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Section:	Prescription Drugs	**Effective Date:**	October 1, 2024
Subsection:	Cardiovascular Agents	**Original Policy Date:**	March 13, 2014
Subject:	Orenitram	**Page:**	1 of 7

Last Review Date: September 8, 2024

Orenitram

Description

Orenitram (treprostinil)

Background
Pulmonary arterial hypertension is a rare disorder of the pulmonary arteries in which the pulmonary arterial pressure rises above normal levels in the absence of left ventricular failure. This condition can progress to cause right-sided heart failure and death (1). Orenitram is indicated for treatment of pulmonary arterial hypertension (PAH) which is classified by WHO as Group 1. Orenitram is used to treat pulmonary arterial hypertension (PAH, high blood pressure in the lungs) to improve exercise ability (1).

The World Health Organization (WHO) has classified pulmonary hypertension into five different groups: (2)

WHO Group 1: Pulmonary Arterial Hypertension (PAH)
1.1 Idiopathic (IPAH)
1.2 Heritable PAH
- 1.2.1 Germline mutations in the bone morphogenetic protein receptor type 2 (BMPR2)
- 1.2.2 Activin receptor-like kinase type 1 (ALK1), endoglin (with or without hereditary hemorrhagic telangiectasia), Smad 9, caveolin-1 (CAV1), potassium channel super family K member-3 (KCNK3)
- 1.2.3 Unknown

1.3 Drug-and toxin-induced
1.4 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'. Pulmonary vena-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

1''. Persistent pulmonary hypertension of the newborn (PPHN)

The diagnosis of WHO Group 1 PAH requires a right heart catheterization to demonstrate an mPAP ≥ 20mmHg at rest and a pulmonary vascular resistance (PVR) ≥ 3 Wood units, mean pulmonary capillary wedge pressure ≤ 15mmHg (to exclude pulmonary hypertension due to left heart disease, i.e., WHO Group 2 pulmonary hypertension) (4-6).

WHO Group 2: Pulmonary Hypertension Owing to Left Heart Disease

2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

WHO Group 3: Pulmonary Hypertension Owing to Lung Disease and/or Hypoxia

3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases 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 abnormalities

WHO Group 4: Chronic Thromboembolic Pulmonary Hypertension <CTEPHI

WHO Group 5: Pulmonary Hypertension with Unclear Multifactorial Mechanisms

5.1 Hematologic disorders: Chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3 Metabolic disorders: glycogen storage disease, Gaucher's disease, thyroid disorders

5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis, segmental PH

The American College of Chest Physicians (ACCP) has published an updated clinical practice guideline for treating PAH. These guidelines use the New York Heart Association (NYHA) functional classification of physical activity scale to classify PAH patients in classes I-IV based on the severity of their symptoms (3). Orenitram is indicated for patients with NYHA Functional Class II & III symptoms (1).

Class I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.
Class II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. These patients are comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.
Class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. These patients are comfortable at rest, but less than ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.
Class IV	Patients with pulmonary hypertension resulting in inability to perform any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present at rest, and discomfort is increased by any physical activity.

(3)

Regulatory Status

FDA-approved indication: Orenitram is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to delay disease progression and to improve exercise capacity. The studies that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (66%) or PAH associated with connective tissue disease (26%) (1).

Orenitram is contraindicated in patients with severe hepatic impairment (Child Pugh Class C). The safety and efficacy of Orenitram have not been established in patients with significant underlying lung disease (such as asthma or chronic obstructive pulmonary disease). Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect. Orenitram is a pulmonary and systemic vasodilator. Concomitant administration of Orenitram with diuretics, antihypertensive agents or other vasodilators may increase the risk of symptomatic hypotension. In patients with low systemic arterial pressure, Orenitram may cause symptomatic hypotension (1).

Orenitram inhibits platelet aggregation, there may be an increased risk of bleeding, particularly in patients receiving anticoagulants (1).

Safety and effectiveness in pediatric patients have not been established. Clinical studies of Orenitram did not include patients younger than 18 years to determine whether they respond differently from older patients (1).

Related policies
Adcirca, Adempas, Flolan/Veletri, Letairis, Opsumit, Opsynvi, PDE5 Inhibitor powders, Remodulin, Revatio, Tracleer, Tyvaso, Uptravi, Ventavis, Winrevair

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Orenitram may be considered **medically necessary** if the conditions indicated below are met.

Orenitram may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 18 years of age or older

Diagnosis

Patient must have **ALL** of the following:

1. Pulmonary Arterial Hypertension (PAH) – **WHO Group I**
   a. NYHA functional classification of physical activity – **Class II or III**

AND ALL of the following:
   a. **NO** severe hepatic impairment (Child Pugh Class C)
   b. Prescribed by or recommended by a cardiologist or pulmonologist

Prior – Approval *Renewal* Requirements

Age 18 years of age or older

Diagnosis

Patient must have the following:

1. Pulmonary Arterial Hypertension (PAH) – **WHO Group I**

AND ALL of the following:

a. Symptoms have improved or stabilized
b. **NO** severe hepatic impairment (Child Pugh Class C)

Policy Guidelines

Pre – PA Allowance

None

Prior - Approval Limits

Duration 2 years

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Pulmonary arterial hypertension is a rare disorder of the pulmonary arteries in which the pulmonary arterial pressure rises above normal levels in the absence of left ventricular failure. This condition can progress to cause right-sided heart failure and death. Orenitram is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in patients with NYHA class II or III symptoms (1).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of Orenitram while maintaining optimal therapeutic outcomes.

References

1. Orenitram [package insert]. Research Triangle Park, NC: United Therapeutics Corp; August 2023.

2. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013; 62:034-841.
3. Taichman DB, Ornelas J, Chung L, et al. Pharmacologic therapy for pulmonary arterial hypertension in adults. CHEST guideline and expert panel report. *Chest.* 2014; 46(2):449-475.
4. Simonneau G, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1) Epub 2019 Jan 24.
5. Rose-Jones LJ and Mclaughlin V. Pulmonary Hypertension: Types and Treatments. Curr Cardiol Rev. 2015 Feb; 11(1): 73–79.
6. Rudolf KF, et al. Usefulness of pulmonary capillary wedge pressure as a correlate of left ventricular filling pressures in pulmonary arterial hypertension. The Journal of Heart and Lung Transplantation, Vol33, No2. February 2014.

Policy History

Date	Action
March 2014	New policy
June 2014	Annual Review and update
June 2016	Annual editorial review and reference update Addition of no severe hepatic impairment and the age of 18 yrs of age and older Policy number changed from 5.06.21 to 5.40.21
September 2017	Annual editorial review and reference update
September 2018	Annual review
September 2019	Annual editorial review. Changed approval duration from lifetime to 2 years
March 2020	Annual review and reference update. Revised background section and added initial requirement of prescribed by or recommended by a cardiologist or pulmonologist per SME
September 2021	Annual review
December 2021	Annual review and reference update
September 2022	Annual review
December 2022	Annual review
September 2023	Annual review and reference update
March 2024	Annual review and reference update
September 2024	Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on September 6, 2024 and is effective on October 1, 2024.