CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214324Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TYVASO DPI safely and effectively. See full prescribing information for TYVASO DPI.

TYVASO DPI™ (treprostinil) inhalation powder, for oral inhalation use
Initial U.S. Approval: 2002

---------- INDICATIONS AND USAGE----------
Tyvaso DPI is a prostacyclin mimetic indicated for the treatment of:
- Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies with Tyvaso establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). (1.1)
- Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study with Tyvaso establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%). (1.2)

----------DOSAGE AND ADMINISTRATION----------
- Use only with the Tyvaso DPI Inhaler. (2.1)
- Administer using a single inhalation per cartridge. (2.1)
- Administer in 4 separate treatment sessions each day approximately 4 hours apart, during waking hours. (2.1)
- Initial dosage: one 16 mcg cartridge per treatment session. (2.2)
- Dosage should be increased by an additional 16 mcg per treatment session at approximately 1- to 2-week intervals, if tolerated. (2.2)
- Titrate to target maintenance doses of 48 mcg to 64 mcg per treatment session, 4 times daily. (2.2)

---------- DOSAGE FORMS AND STRENGTHS----------
Inhalation powder: Single-dose plastic cartridges containing 16, 32, 48, or 64 mcg of treprostinil as a dry powder formulation. (3)

---------- CONTRAINDICATIONS ----------
None. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Tyvaso DPI may cause symptomatic hypotension. (5.1)
- Tyvaso DPI inhibits platelet aggregation and increases the risk of bleeding. (5.2)
- Tyvaso DPI dosage adjustments may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn. (5.3, 7.3)
- May cause bronchospasm: Patients with a history of hyperreactive airway disease may be more sensitive. (5.4)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (≥4%) are cough, headache, throat irritation/pharyngolaryngeal pain, nausea, flushing, dyspnea, and syncope. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact United Therapeutics Corp. at 1-866-458-6479 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 5/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Pulmonary Arterial Hypertension

Tyvaso DPI is indicated for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies with Tyvaso establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

While there are long-term data on use of treprostinil by other routes of administration, nearly all clinical experience with inhaled treprostinil has been on a background of an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor. The controlled clinical experience with Tyvaso was limited to 12 weeks in duration *[see Clinical Studies (14)]*.

1.2 Pulmonary Hypertension Associated with ILD

Tyvaso DPI is indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study with Tyvaso establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%) *[see Clinical Studies (14.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Administration

Use Tyvaso DPI only with the Tyvaso DPI Inhaler. Tyvaso DPI is administered using a single inhalation per cartridge. Administer Tyvaso DPI in 4 separate, equally spaced treatment sessions per day, during waking hours. The treatment sessions should be approximately 4 hours apart.

If the prescribed dose is higher than 64 mcg per treatment session, more than 1 cartridge will be needed per session. Patients should follow the instructions for use for operation and care of the Tyvaso DPI Inhaler.

Do not use the Tyvaso DPI Inhaler with other medications.

Between each of the 4 daily treatment sessions, store the Tyvaso DPI Inhaler with the mouthpiece attached and empty. Wipe the outside of the inhaler with a clean, dry cloth only, if needed. Do not rinse or wash the Tyvaso DPI Inhaler; always keep the inhaler dry. After 7 days of use, throw away the used Tyvaso DPI Inhaler into regular household trash.

2.2 Usual Dosage in Adults

Initial Dosage:

Tyvaso DPI therapy should begin with one 16 mcg cartridge per treatment session, 4 times daily.

Maintenance Dosage:
Increase dosage by an additional 16 mcg per treatment session at approximately 1- to 2-week intervals. The target maintenance dosage is usually 48 mcg to 64 mcg per session.

If adverse effects preclude titration, continue Tyvaso DPI at the highest tolerated dose.

If a scheduled treatment session is missed, resume therapy as soon as possible at the usual dose.

Dosage for Transition from Tyvaso® (treprostinil) Inhalation Solution:

The following regimens of Tyvaso DPI and Tyvaso give similar exposure:

Tyvaso DPI Cartridge Strength	**Tyvaso Number of Breaths**
16 mcg	≤5 (≤30 mcg)
32 mcg	6 to 7 (36 to 42 mcg)
48 mcg	8 to 10 (48 to 60 mcg)
64 mcg	11 to 12 (66 to 72 mcg)

3 DOSAGE FORMS AND STRENGTHS

Inhalation powder: Single-dose plastic cartridges containing 16, 32, 48, or 64 mcg of treprostinil as a dry powder formulation.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Symptomatic Hypotension

Treprostinil is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, treatment with Tyvaso DPI may produce symptomatic hypotension.

5.2 Risk of Bleeding

Tyvaso DPI inhibits platelet aggregation and increases the risk of bleeding.

5.3 Effect of Other Drugs on Treprostinil

Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both C_{max} and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness *[see Drug Interactions (7.3) and Clinical Pharmacology (12.3)]*.

5.4 Bronchospasm

Like other inhaled prostaglandins, Tyvaso DPI may cause acute bronchospasm. Patients with asthma or chronic obstructive pulmonary disease (COPD), or other bronchial hyperreactivity, are at increased risk for bronchospasm. Ensure that such patients are treated optimally for reactive airway disease prior to and during treatment with Tyvaso DPI.

6 ADVERSE REACTIONS

The following potential adverse reactions are described in Warnings and Precautions (5):

- Decrease in systemic blood pressure *[see Warnings and Precautions (5.1)]*.
- Bleeding *[see Warnings and Precautions (5.2)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Pulmonary Arterial Hypertension

Tyvaso DPI

In a 3-week, open-label, single-sequence, safety and tolerability study (BREEZE) conducted in 51 patients on stable doses of Tyvaso Inhalation Solution who switched to a corresponding dose of Tyvaso DPI, the most commonly reported adverse events on Tyvaso DPI during the 3-week treatment phase included cough, headache, dyspnea, and nausea. Patient tolerability, as assessed by incidence of new adverse events following transition to Tyvaso DPI, was consistent with the expected known safety profile of Tyvaso Inhalation Solution. Table 1 lists the adverse events that occurred at a rate of at least 4%.

Table 1: Adverse Events in ≥4% of PAH Patients Receiving Tyvaso DPI in BREEZE (Treatment Phase)

Adverse Event	Tyvaso DPI (n=51) n (%)
Cough	18 (35.3)
Headache	8 (15.7)
Dyspnea	4 (7.8)
Nausea	3 (5.9)

The safety of Tyvaso DPI was also studied in an extension phase of the study in which 49 patients were dosed for a duration of 43 patient-years. Fifty-nine percent (59%) of patients achieved a dose of 64 mcg, 4 times daily or higher. The adverse events during this long-term, extension phase were similar to those observed in the 3-week treatment phase.

Tyvaso Inhalation Solution

In a 12-week, placebo-controlled study (TRIUMPH I) of 235 patients with PAH (WHO Group 1 and nearly all NYHA Functional Class III), the most commonly reported adverse reactions on Tyvaso Inhalation Solution included cough and throat irritation, headache, gastrointestinal effects, muscle, jaw or bone pain, dizziness, flushing, and syncope. Table 2 lists the adverse reactions that occurred at a rate

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