WellMed Doctors helping patients for more than 25 years	**Effective Date:** 05/31/2021	**Revision Date(s):** 6/8/17, 11/8/2018, 2/13/2020, 05/13/2021
Department: PHARMACY	**MMC Review/ Approval Date(s):** 11/13/18, 3/18/20, 05/25/2021	**Page(s):** Page 1 of 8

Policy Number: 041.004

Title: Coverage Determination Policy for Pulmonary Arterial Hypertension (PAH) medications:

- **Trepostinil (Remodulin®, Tyvaso®)**
- **Epoprostenol (Flolan®)**
- **Iloprost (Ventavis®)**

Regions: ☒ **Texas** ☐ **Florida** ☐ **Indiana** ☐ **New Jersey** ☒ **New Mexico**

Impacted Areas:

☒ Network Management/Provider Services	☒ Utilization Management
☐ Member services	☐ Case management
☐ Quality Management	☐ Disease management
☐ Credentialing	☒ Claims
☐ IT	☐ Human resources
☐ Administration	☐ Finance
☐ Compliance/delegation	☒ Pharmacy
	☐ ALL

Available LCD/NCD/LCA:

Local coverage Determination (LCD) (Texas): External Infusion Pumps, available at L33794

Local coverage Determination (LCD) (Texas): Nebulizers, available at L33370

Disclaimer:

WellMed Coverage Determination Policies are developed as needed, are regularly reviewed and updated, and are subject to change. They represent a portion of the resources used to support WellMed coverage decision making. WellMed may modify these Policy Guidelines at any time. Medicare source materials used to develop these guidelines include, but are not limited to, CMS National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), Medicare Benefit Policy Manual, Medicare Claims Processing Manual, Medicare Program Integrity Manual, Medicare Managed Care Manual, etc. The information presented in the WellMed Coverage Determination Policies is believed to be accurate and current as of the date of publication, and is provided on an "AS IS" basis. Where there is a conflict between this document and Medicare source materials, the Medicare source materials will apply.

WellMed Drug and Biologic Coverage Determination Policy

Title: Coverage Determination Policy for Pulmonary Arterial Hypertension (PAH) medications:

- **Trepostinil (Remodulin®, Tyvaso®)**
- **Epoprostenol (Flolan®)**
- **Iloprost (Ventavis®)**

Coverage Policy Number: 041.004

Line of Business: Medicare Part B

Policy Type: Prior Authorization

Coverage Determination:

WellMed Medical Management will cover **Trepostinil (Remodulin®, Tyvaso®), Epoprostenol (Flolan®), and Iloprost (Ventavis)®** as medically necessary *for the treatment of pulmonary arterial hypertension in patients who meet **ALL** of the following criteria:*

A. Patient has a diagnosis of pulmonary artery hypertension
B. 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.)
C. Patient has primary pulmonary hypertension or pulmonary hypertension which is secondary to one of the following conditions: connective tissue disease, thromboembolic disease of the pulmonary arteries, human immunodeficiency virus (HIV) infection, cirrhosis, anorexigens or congenital left to right shunts.
D. The pulmonary hypertension has progressed despite maximal medical and/or surgical treatment of the identified condition
E. The mean pulmonary artery pressure is > 25 mm Hg at rest or > 30 mm Hg with exertion
F. Patient has significant symptoms from the pulmonary hypertension (i.e., severe dyspnea on exertion, and either fatigability, angina, or syncope)

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

WellMed Medical Management will NOT cover treprostinil (Remodulin, Tyvaso) ®, iloprost (Ventavis), and epoprostenol (Flolan®) as medically necessary for any indication not approved by the FDA.

General Background:

Pulmonary arterial hypertension (PAH) is a life threatening and progressive disease characterized by increased pulmonary vascular resistance, leading to chronic elevation in pulmonary arterial pressure due to restricted flow through the pulmonary arterial circulation. Pulmonary hypertension (PH) is defined by a mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest usually confirmed by right heart catheterization. Normal pulmonary arterial systolic pressure ranges from 15 to 30 mmHg, diastolic pressure from 4 to 12 mmHg and normal mPAP is ≤20 mmHg. Pulmonary arterial hypertension makes up Group 1 of the World Health Organization's (WHO) classification of pulmonary hypertension.

Medicare does not have a National Coverage Determination (NCD) for Pulmonary Arterial Hypertension (PAH) medications: Trepostinil (Remodulin®, Tyvaso®), Epoprostenol (Flolan®), Iloprost (Ventavis®). There are Local Coverage Determinations (LCDs) for Texas. Local Coverage Determination (LCD):

External Infusion Pumps (L33794) and Local Coverage Determination (LCD): Nebulizers (L33370).

The New York Heart Association Functional classification in patients with pulmonary hypertension is as follows:

Class I	No symptoms with ordinary physical activity
Class II	Symptoms with ordinary activity; slight limitation of activity
Class III	Symptoms with less than ordinary activity; marked limitation of activity
Class IV	Symptoms with any activity or even at rest

The World Health Organization (WHO) functional classification of pulmonary artery hypertension is as follows:

Group 1	Patients that have PAH. Most patients in this category have idiopathic PAH. However, others include inheritable, drug-related, and connective tissue disease-associated PAH.
Group 2	Patients who have pulmonary venous hypertension, which is usually due to left heart disease.
Group 3	Patients who have PH due to chronic lung disease and/or chronic hypoxemia.
Group 4	Patients with chronic thromboembolic disease causing PH.
Group 5	Patients who have PH that is of uncertain course and likely multifactorial.

*Key symptoms of PAH include fatigue, dizziness, and fainting (near syncope)

The Food and Drug Administration has approved three prostacyclin analogue medications for the treatment of PAH: epoprostenol, treprostinil, and iloprost. These medications replace deficits in endogenous prostacyclin observed in patients with PAH. Parenteral prostanoids are considered the most

potent of the PAH medications and are a mainstay of treatment of patients with advanced disease. Patients with progressive PAH despite oral therapy with endothelin receptor antagonists and/or inhibitors of phosphodiesterase type 5 and patients with severe disease typically require the addition of a prostanoid.

Treprostinil is a stable, long-acting prostacyclin analogue which can be administered as an intravenous therapy (Remodulin®), or subcutaneously (Remodulin®), or intermittently by inhalation (Tyvaso®).

FDA Approved Indications

- Remodulin® is indicated in adults for the treatment of WHO Group I PAH in patients with NYHA Class II-IV symptoms to decrease symptoms associated with exercise. It is also indicated to diminish the rate of clinical deterioration in patients requiring transition from epoprostenol. The risks and benefits of each drug should be carefully considered prior to transition.
- Tyvaso® is indicated in adults for the treatment of WHO Group I PAH in patients with NYHA class III symptoms to improve exercise ability.
- Flolan® is indicated for the treatment of PAH (WHO Group I) in patients with NYHA Class III or IV symptoms to improve exercise capacity
- Ventavis® is indicated for the treatment of PAH (WHO Group I) in patients with New York Heart Association (NYHA) class III or IV symptoms to improve exercise tolerance, symptoms, and diminish clinical deterioration.

Authorization

Drug	Recommended dose
Intravenous Treprostinil (Remodulin ®)	Maximum initial dose of 1.25 nanogram/kg/min continuous SUBQ or central line IV infusion. A reduced dose of 0.625 nanogram/kg/min may be used if initial dose cannot be tolerated. Dose should be increased in increments of 1.25 nanogram/kg/min (ng/kg/min) per week for continuous SUBQ or central line IV infusion for the first 4 weeks and then by 2.5 ng/kg/min per week continuous SUBQ or central line IV infusion for remaining duration.
Inhaled Treprostinil (Tyvaso®)	Initiation: Maximum initial dose of 3 breaths (18 mcg) via ORAL INHALATION per treatment session, 4 times daily during waking hours (approximately 4 hours apart). Dose should be titrated by additional 3 breaths via ORAL INHALATION at approximately 1 to 2 week intervals as tolerated up to a maximum of 9-12 breaths per treatment session, 4 times daily. Maintenance: Maximum dose of 9-12 breaths per treatment session, 4 times daily.

Iloprost (Ventavis®)	Initial: 2.5 mcg/dose; if tolerated, increase to 5 mcg/dose. Administer 6-9 times daily (dosing at intervals ≥2 hours while awake according to individual need and tolerability). Maintenance dose: 2.5-5 mcg/dose; maximum daily dose: 45 mcg (ie, 5 mcg/dose 9 times daily)
Epoprostenol (Flolan®)	Initial: 2 ng/kg/minute; a lower initial dose may be used if patient is intolerant of starting dose. Increase dose in increments of 1 to 2 ng/kg/minute at intervals of ≥15 minutes until dose-limiting side effects (eg, flushing, jaw pain, headache, hypotension, nausea) are noted or response to epoprostenol plateaus. The dose may also be lowered by 1 to 2 ng/kg/minute every 15 minutes to a dose that is tolerated.

Clinical Guidelines

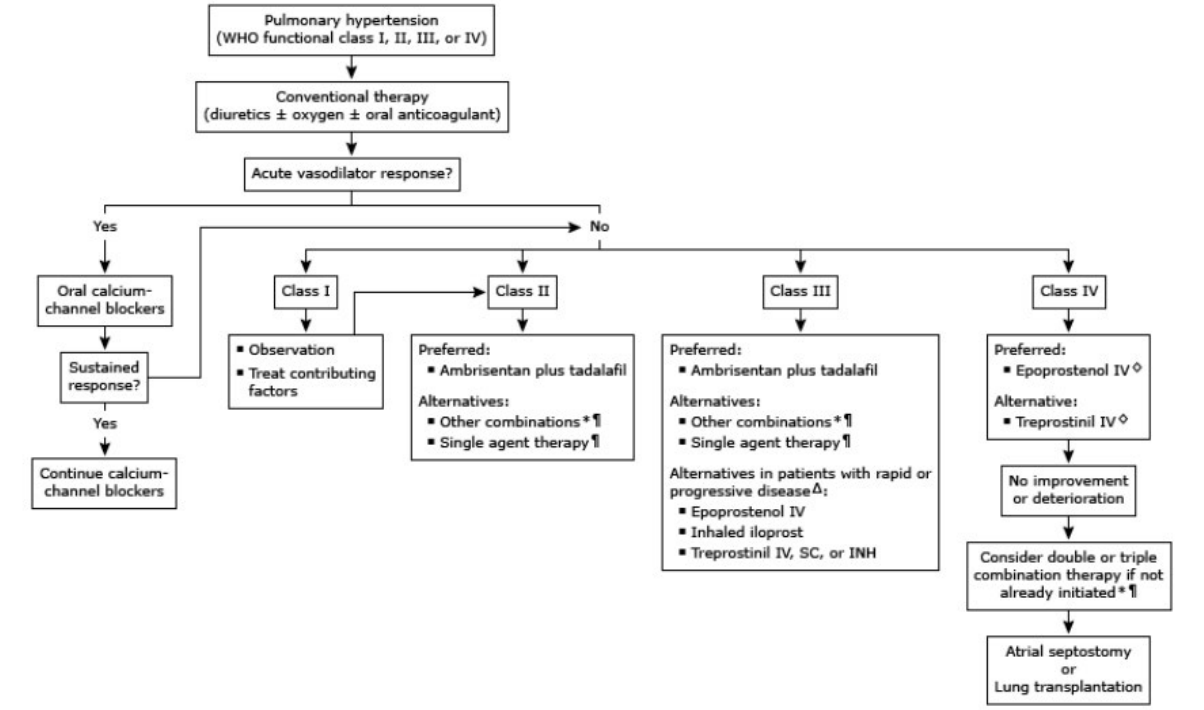
The American College of Chest Physicians recommends the following:

- For Patients with WHO functional class II symptoms:
  - Parenteral or inhaled Treprostinil should not be chosen as first line therapy for treatment of PAH in naïve patients
  - Parenteral or inhaled Treprostinil should not be chosen as a second line therapy for treatment of PAH in patients who have not met their treatment goals
- For patients with WHO functional class III symptoms:
  - Treatment naïve PAH patients who have evidence of rapid progression of their disease, and/ or other markers of poor clinical prognosis should be considered for initial treatment with a parenteral prostanoid.
  - Treatment naïve PAH patients who have evidence of rapid progression of their disease, and/ or other markers of poor clinical prognosis despite treatment with one or two classes of oral agents should be considered for addition of parenteral or inhaled prostanoid.
- For patients with WHO functional class IV symptoms:
  - Monotherapy with parenteral prostanoid is recommended as first line therapy in treatment naïve PAH patients
  - Treatment naïve patients who are unable or do not have the desire to manage parenteral prostanoid therapy should be considered for treatment with an inhaled prostanoid in combination with an endothelin receptor antagonist (ETRA).

According to the American College of Chest Physician's guideline, it is important that the severity of PAH be evaluated in a systematic and consistent manner , using a combination of WHO functional class, exercise capacity, Echocardiogram, laboratory studies and hemodynamic

variables in order to make informed therapeutic decisions.

Treatment of pulmonary arterial hypertension algorithm



If no improvement or patients progress, therapy should be escalated according to WHO functional symptoms.

WHO: World Health Organization; IV: intravenous; SC: subcutaneous; INH: inhaled.
* Endothelin receptor antagonist-phosphodiesterase-5 inhibitor combination is preferred by some experts. Combining phosphodiesterase-5 inhibitors and guanylate cyclase stimulants (riociguat) should be avoided due to the high risk of hypotension.
¶ Options for agents include ambrisentan, bosentan, macitentan, sildenafil, tadalafil, or riociguat. Riociguat is best studied in patients with chronic thromboembolic pulmonary hypertension.
Δ These agents are not approved for this use by regulatory agencies.
◇ Some experts use initial combination therapy with a prostanoid and a phosphodiesterase-5 inhibitor.

Original figure modified for this publication. Reproduced from: Barst RJ, Gibbs US, Ghofrani HA, et al. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. J Am Coll Cardiol 2009; 54:S78. Illustration used with the permission of Elsevier Inc. All rights reserved.

Coding Information:

HCPCS Code: Trepostinil (Remodulin®) injection, 1 MG - J3285

HCPCS Code: Trepostinil (Remodulin®, Tyvaso®) inhalation solution, F-approved final product, non-compounded, administered through DME, unit dose form, 1.74 mg - J7686

HCPCS Code: Epoprostenol (Flolan®) injection, 0.5 MG - J1325

HCPCS Code: Iloprost (Ventavis®) inhalation solution, FDA-approved final product, non-compounded, administered through DME, unit dose form, up to 20 micrograms - Q4074

Acronyms:

PAH- Pulmonary arterial hypertension, PH- Pulmonary hypertension, mPAP- mean pulmonary arterial pressure, WHO- World Health Organization, NYHA- New York Heart Association, NCD- National Coverage Determination , LCD- Local Coverage Determination, FDA- Food and Drug Administration, ETRA- endothelin receptor antagonist

References:

1. Micromedex drug database. Accessed on 8/15/2018.
2. Trepostinil® full prescribing information. Research Triangle Park, NC. United Therapeutics Corp.
3. Simmonneau G, Barst RJ, Galie N et. al. Continuous Subcutaneous Infusion of Treprostinil, a prostacyclin Analogue, in patients with Pulmonary Arterial Hypertension: A double blind, Randomized, Placebo-Controlled Trial. Am. Respir Care Med 2002; 165: 800-804
4. Taichman DB, Ornelas J, Chung L et. al. Pharmacologic Therapy for Pulmonary Arterial Hypertension in Adults: CHEST guideline and Expert panel report. CHEST 2014; 146(2): 449-475.
5. Tyvaso® full prescribing information. Research Triangle Park, NC. United Therapeutics Corp.