



## PRIOR AUTHORIZATION POLICY

**POLICY:** Pulmonary Arterial Hypertension and Related Lung Disease – Inhaled Prostacyclin Products Prior Authorization Policy

- Tyvaso® (treprostinil inhalation solution – United Therapeutics)
- Tyvaso DPI™ (treprostinil oral inhalation powder – MannKind/United Therapeutics)
- Ventavis® (iloprost inhalation solution – Actelion)
- Yutrepia™ (treprostinil oral inhalation powder – Liquidia Technologies)

**REVIEW DATE:** 05/30/2025

### 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

Tyvaso, Tyvaso DPI, Yutrepia, and Ventavis are inhaled prostacyclin vasodilators (prostacyclin mimetics) indicated for the treatment of:<sup>1-4</sup>

- **Pulmonary arterial hypertension (PAH), World Health Organization (WHO) Group 1.** Tyvaso, Tyvaso DPI, and Yutrepia are specifically indicated to improve exercise ability whereas Ventavis is indicated to improve a composite endpoint consisting of exercise tolerance, symptoms, and lack of deterioration.

Tyvaso, Tyvaso DPI, and Yutrepia are also indicated for:<sup>1,2,4</sup>

- **Pulmonary hypertension associated with interstitial lung disease (WHO Group 3).** Tyvaso, Tyvaso DPI, and Yutrepia are indicated to improve exercise ability for this population.

## Disease Overview

PAH is a serious but rare condition impacting fewer than 20,000 patients in the US.<sup>5,6</sup> 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.<sup>12</sup> 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.

Pulmonary hypertension due to interstitial lung disease (WHO Group 3) can complicate the condition and is associated with an increased need for supplemental oxygen, reduced mobility, and decreased survival.<sup>8-11</sup> Over 80% of patients with interstitial lung disease can have pulmonary hypertension; patients tend to be older and male.<sup>7</sup> Severe restrictions on pulmonary function tests and marked fibrosis on computed tomography scans are distinctions. The exact etiology is unknown. The symptoms are non-specific and include increased dyspnea on exertion, cough, fatigue, chest pain, and lower extremity edema. Tyvaso, Tyvaso DPI, and Yutrepia are the only medications indicated for this specific use. Randomized controlled trials utilizing other pulmonary vasodilators indicated for patients with WHO Group 1 PAH in patients with interstitial lung disease have not shown clear benefit and some studies suggest harm with use of some medications (e.g., sildenafil, Tracleer® [bosentan tablets], ambrisentan, Adempas® [riociguat tablets], and Opsumit® [macitentan tablets]).

Yutrepia was recently approved for use with the same indications as Tyvaso and Tyvaso DPI.<sup>4</sup> Its approval for PAH was based on TRIUMPH and its approval for pulmonary hypertension due to interstitial lung disease was based on INCREASE. Its safety and tolerability were further demonstrated in INSPIRE.<sup>15,16</sup> Yutrepia contains PRINT™ technology, which yields uniform, free-flowing particles that are designed for enhanced deep-lung delivery, allowing patients to use it with less inspiratory effort.<sup>16</sup>

## Guidelines

Inhaled prostacyclin products are included in various guidelines regarding PAH (WHO Group 1). Tyvaso DPI and Yutrepia are not addressed yet.

- **Pulmonary Arterial Hypertension (PAH):** The CHEST guideline and Expert Panel Report regarding therapy for PAH (2019) in adults details many medications.<sup>6</sup> One recommendation is that parenteral or inhaled prostanoids should not be used as initial therapy for patients with PAH who are treatment

naïve with WHO functional class II symptoms or as second-line agents for patients with PAH with WHO functional class II symptoms who have not met original treatment goals. In general, these agents are utilized in later stages of therapy. The European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines regarding the treatment of pulmonary hypertension (2022) recognize that inhaled prostacyclin products have a role in therapy, mainly as an agent to be added onto other PAH therapies.<sup>7</sup>

- **Pulmonary Hypertension due to Interstitial Lung Disease:** The ESC/ERS guidelines regarding the treatment of pulmonary hypertension (2022) recommend inhaled treprostinil (Tyvaso) for patients with pulmonary hypertension associated with interstitial lung disease.<sup>7</sup>

## **POLICY STATEMENT**

Prior Authorization is recommended for prescription benefit coverage of Tyvaso, Tyvaso DPI, Yutrepia, and Ventavis. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with these products as well as the monitoring required for adverse events and long-term efficacy, approval requires these agents 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 as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and catheterization laboratory reports. For the use of PAH (WHO Group 1), 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 and Related Lung Disease – Inhaled Prostacyclin Products Prior Authorization Policy* is considered to be met.

- **Tyvaso® (treprostinil inhalation solution – United Therapeutics)**
  - **Tyvaso DPI™ (treprostinil oral inhalation powder – MannKind/United Therapeutics)**
  - **Ventavis® (iloprost inhalation solution - Actelion)**
  - **Yutrepia™ (treprostinil oral inhalation powder – Liquidia Technologies)**
- 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 ONE of the following (a or b):
    - a) Patient is in Functional Class III or IV; OR
    - b) Patient is in Functional Class II and meets ONE of the following [(1) or (2)]:
      - (1) Patient has tried or is currently receiving one oral agent for PAH; OR  
Note: Examples of oral agents for PAH include bosentan, ambrisentan, Opsumit (macitentan tablets), sildenafil, tadalafil, Adempas (riociguat tablets), Orenitram (treprostinil extended-release tablets), and Uptravi (selexipag tablets).
      - (2) Patient has tried one inhaled or parenteral prostacyclin product for PAH; AND  
Note: Examples of inhaled and parenteral prostacyclin products for PAH include Tyvaso (treprostinil inhalation solution), Tyvaso DPI (treprostinil oral inhalation powder), Yutrepia (treprostinil oral inhalation powder), Ventavis (iloprost inhalation solution), treprostinil injection, and epoprostenol injection.
  - iii. Patient meets BOTH of the following (a and b):
    - a) The patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND
    - b) The results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
  - iv. The medication is prescribed by or in consultation with a cardiologist or a pulmonologist; OR
- B) Patient is Currently Receiving the Requested Inhaled Prostacyclin.** 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 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.

**II. Tyvaso® (treprostinil inhalation solution – United Therapeutics)  
 Tyvaso DPI™ (treprostinil oral inhalation powder – MannKind/United Therapeutics)  
 Yutrepia™ (treprostinil oral inhalation powder – Liquidia Technologies)  
 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**

**2. Pulmonary Hypertension Associated with Interstitial Lung Disease (World Health Organization [WHO] Group 3).** Approve for the duration noted if the patient meets ONE of the following (A or B):

Note: This involves diagnosis such as idiopathic interstitial pneumonia, combined pulmonary fibrosis and emphysema, WHO Group 3 connective disease, and chronic hypersensitivity pneumonitis.

**A) Initial Therapy.** Approve for 4 months if the patient meets ALL of the following (i, ii, iii, iv, and v):

- i.** Patient has a diagnosis of World Health Organization (WHO) Group 3 pulmonary hypertension associated with interstitial lung disease; AND
- ii.** Patient with connective tissue disease is required to have a baseline forced vital capacity < 70%; AND
- iii.** Patient has evidence of diffuse parenchymal lung disease on computed tomography of the chest; AND
- iv.** 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 3 pulmonary hypertension associated with interstitial lung disease; AND
- v.** The medication is prescribed by or in consultation with a cardiologist or a pulmonologist; OR

**B) Patient is Currently Receiving Tyvaso, Tyvaso DPI, or Yutrepia for pulmonary hypertension associated with interstitial lung disease.** 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 3 pulmonary hypertension associated with interstitial lung disease; 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 3 PAH.
  - b)** Results of the right heart catheterization confirm the diagnosis of World Health Organization (WHO) Group 3 pulmonary hypertension associated with interstitial lung disease; AND
- iii.** According to the prescriber, patient has had a response to therapy; AND  
Note: Examples of a response include an increase or maintenance in the six-minute walk distance from baseline, improved exercise capacity, decrease in N-terminal pro-B-type natriuretic peptide levels, lessened clinical worsening, and a reduced rate of exacerbations of underlying lung disease.
- iv.** The medication is prescribed by or in consultation with a cardiologist or a pulmonologist.

**CONDITIONS NOT COVERED**

- **Tyvaso® (treprostinil inhalation solution – United Therapeutics)**

- **Tyvaso DPI™ (treprostinil oral inhalation powder – MannKind/United Therapeutics)**
- **Ventavis® (iloprost inhalation solution - Actelion)**
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**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 Oral or Parenteral Prostacyclin Agents Used for Pulmonary Hypertension.** Concomitant use is not recommended.

Note: Examples of medications include Orenitram (treprostinil extended-release tablets), Uptravi (selexipag tablets and intravenous infusion), epoprostenol intravenous infusion, and treprostinil subcutaneous or intravenous infusion (Remodulin, generic).

## REFERENCES

1. Tyvaso® inhalation solution [prescribing information]. Research Triangle Park, NC: United Therapeutics; May 2022.
2. Tyvaso DPI™ oral inhalation powder [prescribing information]. Danbury, CT and Research Triangle Park, NC: MannKind and United Therapeutics; June 2023.
3. Ventavis® inhalation solution [prescribing information]. South San Francisco, CA: Actelion; March 2022.
4. Yutrepia™ oral inhalation powder [prescribing information]. Morrisville, NC: Liquidia Technologies; June 2025.
5. Ruopp NF, Cockrill BA. Diagnosis and treatment of pulmonary arterial hypertension. A review. *JAMA*. 2022;327(14):1379-1391.
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9. King CS, Nathan SD. Pulmonary hypertension due to interstitial lung disease. *Curr Opin Pulm Med*. 2019;25:459-467.
10. King CS, Shlobin OA. The trouble with Group 3 pulmonary hypertension in interstitial lung disease. Dilemmas in diagnosis and the conundrum of treatment. *CHEST*. 2020;158(4):1651-1664.
11. Shiolen AM, Ruopp NF. Group 3 pulmonary hypertension: a review of diagnostics and clinical trials. *Clin Chest Med*. 2021;42:59-70.
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14. Liquidia Press Release US FDA approves Liquidia's Yutrepia (treprostinil) inhalation powder for patients with pulmonary arterial hypertension (PAH) and pulmonary arterial hypertension associated with interstitial lung disease (PH-ILD). Available at: <https://liquidia.com/news-releases/news-release-details/us-fda-approves-liquidias-yutrepia-tm-treprostinil-inhalation>. Accessed on May 29, 2025.

## HISTORY

Type of Revision	Summary of Changes	Review Date
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Annual Revision	No criteria changes.	10/04/2023
Update	01/09/2024: <b>Interstitial Lung Disease Associated Pulmonary Hypertension:</b> It was clarified that only a patient with connective tissue disease is required to have a baseline forced vital capacity < 70%.	--
Annual Revision	<b>Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1]:</b> For a patient currently receiving the requested inhaled prostacyclin product, 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. <b>Pulmonary Hypertension Associated with Interstitial Lung Disease (World Health Organization [WHO] Group 3).</b> For a patient currently receiving Tyvaso or Tyvaso DPI, 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 3 PAH.	10/02/2024
Early Annual Revision	<b>Yutrepia:</b> This formulation and conditions for approval were added to the policy. <b>Pulmonary Arterial Hypertension (PAH) [World Health Organization {WHO} Group 1].</b> Yutrepia (treprostinil oral inhalation powder) was added to the Note of medications a patient could try under inhaled or parenteral prostacyclin products. <b>Pulmonary Hypertension Associated with Interstitial Lung Disease (World Health Organization [WHO] Group 3):</b> The requirement for a patient to be ≥ 18 years of age was removed.	05/30/2025

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