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)

REVIEW DATE: 10/02/2024

OVERVIEW

Tyvaso, Tyvaso DPI, and Ventavis are inhaled prostacyclin vasodilators (prostacyclin mimetics) indicated for the treatment of:[1-3]

- **Pulmonary arterial hypertension (PAH), World Health Organization (WHO) Group 1**. Tyvaso and Tyvaso DPI 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 and Tyvaso DPI are also indicated for:[1,2]

- **Pulmonary hypertension associated with interstitial lung disease (WHO Group 3)**. Tyvaso and Tyvaso DPI 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.[4,5] 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.[11] 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.[7-10] Over 80% of patients with interstitial lung disease can have pulmonary hypertension; patients tend to be older and male.[6] 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 is the only medication 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]).

Guidelines

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

- **Pulmonary Arterial Hypertension (PAH):** The CHEST guideline and Expert Panel Report regarding therapy for PAH (2019) in adults details many medications.[5] 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.[6]
- **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.[6]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Tyvaso, Tyvaso DPI, 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Tyvaso, Tyvaso DPI, and Ventavis is recommended in those who meet the following criteria:

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), 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.

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. Coverage of Tyvaso and Tyvaso DPI is recommended in those who meet the following criteria:

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, v, and vi):
- **i.** Patient is ≥ 18 years of age; AND
- **ii.** Patient has a diagnosis of World Health Organization (WHO) Group 3 pulmonary hypertension associated with interstitial lung disease; AND
- **iii.** Patient with connective tissue disease is required to have a baseline forced vital capacity < 70%; AND
- **iv.** Patient has evidence of diffuse parenchymal lung disease on computed tomography of the chest; AND
- **v.** 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
- **vi.** The medication is prescribed by or in consultation with a cardiologist or a pulmonologist.

B) Patient is Currently Receiving Tyvaso or Tyvaso DPI for pulmonary hypertension associated with interstitial lung disease. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, iv and v):

i. Patient is ≥ 18 years of age; AND
ii. Patient has a diagnosis of World Health Organization (WHO) Group 3 pulmonary hypertension associated with interstitial lung disease; AND
iii. 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
iv. 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.
v. The medication is prescribed by or in consultation with a cardiologist or a pulmonologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Tyvaso, Tyvaso DPI, and Ventavis is not recommended in the following situations:

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).

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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. Ruopp NF, Cockrill BA. Diagnosis and treatment of pulmonary arterial hypertension. A review. *JAMA*. 2022;327(14):1379-1391.
5. 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.
6. 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.
7. Waxman A, Restrepp-Jaramillo R, Thenappan T, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *N Engl J Med*. 2021;384:325-334.
8. King CS, Nathan SD. Pulmonary hypertension due to interstitial lung disease. *Curr Opin Pulm Med*. 2019;25:459-467.
9. 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.
10. Shioleno AM, Ruopp NF. Group 3 pulmonary hypertension: a review of diagnostics and clinical trials. *Clin Chest Med*. 2021;42:59-70.
11. Maron BA. Revised Definition of Pulmonary Hypertension and Approach to Management: A Clinical Primer. *J Am Heart Assoc*. 2023 Apr 18;12(8):e029024. [Epub].