PRIOR AUTHORIZATION POLICY

POLICY: Pulmonary Arterial Hypertension – Orenitram Prior Authorization Policy
- Orenitram® (treprostinil extended-release tablets – United Therapeutics)

REVIEW DATE: 03/04/2026

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT WHERE APPROPRIATE AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. WHERE COVERAGE FOR CARE OR SERVICES DOES NOT DEPEND ON SPECIFIC CIRCUMSTANCES, REIMBURSEMENT WILL ONLY BE PROVIDED IF A REQUESTED SERVICE(S) IS SUBMITTED IN ACCORDANCE WITH THE RELEVANT CRITERIA OUTLINED IN THE APPLICABLE COVERAGE POLICY, INCLUDING COVERED DIAGNOSIS AND/OR PROCEDURE CODE(S). REIMBURSEMENT IS NOT ALLOWED FOR SERVICES WHEN BILLED FOR CONDITIONS OR DIAGNOSES THAT ARE NOT COVERED UNDER THIS COVERAGE POLICY (SEE "CODING INFORMATION" BELOW). WHEN BILLING, PROVIDERS MUST USE THE MOST APPROPRIATE CODES AS OF THE EFFECTIVE DATE OF THE SUBMISSION. CLAIMS SUBMITTED FOR SERVICES THAT ARE NOT ACCOMPANIED BY COVERED CODE(S) UNDER THE APPLICABLE COVERAGE POLICY WILL BE DENIED AS NOT COVERED. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Orenitram, a prostacyclin mimetic, is indicated for the treatment of **pulmonary arterial hypertension (PAH) World Health Organization (WHO) Group 1** to delay disease progression and to improve exercise capacity.[1]

Disease Overview

PAH is a serious but rare condition impacting fewer than 20,000 patients in the US.[2,3] It is classified within Group 1 pulmonary hypertension among the five different groups that are recognized. In this progressive disorder, the small arteries in the lungs become narrowed, restricted, or blocked causing the heart to work harder to pump blood, leading to activity impairment. Although the mean age of diagnosis is between 36 and 50 years, patients of any age may be affected,

including pediatric patients. PAH is defined as a mean pulmonary artery pressure (mPAP) > 20 mmHg (at rest) with a pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and a pulmonary vascular resistance > 2 Wood units measured by cardiac catheterization.[5] The prognosis in PAH has been described as poor, with the median survival being approximately 3 years. However, primarily due to advances in pharmacological therapies, the long-term prognosis has improved.

Guidelines

Various guidelines address oral prostacyclin products.[3,4] The CHEST guideline and Expert Panel Report regarding therapy for pulmonary arterial hypertension (2019) in adults details many medications.[3] It was cited that many agents with varying mechanisms of action are used for the management of PAH. It was noted that the addition of an oral prostanoid product may be considered in patients with PAH who are in Functional Class III with evidence of rapid disease progression or a poor prognosis among those not willing or able to manage parenteral prostanoids. The European Society of Cardiology and the European Respiratory Society guidelines regarding the treatment of pulmonary hypertension (2022) also recognize Orenitram as having a role in therapy.[4] It may be considered in select patients receiving monotherapy with an endothelin receptor antagonist (ERA), phosphodiesterase type 5 inhibitor (PDE5), or soluble guanylate cyclase stimulator (sGCS) to reduce the risk of morbidity/mortality events. A simplified treatment algorithm that utilizes risk classification was introduced in these guidelines and reaffirmed in the 2024 World Symposium on Pulmonary Hypertension.[6] An initial risk assessment is recommended at baseline, 3 to 4 months after, and periodically thereafter; it is based on functional class, 6-minute walk distance, and natriuretic peptides. Hemodynamics and right ventricle imaging can be used to supplement this assessment. For initial risk assessment, patient are classified as not high-risk or high-risk. Patients who are not high-risk are recommended to receive a combination of ERAs and PDE5 inhibitors, whereas those who are high-risk may require intravenous or subcutaneous therapies. For follow-up risk assessments, patients are classified into four categories: low-risk, intermediate-low risk, intermediate-high risk, and high-risk. Recommendations are made for the addition of an activin-signaling inhibitor (Winrevair® [sotatercept-csrk subcutaneous injection]), oral or inhaled prostacyclin therapies, or the switch to an sGCS (Adempas® [riociguat tablets]). Patients who are classified as persistent intermediate-high or high-risk may need maximal four-drug therapies and a lung transplant evaluation.

Safety

Abrupt discontinuation or sudden large reductions in the dosage of Orenitram may cause PAH symptoms to worsen.[1] In the event of a planned short-term treatment interruption for patients unable to take oral medication, consider a temporary infusion of subcutaneous or intravenous treprostinil.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Orenitram. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Orenitram as well

as the monitoring required for adverse events and long-term efficacy, approval requires Orenitram to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for initiation of therapy where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory reports. All documentation must include patient-specific identifying information. For a patient case in which the documentation requirement of the right heart catheterization upon prior authorization coverage review for a different medication indicated for WHO Group 1 PAH has been previously provided, the documentation requirement in this *Pulmonary Arterial Hypertension – Orenitram Prior Authorization Policy* is considered to be met.

Orenitram® (treprostinil extended-release tablets - United Therapeutics) is(are) covered as medically necessary when the following criteria is(are) met for fda-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indication

1. **Pulmonary Arterial Hypertension (PAH) World Health Organization (WHO) Group 1.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND
     - **ii.** Patient meets BOTH of the following (a and b):
       - **a)** Patient has had a right heart catheterization **[documentation required]** ; AND
       - **b)** Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
     - **iii.** Patient meets ONE of the following (a or b):
       - **a)** According to the prescriber, patient is intermediate-high risk or high risk; OR
       - **b)** According to the prescriber, patient is low-risk or intermediate-low risk and has tried or is currently receiving one or more agents for PAH from the following different categories (either alone or in combination with another therapy) for ≥ 60 days ([1], [2], [3]. [4], or [5]):
         - **(1)** Phosphodiesterase type 5 (PDE5) inhibitors; OR
         - **(2)** Endothelin receptor antagonists (ERAs); OR
         - **(3)** Adempas (riociguat tablets); OR
         - **(4)** Winrevair (sotatercept-csrk subcutaneous injection); OR
         - **(5)** Prostacyclin analogs/mimetics; AND

Note: Examples of phosphodiesterase type 5 (PDE5) inhibitors include sildenafil and tadalafil. Endothelin receptor antagonists (ERAs) include bosentan, ambrisentan, Opsumit {macitentan tablets. Prostacyclin analogs mimetics include Tyvaso (treprostinil inhalation solution), Tyvaso DPI (treprostinil oral inhalation powder), treprostinil injection, epoprostenol injection, Uptravi (selexipag tablets) and Yutrepia (treprostinil inhalation powder).

iv. Medication is prescribed by or in consultation with a cardiologist or a pulmonologist; OR

B) Patient is Currently Receiving Orenitram. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has a diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH); AND

ii. Patient meets BOTH of the following (a and b):

a) Patient has had a right heart catheterization; AND
Note: This refers to prior to starting therapy with a medication for WHO Group 1 PAH.

b) Results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND

iii. The medication is prescribed by, or in consultation with, a cardiologist or a pulmonologist.

CONDITIONS NOT COVERED

Orenitram® (treprostinil extended-release tablets - United Therapeutics) is(are) considered not medically necessary for ANY other use(s) including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Concurrent Use with Uptravi (selexipag tablets and intravenous infusion), Inhaled Prostacyclin Products, or Parenteral Prostacyclin Agents Used for Pulmonary Hypertension.**
   Note: Examples of medications include Tyvaso (treprostinil inhalation solution), Tyvaso DPI (treprostinil oral inhalation powder), epoprostenol intravenous infusion, and treprostinil subcutaneous or intravenous infusion (Remodulin, generic).

REFERENCES

1. Orenitram® extended-release tablets [prescribing information]. Research Triangle Park, NC: United Therapeutics; August 2023.
2. Ruopp NF, Cockrill BA. Diagnosis and treatment of pulmonary arterial hypertension. A review. *JAMA*. 2022;327(14):1379-1391.
3. Klinger JR, Elliott CG, Levine DJ, et al. Therapy for pulmonary arterial hypertension in adults. Update of the CHEST guideline and Expert Panel Report. *CHEST*. 2019;155(3):565-586.

4. Humbert M, Kovacs G, Hoeper MM, et al, for the ESC/ERS Scientific Document Group. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43(38):3618-3731.
5. Maron B. Revised definition of pulmonary hypertension and approach to management: a clinical primer. *J Am Heart Assoc*. 2023 Apr 18;12(8):e029024. [Epub].
6. Chin KM, Gaine SP, Gerges C, et al. Treatment algorithm for pulmonary arterial hypertension. *Eur Respir J*. 2024;64(4):2401325.

HISTORY

Type of Revision	Summary of Changes	Review Date
Selected Revision	Pulmonary Arterial Hypertension (World Health Organization Group 1). Option of approval stating the patient has tried or is currently receiving two oral PAH medications was changed to require trial of (or currently be receiving) one other oral PAH medication.	06/05/2024
Annual Revision	**Pulmonary Arterial Hypertension (PAH) World Health Organization (WHO) Group 1:** For a patient currently receiving Orenitram, added a Note to indicate that requirement of a right heart catheterization (RHC) refers to a RHC prior to starting therapy with a medication for WHO Group 1 PAH.	10/09/2024
Annual Revision	No criteria changes.	10/08/2025
Early Annual Revision	**Pulmonary Arterial Hypertension (PAH) World Health Organization (WHO) Group 1:** A requirement that, according to the prescriber, the patient is intermediate or high-risk or is low-risk or intermediate-low risk was added. For a patient with low-risk or intermediate-low risk, a requirement and associated Note was added that the patient has tried or is currently receiving one or more agents from the following different categories (either alone or in combination with another therapy) for ≥ 60 days: phosphodiesterase type 5 (PDE5) inhibitors, endothelin receptor antagonists (ERAs), Adempas, Winrevair, or prostacyclin analogs/mimetics. The previous requirement for systemic therapy that applied to all patients was removed. **Conditions Not Covered:** Ventavis was removed from the Note that lists examples of medications that should not be taken in combination with Orenitram.	03/04/2026