Requiring Transition from Epoprostenol
   Indicated in patients with PAH, requiring transition from epoprostenol, to diminish the rate of clinical deterioration. Consider the risks and benefits of each drug prior to transition.

Compendial Use
Severe peripheral ischemia

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 Arterial Hypertension (PAH)
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, 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. Severe Peripheral Ischemia
Authorization of 12 months may be granted for treatment of severe peripheral ischemia.

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. Severe Peripheral Ischemia
Authorization for 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 severe peripheral ischemia.
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 tumors of the testis
Other tumors
4.2.3 Non-malignant tumors
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 Remodulin and generic treprostinil.
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 Remodulin and generic treprostinil are covered in addition to severe peripheral ischemia.

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 Remodulin or generic treprostinil to treat severe peripheral ischemia can be found in two small studies. Berman et al (2006) conducted an open-label study of 10 patients with at least 1 ischemic wound received treprostinil via an ambulatory subcutaneous infusion pump. The mean worst ischemic rest pain score decreased from baseline to week 12 by 62% and the mean average ischemic rest pain score

decreased from baseline to week 12 by 57%. Three patients with small wounds (0.2 to 2 cm^2) had complete wound healing and no new wounds developed in any patient during the study period. Within 2 months following the end of the study, 3 patients had below the knee amputations as a result of wound progression. Additionally, Moher and colleagues conducted a sequential dose-escalation trial where 8 patients received an initial infusion rate of treprostinil 10 nanograms/kg/min followed by doubling of the infusion rate every 60 minutes until dose-limiting side effects (i.e., severe flushing, headache, nausea, or diarrhea) occurred. The maximum tolerated dose was determined to be 10 to 20 nanograms/kg/min. Blood flow in the common femoral artery was increased by 35% over baseline at the end of the maximum dosage, 29% over baseline at the end of the maintenance dosage, and 28% over baseline at the end of the washout phase.

VII. REFERENCES

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