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

TYVASO (treprostinil) inhalation solution
Initial U.S. Approval: 2002
For Oral Inhalation Only

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

---------------------DOSAGE AND ADMINISTRATION---------------------
- Use only with the Tyvaso Inhalation System. (2.1)
- Administer undiluted, as supplied. A single breath of Tyvaso delivers
  approximately 6 mcg of treprostinil. (2.1)
- Administer in 4 separate treatment sessions each day approximately four
  hours apart, during waking hours. (2.1)
- Initial dosage: 3 breaths [18 mcg] per treatment session. If 3 breaths are
  not tolerated, reduce to 1 or 2 breaths. (2.1)
- Dosage should be increased by an additional 3 breaths at approximately
  1-2 week intervals, if tolerated. (2.1)
- Titrate to target maintenance dosage of 9 breaths or 54 mcg per
  treatment session as tolerated. (2.1)

--------------------DOSAGE FORMS AND STRENGTHS--------------------
Sterile solution for oral inhalation: 2.9 mL ampule containing 1.74 mg
treprostinil (0.6 mg per mL). (3)

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

----------------------WARNINGS AND PRECAUTIONS--------------------
- Safety and efficacy have not been established in patients with significant
  underlying lung disease (such as asthma or chronic obstructive
  pulmonary disease). (5.1)
- In patients with low systemic arterial pressure, Tyvaso may cause
  symptomatic hypotension. (5.2)
- Tyvaso may increase the risk of bleeding, particularly in patients
  receiving anticoagulants. (5.4, 7.2)
- Tyvaso dosage adjustments may be necessary if inhibitors or inducers of
  CYP2C8 are added or withdrawn. (5.5, 7.5)
- Hepatic or renal insufficiency may increase exposure and decrease
  tolerability. (2.2, 2.3, 5.3)

------------------------------ADVERSE REACTIONS----------------------------
Most common adverse reactions (≥ 10%) are cough, headache, nausea
dizziness, flushing, throat irritation, pharyngolaryngeal pain and diarrhea. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact United
Therapeutics Corp. at 1-866-458-6479 or via e-mail at
drugsafety@unither.com, or FDA at 1-800-FDA-1088 or
*www.fda.gov/medwatch.***

------------------------------DRUG INTERACTIONS--------------------------
- Concomitant diuretics, antihypertensives or other vasodilators may
  increase the risk of systemic hypotension. (7.1)

----------------------USE IN SPECIFIC POPULATIONS--------------------
- Pregnancy: Tyvaso should be used only if clearly needed. (8.1)
- Nursing women: Caution should be exercised when administered to a
  nursing woman. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

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

Revised: 2/2011

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FULL PRESCRIBING INFORMATION
Tyvaso® (treprostinil) inhalation solution

For Oral Inhalation Only

1   INDICATIONS AND USAGE

Tyvaso is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately 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 controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration *[see Clinical Studies (14)]*.

2   DOSAGE AND ADMINISTRATION

2.1   Usual Dosage in Adults

Tyvaso is intended for oral inhalation using the Tyvaso Inhalation System, which consists of the Optineb-ir Model ON-100/7 (an ultrasonic, pulsed-delivery device) and its accessories.

Tyvaso is dosed in 4 separate, equally spaced treatment sessions per day, during waking hours. The treatment sessions should be approximately 4 hours apart.

Initial Dosage:

Therapy should begin with 3 breaths of Tyvaso (18 mcg of treprostinil), per treatment session, 4 times daily. If 3 breaths are not tolerated, reduce to 1 or 2 breaths and subsequently increase to 3 breaths, as tolerated.

Maintenance Dosage:

Dosage should be increased by an additional 3 breaths at approximately 1-2 week intervals, if tolerated, until the target dose of 9 breaths (54 mcg of treprostinil) is reached per treatment session, 4 times daily. If adverse effects preclude titration to target dose, Tyvaso should be continued at the highest tolerated dose.

If a scheduled treatment session is missed or interrupted, therapy should be resumed as soon as possible at the usual dose.

The maximum recommended dosage is 9 breaths per treatment session, 4 times daily.

2.2 Patients with Hepatic Insufficiency

Plasma clearance of treprostinil is reduced in patients with hepatic insufficiency. Patients with hepatic insufficiency may therefore be at increased risk of dose-dependent adverse reactions because of an increase in systemic exposure *[see Warnings and Precautions (5.3), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.3 Patients with Renal Insufficiency

Plasma clearance of treprostinil may be reduced in patients with renal insufficiency, since treprostinil and its metabolites are excreted mainly through the urinary route. Patients with renal insufficiency may therefore be at increased risk of dose-dependent adverse reactions *[see Warnings and Precautions (5.3), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

2.4 Administration

Tyvaso must be used only with the Tyvaso Inhalation System. Patients should follow the instructions for use for operation of the Tyvaso Inhalation System and for daily cleaning of the device components after the last treatment session of the day. To avoid potential interruptions in drug delivery because of equipment malfunction, patients should have access to a back-up Optineb-ir device.

Do not mix Tyvaso with other medications in the Optineb-ir device. Compatibility of Tyvaso with other medications has not been studied.

The Tyvaso Inhalation System should be prepared for use each day according to the instructions for use. One ampule of Tyvaso contains a sufficient volume of medication for all 4 treatment sessions in a single day. Prior to the first treatment session, the patient should twist the top off a single Tyvaso ampule and squeeze the entire contents into the medicine cup. Between each of the 4 daily treatment sessions, the device should be capped and stored upright with the remaining medication inside.

At the end of each day, the medicine cup and any remaining medication must be discarded. The device must be cleaned each day according to the instructions for use.

Avoid skin or eye contact with Tyvaso solution. Do not orally ingest the Tyvaso solution.

3 DOSAGE FORMS AND STRENGTHS

Sterile solution for oral inhalation: 2.9 mL ampule containing 1.74 mg of treprostinil (0.6 mg per mL).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Patients with Pulmonary Disease or Pulmonary Infections

The safety and efficacy of Tyvaso have not been established in patients with significant underlying lung disease (e.g., 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.

5.2 Risk of Symptomatic Hypotension

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

5.3 Patients with Hepatic or Renal Insufficiency

Titrate slowly in patients with hepatic or renal insufficiency, because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic or renal function *[see Dosage and Administration (2.2, 2.3), Use in Specific Populations (8.6, 8.7) and Clinical Pharmacology (12.3)]*.

5.4 Risk of Bleeding

Since Tyvaso inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulant therapy.

5.5 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 (7.5) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following potential adverse reactions are described in Warnings and Precautions (5):
- Decrease in systemic blood pressure *[see Warnings and Precautions (5.2)]*.
- Bleeding [*see Warnings and Precautions (5.4)*].

6.1   Adverse Reactions Identified in Clinical Trials

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.

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 included: cough and throat irritation; headache, gastrointestinal effects, muscle, jaw or bone pain, flushing and syncope. Table 1 lists the adverse reactions that occurred at a rate of at least 4% and were more frequent in patients treated with Tyvaso than with placebo.

Table 1: Adverse Events in ≥ 4% of PAH Patients Receiving Tyvaso and More Frequent* than Placebo		
Adverse Event	**Treatment n (%)**	
	Tyvaso n = 115	**Placebo n = 120**
Cough	62 (54)	35 (29)
Headache	47 (41)	27 (23)
Throat Irritation / Pharyngolaryngeal Pain	29 (25)	17 (14)
Nausea	22 (19)	13 (11)
Flushing	17 (15)	1 (<1)
Syncope	7 (6)	1 (<1)

*More than 3% greater than placebo

The safety of Tyvaso was also studied in a long-term, open-label extension study in which 206 patients were dosed for a mean duration of one year. The adverse events during this chronic dosing study were qualitatively similar to those observed in the 12-week placebo controlled trial.

Adverse Events Associated with Route of Administration

Adverse events in the treated group during the double-blind and open-label phase reflecting irritation to the respiratory tract included: cough, throat irritation, pharyngeal pain, epistaxis, hemoptysis and wheezing. Serious adverse events during the open-label portion of the study included pneumonia in 8 subjects. There were three serious episodes of hemoptysis (one fatal) noted during the open-label experience.

7   DRUG INTERACTIONS

Pharmacokinetic/pharmacodynamic interaction studies have not been conducted with inhaled treprostinil (Tyvaso); however, some of such studies have been conducted with orally (treprostinil diethanolamine) and subcutaneously administered treprostinil (Remodulin®).

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