Prostacyclins for Pulmonary Arterial Hypertension

Override(s)	Approval Duration
Prior Authorization Quantity Limit	1 year

Medications	Quantity limit
Flolan (epoprostenol sodium) Remodulin (treprostinil) Veletri (epoprostenol)	N/A
Tyvaso (treprostinil) Ventavis (iloprost) Yutrepia (treprostinil)	May be subject to quantity limit

APPROVAL CRITERIA

Epoprostenol Agents (Flolan, Veletri)

Initial requests for continuous **intravenous** infusion of epoprostenol (Flolan, Veletri) may be approved if the following criteria are met:

I. Individual has a diagnosis of pulmonary arterial hypertension (PAH) confirmed by right-heart catheterization showing all of the following (Hoeper, 2013; Ivy, 2013; Abman, 2015):
   A. Mean pulmonary artery pressure (mPAP) greater than or equal to 25 mm Hg at rest; **AND**
   B. Pulmonary capillary wedge pressure (PCWP), mean pulmonary artery wedge pressure (PAWP), left atrial pressure, or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mm Hg; **AND**
   C. Pulmonary vascular resistance (PVR) greater than 3 Wood units;

AND

II. Individual has World Health Organization (WHO) Group I PAH (idiopathic PAH, PAH associated with connective tissue disorders, PAH associated with congenital heart defects, and all Group 1 subtypes);

AND

III. Individual has New York Heart Association Functional Class III or IV symptoms.

Continuation requests for continuous intravenous infusion epoprostenol (Flolan, Veletri) may be approved if the following criterion is met:

I. There is confirmation of clinically significant improvement or stabilization in clinical signs and symptoms of disease (including but not limited to improvement in walk distance, dyspnea and/or functional class).

Continuous **intravenous** infusion epoprostenol (Flolan, Veletri) may **not** be approved for the following:

I. Individual with WHO Group II-V pulmonary hypertension; **OR**
II. Individuals with heart failure due to severe left ventricular systolic dysfunction; **OR**
III. In combination with other prostacyclin analogs [including but not limited to treprostinil (Orenitram, Remodulin, Tyvaso, Yutrepia), Ventavis (iloprost)] or prostacyclin receptor agonists [including but not limited to Uptravi (selexipag)]; **OR**
IV. May not be approved when the above criteria are not met and for all other indications.

Remodulin (treprostinil)

Initial requests for continuous **subcutaneous** infusion of Remodulin (treprostinil) may be approved if the following criteria are met:

I. Individual has a diagnosis of pulmonary arterial hypertention (PAH) confirmed by right-heart catheterization showing all of the following (Hoeper, 2013; Ivy, 2013; Abman, 2015):
   A. Mean pulmonary artery pressure (mPAP) greater than or equal to 25 mm Hg at rest; **AND**
   B. Pulmonary capillary wedge pressure (PCWP), mean pulmonary artery wedge pressure (PAWP), left atrial pressure, or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mm Hg; **AND**
   C. Pulmonary vascular resistance (PVR) greater than 3 Wood units;

AND

II. Individual has World Health Organization (WHO) Group I PAH (idiopathic PAH, PAH associated with connective tissue disorders, PAH associated with congenital heart defects, and all Group 1 subtypes);

AND

III. Individual has New York Heart Association Functional Class II, III or IV symptoms.

Continuation requests for continuous subcutaneous infusion of Remodulin (treprostinil) may be approved if the following criterion is met:

I. There is confirmation of clinically significant improvement or stabilization in clinical signs and symptoms of disease (including but not limited to improvement in walk distance, dyspnea and/or functional class).

Initial requests for continuous **intravenous** infusion of Remodulin (treprostinil) may be

approved if the following criteria are met:

I. Individual has a diagnosis of pulmonary arterial hypertension (PAH) confirmed by a right-heart catheterization showing all of the following (Hoeper, 2013; Ivy, 2013; Abman, 2015):
   A. Mean pulmonary artery pressure (mPAP) greater than or equal to 25 mm Hg at rest; **AND**
   B. Pulmonary capillary wedge pressure (PCWP), mean pulmonary artery wedge pressure (PAWP), left atrial pressure, or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mm Hg; **AND**
   C. Pulmonary vascular resistance (PVR) greater than 3 Wood units;

AND

II. Individual has World Health Organization (WHO) Group I PAH (idiopathic PAH, PAH associated with connective tissue disorders, PAH associated with congenital heart defects, including and all Group 1 subtypes);

AND

III. Individual has New York Heart Association Functional Class II, III or IV symptoms;

AND

IV. Individual has confirmed inability to tolerate treatment by subcutaneous infusion of Remodulin.

Continuation requests for continuous intravenous infusion of Remodulin (treprostinil) may be approved if the following criterion is met:

I. There is confirmation of clinically significant improvement or stabilization in clinical signs and symptoms of disease (including but not limited to improvement in walk distance, dyspnea and/or functional class).

Continuous subcutaneous or **intravenous** infusion of Remodulin (treprostinil) may **not** be approved for the following:

I. Individual with WHO Group II-V pulmonary hypertension; **OR**
II. In combination with other prostacyclin analogs [including but not limited to epoprostenol (Flolan, Veletri), Ventavis (iloprost)] or prostacyclin receptor agonists [including but not limited to Uptravi (selexipag)]; **OR**
III. In combination with other treprostinil dosage forms (oral, inhalation) unless transitioning from one dose form to another; **OR**
IV. May not be approved when the above criteria are not met and for all other indications.

Treprostinil Agents (Tyvaso, Yutrepia)

Initial requests for **inhalation** therapy with treprostinil (Tyvaso, Yutrepia) may be approved if the following criteria are met:

I. Individual has a diagnosis of pulmonary arterial hypertension (PAH) confirmed by a right-heart catheterization showing all of the following (Hoeper, 2013; Ivy, 2013; Abman, 2015):
   A. Mean pulmonary artery pressure (mPAP) greater than or equal to 25 mm Hg at rest; **AND**
   B. Pulmonary capillary wedge pressure (PCWP), mean pulmonary artery wedge pressure (PAWP), left atrial pressure, or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mm Hg; **AND**
   C. Pulmonary vascular resistance (PVR) greater than 3 Wood units;

AND

II. Individual has World Health Organization (WHO) Group I PAH (idiopathic PAH, PAH associated with connective tissue disorders, PAH associated with congenital heart defects, and all Group 1 subtypes);

AND

III. Individual has New York Heart Association Functional Class III or IV symptoms;

OR

VI. Individual has a diagnosis of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3); **AND**

VII. Diagnosis is confirmed by (Waxman 2021):
   A. Right-heart catheterization showing all of the following:
      1. Mean pulmonary arterial pressure (mPAP) greater than or equal to 25 mm Hg;
      2. Pulmonary capillary wedge pressure (PCWP) less than or equal to 15 mm Hg;
      3. Pulmonary vascular resistance (PVR) greater than 3 Wood units; **AND**
   B. Chest high resolution computed tomography (HRCT) demonstrating diffuse parenchymal lung disease.

Continuation requests for treprostinil (Tyvaso, Yutrepia) may be approved if the following criterion is met:

I. There is confirmation of clinically significant improvement or stabilization in clinical signs and symptoms of disease (including but not limited to improvement in walk distance, dyspnea and/or functional class).

Inhalation therapy with treprostinil (Tyvaso, Yutrepia) may **not** be approved for the following:

I. Individual with WHO Group II, IV or V pulmonary hypertension; **OR**

II. In combination with other prostacyclin analogs [including but not limited to epoprostenol (Flolan, Veletri), treprostinil (Orenitram, Remodulin), Ventavis (iloprost)] or prostacyclin

receptor agonists [including but not limited to Uptravi (selexipag)]; **OR**

III. May not be approved when the above criteria are not met and for all other indications.

Ventavis (iloprost)

Initial requests for **inhalation** therapy with Ventavis (iloprost) may be approved if the following criteria are met:

I. Individual has a diagnosis of pulmonary arterial hypertension (PAH) confirmed by a right-heart catheterization showing all of the following (Hoeper, 2013; Ivy, 2013; Abman, 2015):
   A. Mean pulmonary artery pressure (mPAP) greater than or equal to 25 mm Hg at rest; **AND**
   B. Pulmonary capillary wedge pressure (PCWP), mean pulmonary artery wedge pressure (PAWP), left atrial pressure, or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mm Hg; **AND**
   C. Pulmonary vascular resistance (PVR) greater than 3 Wood units;

AND

II. Individual has World Health Organization (WHO) Group I PAH (idiopathic PAH, PAH associated with connective tissue disorders, PAH associated with congenital heart defects, and all Group 1 subtypes);

AND

III. Individual has New York Heart Association Functional Class III or IV symptoms.

Continuation requests for Ventavis (iloprost) may be approved if the following criterion is met:

I. There is confirmation of clinically significant improvement or stabilization in clinical signs and symptoms of disease (including but not limited to improvement in walk distance, dyspnea and/or functional class).

Inhalation therapy with Ventavis (iloprost) may **not** be approved for the following:

I. Individual with WHO Group II-V pulmonary hypertension; **OR**

II. In combination with other prostacyclin analogs [including but not limited to epoprostenol (Flolan, Veletri), treprostinil (Orenitram, Remodulin, Tyvaso, Yutrepia)] or prostacyclin receptor agonists [including but not limited to Uptravi (selexipag)]; **OR**

III. May not be approved when the above criteria are not met and for all other indications.

New York Heart Association (NYHA) Functional Classification for Heart Failure Symptoms

Class I: No limitation with ordinary physical activity
Class II: Slight limitation with fatigue, dyspnea, palpitations, or angina resulting from ordinary physical activity
Class III: Marked limitation; symptomatic with less than ordinary activity
Class IV: Symptoms present while at rest

World Health Organization (WHO) – group classification of pulmonary hypertension (PH) (CHEST 2019)			
1.	Pulmonary arterial hypertension (PAH)		
	1.1	Idiopathic PAH	
	1.2	Heritable PAH	
		1.2.1	*BMPR2*
		1.2.2	*ALK-1, ENG, SMAD9, CAV1, KCNK3*
		1.2.3	Unknown
	1.3	Drug and toxin induced	
	1.4	Associated with	
		1.4.1	Connective tissue disease
		1.4.2	HIV infection
		1.4.3	Portal hypertension
		1.4.4	Congenital heart disease
		1.4.5	Schistosomiasis
1'.	Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis		
	1'.1	Idiopathic	
	1'.2	Heritable	
		1'.2.1	*EIF2AK4* mutation
		1'.2.2	Other mutations

	1’.3	Drugs, toxins, and radiation induced	
	1’.4	Associated with:	
		1’.4.1	Connective tissue disease
		1’.4.2	HIV infection
1’’.	Persistent pulmonary hypertension of the newborn		
2.	Pulmonary hypertension because of left heart diseases		
	2.1	Left ventricular systolic dysfunction	
	2.2	Leftventriculary diastolic dysfunction	
	2.3	Valvular disease	
	2.4	Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies	
3.	Pulmonary hypertension because of lung diseases and/or hypoxemia		
	3.1	Chronic obstructive pulmonary disease (COPD)	
	3.2	Interstitial lung disease	
	3.3	Other pulmonary disease with mixed restrictive and obstructive pattern	
	3.4	Sleep-disordered breathing	
	3.5	Alveolar hypoventilation disorders	
	3.6	Chronic exposure to high altitude	
	3.7	Developmental lung diseases	
4.	Chronic thrombotic pulmonary hypertension		
	4.1	Chronic thromboembolic pulmonary hypertension	
	4.2	Other pulmonary artery obstructions	
		4.2.1	Angiosarcoma
		4.2.2	Other intravascular tumors

		4.2.3	Arteritis
		4.2.4	Congenital pulmonary arteries
5.	Pulmonary hypertension with unclear multifactorial mechanisms		
	5.1	Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy	
	5.2	Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis	
	5.3	Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders	
	5.4	Others: tumoral	

Key References:

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3. Chin KM, Gaine SP, Gerges C, et al. Treatment algorithm for pulmonary arterial hypertension. *Eur Respir J*. 2024; 2401325.
4. The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels, 9th ed, Little, Brown & Co, Boston, 1994. p.253.
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7. Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and Diagnosis of Pulmonary Hypertension. *J Am Coll Cardiol*. 2013; 62(suppl 25):D42- D50.
8. Ivy DD, Abman SH, Barst RJ, et al. Pediatric Pulmonary Hypertension. *J Am Coll Cardiol*. 2013; 62(suppl 25):D117- D126.
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10. Kovacs G, Bartolome S, Denton CP, et al. Definition, classification and diagnosis of pulmonary hypertension. *Eur Respir J*. 2024; 64: 2401324.
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14. Waxman A, Restrepo-Jaramillo R, Thenappan T, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *N Engl J Med*. 2021 Jan 28;384(4):325-334.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.