

## **PATIENT PACKAGE INSERT**

**Tyvaso (Ti-vāsō)**

**(treprostinil)**

**Inhalation Solution**

Read this Patient Package Insert before you start taking Tyvaso and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or your treatment.

### **What is Tyvaso?**

Tyvaso is a prescription medicine used in adults to treat pulmonary arterial hypertension (PAH), which is high blood pressure in the arteries of your lungs. Tyvaso can improve the ability to do exercise in people who also take bosentan (an endothelin receptor antagonist (ERA)) or sildenafil (a phosphodiesterase-5 (PDE-5) inhibitor). Your ability to do exercise decreases 4 hours after taking Tyvaso.

It is not known if Tyvaso is safe or effective in people under 18 years of age.

### **What should I tell my healthcare provider before taking Tyvaso?**

Before taking Tyvaso, tell your healthcare provider about all of your medical conditions, including if you:

- have lung disease, such as asthma or chronic obstructive pulmonary disease (COPD)
- have a lung infection
- have liver problems or kidney problems
- have low blood pressure
- are pregnant or plan to become pregnant. It is not known if Tyvaso will harm your unborn baby. Women who can become pregnant should use effective birth control while taking Tyvaso.
- are breast-feeding or plan to breast-feed. It is not known if Tyvaso passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking Tyvaso.

**Tell your healthcare provider about all the medicines you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements. Tyvaso and other medicines may affect each other.

Especially tell your healthcare provider if you take any of these medicines:

- medicines that decrease blood clotting
- water pills (diuretics)
- medicines used to treat high blood pressure or heart disease
- gemfibrozil (Lopid) (for high cholesterol)
- rifampin (Rimactane, Rifadin, Rifamate, Rifater) (for infection)

Know the medicines you take. Keep a list of them and show it to your healthcare provider and specialty pharmacist when you get a new medicine.

**How should I take Tyvaso?**

- Take Tyvaso each day exactly as your healthcare provider tells you.
- See the detailed Tyvaso Inhalation System Instructions for Use.
- Tyvaso is breathed in (inhaled) through your mouth into your lungs. Tyvaso should only be used with the Tyvaso Inhalation System.
- Tyvaso is taken in 4 treatment sessions each day during waking hours. The sessions should be at about 4 hours apart.
- At the beginning of each day, it will take about 5 minutes to prepare the Tyvaso Inhalation System. Each treatment session will take 2 to 3 minutes.
- Take your first Tyvaso treatment session in the morning and take your last treatment session before bedtime.
- Your healthcare provider may change your dose if needed.
- If you miss a dose of Tyvaso take it as soon as you remember.
- Do not let Tyvaso solution get into your eyes or onto your skin. If it does, rinse your skin or eyes right away with water.

**What are the possible side effects of Tyvaso?**

Tyvaso can cause serious side effects, including:

- Tyvaso may increase the risk of bleeding in people who take blood thinners (anticoagulants).
- If you have low blood pressure, Tyvaso may lower your blood pressure further.

Ask your healthcare provider if you are not sure if this applies to you.

The most common side effects of Tyvaso include:

- coughing
- headache
- nausea
- reddening of your face and neck (flushing)
- throat irritation and pain
- fainting or loss of consciousness

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Tyvaso. For more information, ask your healthcare provider or specialty pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store Tyvaso?**

- Store Tyvaso ampules in the unopened foil pack between 59°F to 86°F (15°C to 30°C) until ready to use.
- When the foil pouch is opened, Tyvaso ampules should be used within 7 days.
- Tyvaso is sensitive to light. The unopened Tyvaso ampules should be stored in the foil pouch.
- After a Tyvaso ampule is opened and put into the medicine cup in the Tyvaso Inhalation System, Tyvaso can be kept in the medicine cup for no more than 1 day (24 hours).
- Tyvaso that is left in the medicine cup at the end of the day must be thrown away.

**Keep Tyvaso and all medicines out of the reach of children.**

**General information about the safe and effective use of Tyvaso.**

Medicines are sometimes prescribed for conditions that are not mentioned in a patient information leaflet. Do not use Tyvaso for a condition for which it was not prescribed. Do not give Tyvaso to other people, even if they have the same symptoms you have. It may harm them.

This patient information leaflet summarizes the most important information about Tyvaso. You can ask your healthcare provider or specialty pharmacist for information about Tyvaso that is written for health professionals.

For more information, go to [www.tyvaso.com](http://www.tyvaso.com) or call 1-866-458-6479.

**What are the ingredients in Tyvaso?**

Active ingredient: treprostinil

Inactive ingredients: sodium chloride, sodium citrate, sodium hydroxide, hydrochloric acid, and water for injection.

Tyvaso is a trademark of United Therapeutics Corporation.

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**United Therapeutics Corp.**

**Research Triangle Park, NC 27709 USA**

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## 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 ( $\geq 10\%$ ) 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](mailto:drugsafety@unither.com), or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://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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### **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.

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®).

## ***Pharmacodynamics***

### **7.1 Antihypertensive Agents or Other Vasodilators**

Concomitant administration of Tyvaso with diuretics, antihypertensive agents or other vasodilators may increase the risk of symptomatic hypotension.

### **7.2 Anticoagulants**

Since treprostinil inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulants.

## ***Pharmacokinetics***

### **7.3 Bosentan**

In a human pharmacokinetic study conducted with bosentan (250 mg/day) and an oral formulation of treprostinil (treprostinil diethanolamine), no pharmacokinetic interactions between treprostinil and bosentan were observed.

### **7.4 Sildenafil**

In a human pharmacokinetic study conducted with sildenafil (60 mg/day) and an oral formulation of treprostinil (treprostinil diethanolamine), no pharmacokinetic interactions between treprostinil and sildenafil were observed.

### **7.5 Effect of Cytochrome P450 Inhibitors and Inducers**

*In vitro* studies of human hepatic microsomes showed that treprostinil does not inhibit cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A. Additionally, treprostinil does not induce cytochrome P450 isoenzymes CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A.

Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil diethanolamine) indicated that co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor gemfibrozil increases exposure (both  $C_{max}$  and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inducer rifampin decreases exposure to treprostinil. It is unclear if the safety and efficacy of treprostinil by the inhalation route are altered by inhibitors or inducers of CYP2C8 [*see Warnings and Precautions (5.5)*].

### **7.6 Effect of Other Drugs on Treprostinil**

Drug interaction studies have been carried out with treprostinil (oral or subcutaneous) co-administered with acetaminophen (4 g/day), warfarin (25 mg/day), and fluconazole (200 mg/day), respectively in healthy volunteers. These studies did not show a clinically significant effect on the pharmacokinetics of treprostinil. Treprostinil does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S- warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous infusion of treprostinil at an infusion rate of 10 ng/kg/min.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Pregnancy Category B

There are no adequate and well controlled studies with Tyvaso in pregnant women. Animal reproduction studies have not been conducted with treprostinil administered by the inhalation route. However, studies in pregnant rabbits using continuous subcutaneous (sc) infusions of treprostinil sodium at infusion rates higher than the recommended human sc infusion rate resulted in an increased incidence of fetal skeletal variations associated with maternal toxicity [*see Developmental Toxicity (13.3)*]. Animal reproduction studies are not always predictive of human response; Tyvaso should be used during pregnancy only if clearly needed.

### **8.2 Labor and Delivery**

No treprostinil treatment-related effects on labor and delivery were seen in animal studies. The effect of treprostinil on labor and delivery in humans is unknown.

### **8.3 Nursing Mothers**

It is not known whether treprostinil is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when treprostinil is administered to nursing women.

### **8.4 Pediatric Use**

Safety and effectiveness in pediatric patients have not been established. Clinical studies of Tyvaso did not include patients younger than 18 years to determine whether they respond differently from older patients.

### **8.5 Geriatric Use**

Clinical studies of Tyvaso did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of hepatic, renal, or cardiac dysfunction, and of concomitant diseases or other drug therapy.

### **8.6 Patients with Hepatic Insufficiency**

Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects with mild-to-moderate hepatic insufficiency. Uptitrate slowly when treating patients with hepatic insufficiency because of the risk of an increase in systemic exposure which may lead to an increase in dose-dependent adverse effects. Treprostinil has not been studied in patients with severe hepatic insufficiency [*see Clinical Pharmacology (12.3), Dosage and Administration (2.2) and Warnings and Precautions (5.3)*].

### **8.7 Patients with Renal Insufficiency**

No studies have been performed in patients with renal insufficiency. Since treprostinil and its metabolites are excreted mainly through the urinary route, patients with renal insufficiency may have decreased clearance of the drug and its metabolites and consequently, dose-related adverse outcomes may be more frequent [*see Clinical Pharmacology (12.3), Dosage and Administration (2.3) and Warnings and Precautions (5.3)*].

## 10 OVERDOSAGE

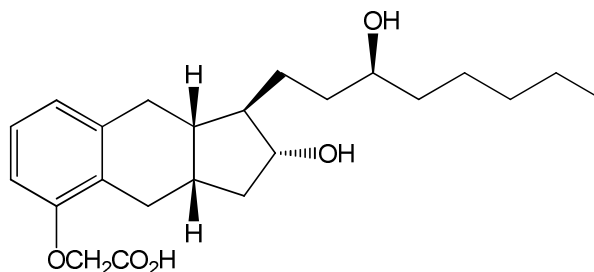
In general, symptoms of overdose with Tyvaso include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Provide general supportive care until the symptoms of overdose have resolved.

## 11 DESCRIPTION

Tyvaso is a sterile formulation of treprostinil intended for administration by oral inhalation using the Optineb-ir device. Tyvaso is supplied in 2.9 mL low density polyethylene (LDPE) ampules, containing 1.74 mg treprostinil (0.6 mg/mL). Each ampule also contains 18.9 mg sodium chloride, 18.3 mg sodium citrate, 0.58 mg sodium hydroxide, 11.7 mg 1 N hydrochloric acid, and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2.

Treprostinil is (1R,2R,3aS,9aS)-[[2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]acetic acid. Treprostinil has a molecular weight of 390.51 and a molecular formula of C<sub>23</sub>H<sub>34</sub>O<sub>5</sub>.

The structural formula of treprostinil is:



## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Treprostinil is a prostacyclin analogue. The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.

### 12.2 Pharmacodynamics

In a clinical trial of 240 healthy volunteers, single doses of Tyvaso 54 mcg (the target maintenance dose per session) and 84 mcg (supratherapeutic inhalation dose) prolonged the corrected QTc interval by approximately 10 ms. The QTc effect dissipated rapidly as the concentration of treprostinil decreased.

### 12.3 Pharmacokinetics

Pharmacokinetic information for single doses of inhaled treprostinil was obtained in healthy volunteers in three separate studies. Treprostinil systemic exposure (AUC and C<sub>max</sub>) post-inhalation was shown to be proportional to the doses administered (18 mcg – 90 mcg).

#### Absorption and Distribution

In a three-period crossover study, the bioavailability of two single doses of Tyvaso (18 mcg and 36 mcg) was compared with that of intravenous treprostinil in 18 healthy volunteers. Mean estimates of the

absolute systemic bioavailability of treprostinil after inhalation were approximately 64% (18 mcg) and 72% (36 mcg).

Treprostinil plasma exposure data were obtained from two studies at the target maintenance dose, 54 mcg. The mean  $C_{max}$  at the target dose was 0.91 and 1.32 ng/mL with corresponding mean  $T_{max}$  of 0.25 and 0.12 hr, respectively. The mean AUC for the 54 mcg dose was 0.81 and 0.97 hr•ng/mL, respectively.

Following parenteral infusion, the apparent steady state volume of distribution ( $V_{ss}$ ) of treprostinil is approximately 14 L/70 kg ideal body weight.

*In vitro* treprostinil is 91% bound to human plasma proteins over the 330-10,000 mcg/L concentration range.

### **Metabolism and Excretion**

Of subcutaneously administered treprostinil, only 4% is excreted unchanged in urine. Treprostinil is substantially metabolized by the liver, primarily by CYP2C8. Metabolites are excreted in urine (79%) and feces (13%) over 10 days. Five apparently inactive metabolites were detected in the urine, each accounting for 10-15% of the dose administered. Four of the metabolites are products of oxidation of the 3-hydroxyoctyl side chain and one is a glucuroconjugated derivative (treprostinil glucuronide).

The elimination of treprostinil (following subcutaneous administration of treprostinil) is biphasic, with a terminal elimination half-life of approximately 4 hours using a two compartment model.

### **Special Populations**

#### *Hepatic Insufficiency*

Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects presenting with mild-to-moderate hepatic insufficiency. Treprostinil has not been studied in patients with severe hepatic insufficiency [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.3)* and *Use in Specific Populations (8.6)*].

#### *Renal Insufficiency*

No studies have been performed in patients with renal insufficiency; therefore, since treprostinil and its metabolites are excreted mainly through the urinary route, there is the potential for an increase in both parent drug and its metabolites and an increase in systemic exposure [see *Dosage and Administration (2.3)*, *Warnings and Precautions (5.3)* and *Use in Specific Populations (8.7)*].

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

Long-term studies have not been performed to evaluate the carcinogenic potential of treprostinil. In vitro and in vivo genetic toxicology studies did not demonstrate any mutagenic or clastogenic effects of treprostinil. Treprostinil sodium did not affect fertility or mating performance of male or female rats given continuous subcutaneous (sc) infusions at rates of up to 450 ng treprostinil/kg/min [about 59 times the recommended starting human sc infusion rate (1.25 ng/kg/min) and 8 times the average rate (9.3 ng/kg/min) achieved in clinical trials, on a  $\text{ng}/\text{m}^2$  basis]. In this study, males were dosed from 10 weeks prior to mating and through the 2-week mating period. Females were dosed from 2 weeks prior to mating until gestational day 6.

### **13.3 Developmental Toxicity**

In pregnant rats, continuous sc infusions of treprostinil sodium during organogenesis and late gestational development, at rates as high as 900 ng treprostinil/kg/min (about 117 times the recommended starting human sc infusion rate and about 16 times the average rate achieved in clinical trials, on a  $\text{ng}/\text{m}^2$  basis), resulted in no evidence of harm to the fetus. In pregnant rabbits, effects of continuous sc infusions of treprostinil during organogenesis were limited to an increased incidence of fetal skeletal variations (bilateral full rib or right rudimentary rib on lumbar vertebra 1) associated with maternal toxicity (reduction in body weight and food consumption) at an infusion rate of 150 ng treprostinil/kg/min (about 41 times the starting human sc infusion rate and 5 times the average rate achieved in clinical trials, on a  $\text{ng}/\text{m}^2$  basis).

### **13.4 Inhalational Toxicity**

Rats and dogs that received daily administrations of treprostinil by inhalation for 3 months developed respiratory tract lesions (respiratory epithelial degeneration, goblet cell hyperplasia/hypertrophy, epithelial ulceration, squamous epithelial degeneration and necrosis, and lung hemorrhage). Some of the same lesions seen in animals sacrificed at the end of treatment (larynx, lung and nasal cavity lesions in rats, and lesions of the larynx in dogs) were also observed in animals sacrificed after a 4-week recovery period. Rats also developed cardiac changes (degeneration/fibrosis). A no-effect dose level for these effects was not demonstrated in rats (doses as low as 7  $\mu\text{g}/\text{kg}/\text{day}$  were administered); whereas 107  $\mu\text{g}/\text{kg}/\text{day}$  was a no-effect dose level in dogs.

## 14 CLINICAL STUDIES

TRIUMPH I, was a 12-week, randomized, double-blind, placebo-controlled multi-center study of patients with PAH. The study population included 235 clinically stable subjects with pulmonary arterial hypertension (WHO Group 1), nearly all with NYHA Class III (98%) symptoms who were receiving either bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase-5 inhibitor) for at least three months prior to study initiation. Concomitant therapy also could have included anticoagulants, other vasodilators (e.g., calcium channel blockers), diuretics, oxygen, and digitalis, but not a prostacyclin. These patients were administered either placebo or Tyvaso in four daily treatment sessions with a target dose of 9 breaths (54 mcg) per session over the course of the 12-week study. Patients were predominantly female (82%), had the origin of PAH as idiopathic/heritable (56%), secondary to connective tissue diseases (33%) or secondary to HIV or previous use of anorexigens (12%); bosentan was the concomitant oral medication in 70% of those enrolled, sildenafil in 30%.

The primary efficacy endpoint of the trial was the change in six-minute walk distance (6MWD) relative to baseline at 12 weeks. 6MWD was measured at peak exposure (between 10 and 60 minutes after dosing), and 3-5 hours after bosentan or 0.5-2 hours after sildenafil. Patients receiving Tyvaso had a placebo-corrected median change from baseline in peak 6MWD of 20 meters at Week 12 ( $p < 0.001$ ). The distribution of these 6MWD changes from baseline at Week 12 were plotted across the range of observed values (Figure 1). 6MWD measured at trough exposure (defined as measurement of 6MWD at least 4 hours after dosing) improved by 14 meters. There were no placebo-controlled 6MWD assessments made after 12 weeks.

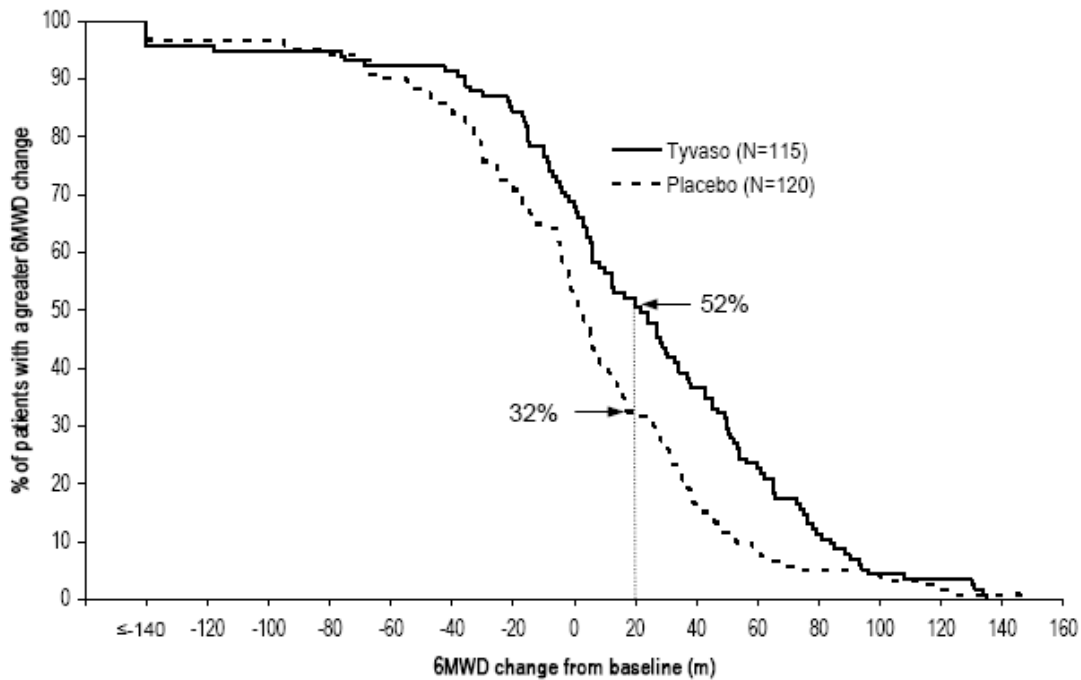
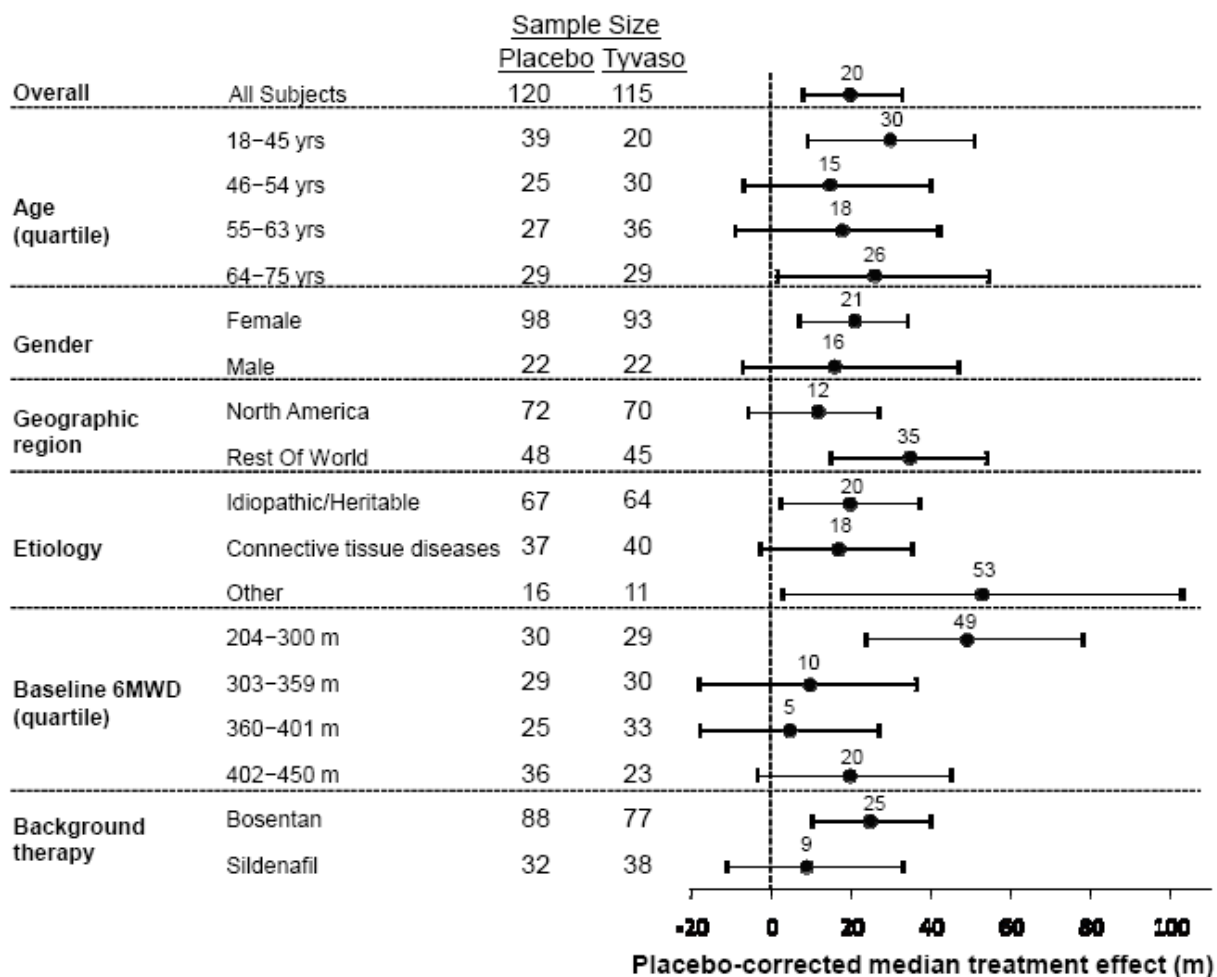


Figure 1: Distributions of 6MWD Changes from Baseline at Week 12 during Peak Plasma Concentration of Tyvaso

The placebo-corrected median treatment effect on 6MWD was estimated (using the Hodges-Lehmann estimator) within various subpopulations defined by age quartile, gender, geographic region of the study site, disease etiology, baseline 6MWD quartile, and type of background therapy (Figure 2).



**Figure 2. Placebo Corrected Median Treatment Effect (Hodges-Lehmann estimate with 95% CI) on 6MWD Change from Baseline at Week 12 During Peak Plasma Concentration of Tyvaso for Various Subgroups**

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Tyvaso (treprostinil) inhalation solution is supplied in 2.9 mL clear LDPE ampules packaged as four ampules in a foil pouch. Tyvaso is a clear colorless to slightly yellow solution containing 1.74 mg treprostinil per ampule at a concentration of 0.6 mg/mL.

Ampules of Tyvaso are stable until the date indicated when stored in the unopened foil pouch at 25°C (77°F), with excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Once the foil pack is opened, ampules should be used within 7 days. Because Tyvaso is light-sensitive, unopened ampules should be stored in the foil pouch.

One ampule of Tyvaso should be used each day in the Tyvaso Inhalation System. After a Tyvaso ampule is opened and transferred to the medicine cup, the solution should remain in the device for no more than one day (24 hours). Any remaining solution should be discarded at the end of the day.

Tyvaso Inhalation System Starter Kit containing 28 ampule carton of Tyvaso [seven foil pouches each containing four 2.9 mL ampules. Each ampule contains 1.74 mg treprostinil (0.6 mg per mL)] and the Tyvaso Inhalation System. (NDC 66302-206-01)

Tyvaso Inhalation System Refill Kit containing 28 ampule carton of Tyvaso [seven foil pouches each containing four 2.9 mL ampules. Each ampule contains 1.74 mg treprostinil (0.6 mg per mL)] and accessories. (NDC 66302-206-02)

2.9 mL LDPE ampule containing 1.74 mg treprostinil (0.6 mg per mL), carton containing 1 foil pouch with 4 ampules. (NDC 66302-206-03)

## **17 PATIENT COUNSELING INFORMATION**

Patients should be properly trained in the administration process for Tyvaso, including dosing, Optineb-ir device set up, operation, cleaning, and maintenance, according to the instructions for use [*see Dosage and Administration (2.1)*].

To avoid potential interruptions in drug delivery because of equipment malfunction, patients should have access to a back-up Optineb-ir device [*see Dosage and Administration (2.4)*].

In the event that a scheduled treatment session is missed or interrupted, therapy should be resumed as soon as possible [*see Dosage and Administration (2.1)*].

Patients should avoid skin or eye contact with Tyvaso. If Tyvaso comes in contact with the skin or eyes, instruct patients to rinse immediately with water [*see Dosage and Administration (2.4)*].

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US Patent No. 6,765,117

US Patent No. 6,521,212

US Patent No. 6,756,033

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