

## 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, for oral inhalation only**  
**Initial U.S. Approval: 2002**

### 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

- Efficacy has 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 inhibits platelet aggregation and increases 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- Tyvaso dosage adjustments may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn.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 1-877-UNITHER (1-877-864-8437) 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: No experience. (8.1)
- Nursing women: No experience. (8.3)

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

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## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

### 2 DOSAGE AND ADMINISTRATION

- 2.1 Usual Dosage in Adults
- 2.2 Patients with Hepatic Insufficiency
- 2.3 Patients with Renal Insufficiency
- 2.4 Administration

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

### 5 WARNINGS AND PRECAUTIONS

- 5.1 Patients with Pulmonary Disease or Pulmonary Infections
- 5.2 Risk of Symptomatic Hypotension
- 5.3 Patients with Hepatic or Renal Insufficiency
- 5.4 Risk of Bleeding
- 5.5 Effect of Other Drugs on Treprostinil

### 6 ADVERSE REACTIONS

- 6.1 Adverse Reactions Identified in Clinical Trials
- 6.2 Adverse Reactions Identified in Post-Marketing Experience

### 7 DRUG INTERACTIONS

- 7.1 Antihypertensive Agents or Other Vasodilators
- 7.2 Anticoagulants
- 7.3 Bosentan
- 7.4 Sildenafil
- 7.5 Effect of Cytochrome P450 Inhibitors and Inducers
- 7.6 Effect of Other Drugs on Treprostinil

### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Patients with Hepatic Insufficiency
- 8.7 Patients with Renal Insufficiency

### 10 OVERDOSAGE

### 11 DESCRIPTION

### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.3 Developmental Toxicity
- 13.4 Inhalational Toxicity

### 14 CLINICAL STUDIES

- 14.1 Pulmonary Arterial Hypertension (WHO Group I)
- 14.2 Long-term Treatment of PAH

### 16 HOW SUPPLIED/STORAGE AND HANDLING

### 17 PATIENT COUNSELING INFORMATION

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

## **FULL PRESCRIBING INFORMATION**

### **Tyvaso<sup>®</sup> (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 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 Tyvaso Inhalation System device.

Do not mix Tyvaso with other medications in the Tyvaso Inhalation System. 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 efficacy of Tyvaso has 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

Tyvaso inhibits platelet aggregation and increases the risk of bleeding.

## 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.

<b>Table 1: Adverse Events in <math>\geq 4\%</math> of PAH Patients Receiving Tyvaso and More Frequent* than Placebo</b>		
<b>Adverse Event</b>	<b>Treatment n (%)</b>	
	<b>Tyvaso n = 115</b>	<b>Placebo n = 120</b>
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 2.3 years, with a maximum exposure of 5.4 years. Eighty-nine (89%) percent of patients achieved the target dose of nine breaths, four times daily. Forty-two (42%) percent achieved a dose of 12 breaths four times daily. The adverse events during this chronic dosing study were qualitatively similar to those observed in the 12-week placebo controlled trial.

In a prospective, observational study comparing patients taking Tyvaso (958 patient-years of exposure) and a control group (treatment with other approved therapies for PAH; 1094 patient-years), Tyvaso was associated with a higher rate of cough (16.2 per 100 patient-years vs. 10.9 per 100 pt-years), throat irritation (4.5 per 100 pt-years vs. 1.2 per 100 pt-years), nasal discomfort (2.6 per 100 pt-years vs. 1.3 per 100 pt-years), and haemoptysis (2.5 per 100 pt-years vs. 1.3 per 100 pt-years) compared to the control group.

### ***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

fifteen subjects. There were three serious episodes of hemoptysis (one fatal) noted during the open-label experience.

## 6.2 Adverse Reactions Identified in Post-Marketing Experience

The following adverse reaction has been identified during the postapproval use of Tyvaso. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure:

Angioedema.

## 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 diolamine) 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 diolamine), 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 diolamine), 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 diolamine) 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. Also, a study in pregnant rabbits administered oral treprostinil diolamine at exposures higher than those in humans resulted in external fetal and soft tissue malformations and fetal skeletal malformations [see *Nonclinical Toxicology* (13.3)]. Animal reproduction studies are not always predictive of human response.

### 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.

### 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

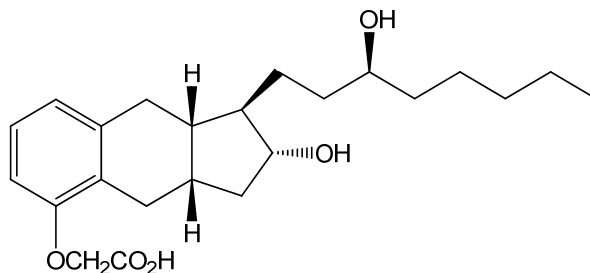
In general, symptoms of overdose with Tyvaso include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Provide general supportive care until the symptoms of overdose have resolved.

## 11 DESCRIPTION

Tyvaso is a sterile formulation of treprostinil intended for administration by oral inhalation using the Tyvaso Inhalation System. 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  $C_{max}$ ) 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**

A two-year rat carcinogenicity study was performed with treprostinil inhalation at target doses of 5.26, 10.6, and 34.1 mcg/kg/day. There was no evidence for carcinogenic potential associated with treprostinil inhalation in rats at systemic exposure levels up to 35 times the clinical exposure at the target maintenance dose of 54 mcg. *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 ng/m<sup>2</sup> 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.

Oral administration of treprostinil diolamine to Tg.rasH2 mice at 0, 5, 10 and 20 mg/kg/day in males and 0, 3, 7.5 and 15 mg/kg/day in females daily for 26 weeks did not significantly increase the incidence of tumors. The exposures, when based on AUC, obtained at the highest dose levels used in males and females are about 208- and 460-fold, respectively, the human exposure following a single inhaled dose of 54 mcg.

Treprostinil diolamine was tested *in vivo* in a rat micronucleus assay and did not induce an increased incidence of micronucleated polychromatic erythrocytes.

### **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 ng/m<sup>2</sup> 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 ng/m<sup>2</sup> basis).

In studies with treprostinil diolamine, no adverse effect doses for fetal viability / growth, fetal development (teratogenicity), and postnatal development were determined in rats. In pregnant rats, no evidence of harm to the fetus was observed following oral administration of treprostinil diolamine at the highest dose tested (20 mg/kg/day), which represents about 154 and 1479 times the human exposure, when based on  $C_{max}$  and AUC following a single dose of 54 mcg, respectively. In pregnant rabbits, external fetal and soft tissue malformations and fetal skeletal malformation occurred. The dose at which no adverse effects were seen (0.5 mg/kg/day) represents about 9 and 145 times the human exposure, when based on  $C_{max}$  and AUC following a single dose of 54 mcg, respectively.

### 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 µg/kg/day were administered); whereas 107 µg/kg/day was a no-effect dose level in dogs.

In a 2-year rat study with treprostinil inhalation at target doses of 5.26, 10.6, and 34.1 mcg/kg/day, there were more deaths (11) in the mid and high dose treprostinil groups during the first 9 weeks of the study, compared to 1 in control groups. At the high dose level, males showed a higher incidence of inflammation in teeth and preputial gland, and females showed higher incidences of inflammation and urothelial hyperplasia in the urinary bladder. The exposures in rats at mid and high dose levels were about 15 and 35 times, respectively, the clinical exposure at the target maintenance dose of 54 mcg.

## 14 CLINICAL STUDIES

### 14.1 Pulmonary Arterial Hypertension (WHO Group I)

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 I), 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.

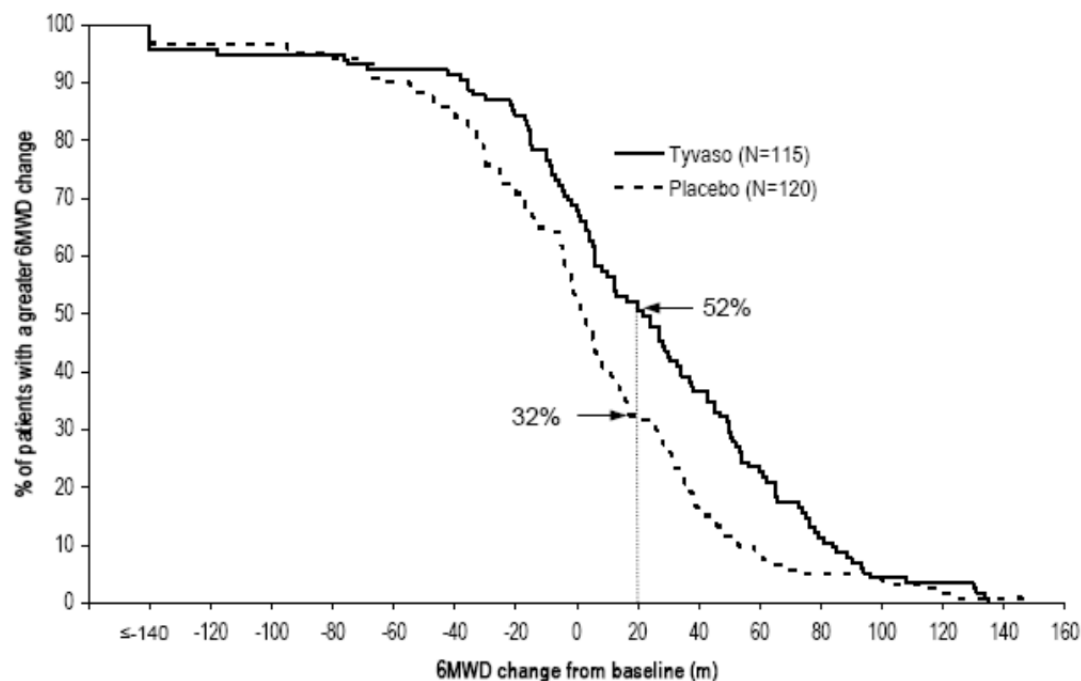


Figure 1: Distributions of 6MWD Changes from Baseline at Week 12 during Peak Plasma Concentration of Tyvaso

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).

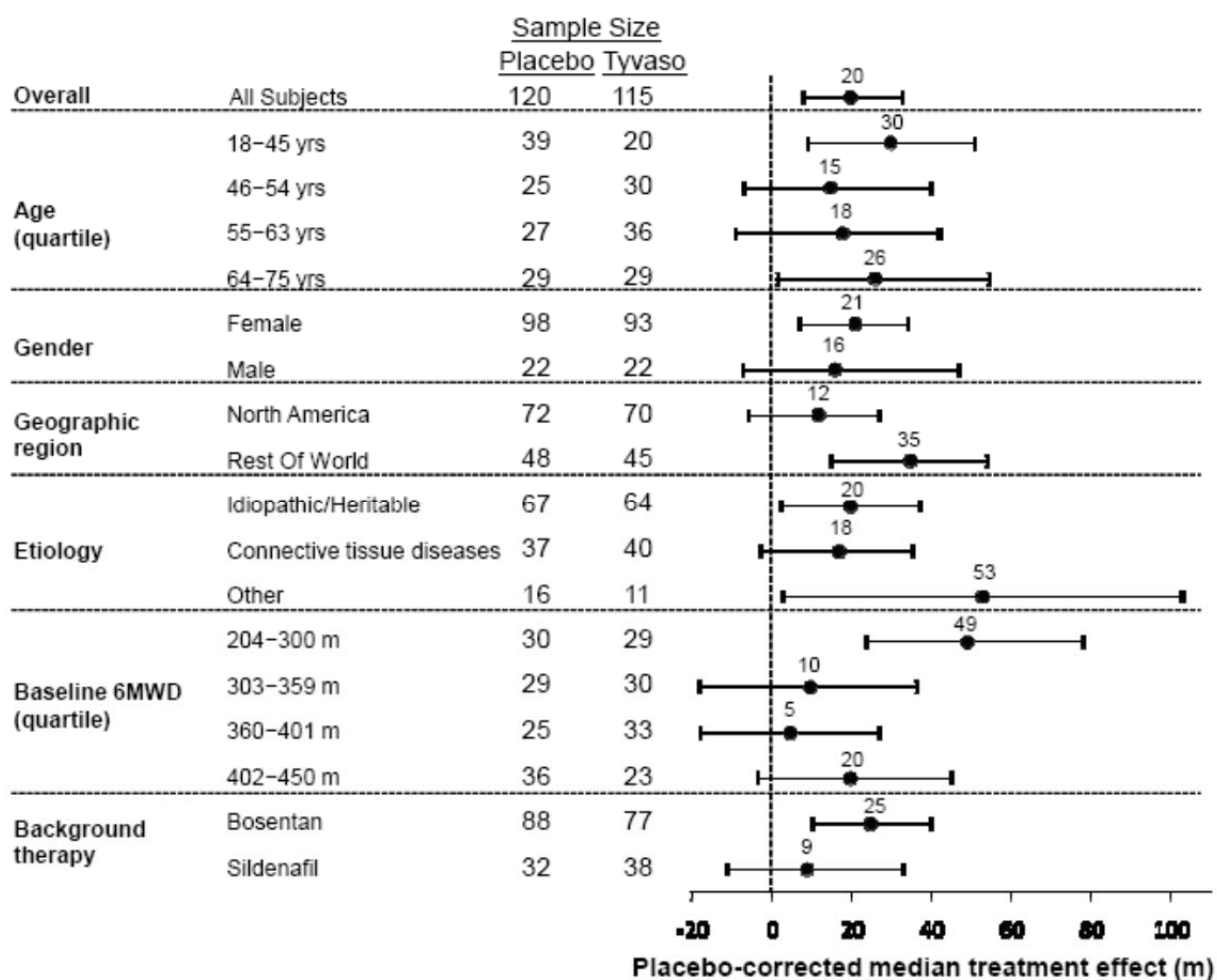


Figure 2. Placebo Corrected Median Treatment Effect (Hodges-Lehmann estimate with 95% CI) on 6MWD Change from Baseline at Week 12 During Peak Plasma Concentration of Tyvaso for Various Subgroups

## 14.2 Long-term Treatment of PAH

In long-term follow-up of patients who were treated with Tyvaso in the pivotal study and the open-label extension (N=206), Kaplan-Meier estimates of survival at 1, 2, and 3 years were 97%, 91%, and 82%, respectively. These uncontrolled observations do not allow comparison with a control group not given Tyvaso and cannot be used to determine the long-term effect of Tyvaso on mortality.

## 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 a 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 a 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)

Tyvaso 4 Pack Carton with one foil pouch containing four 2.9 mL ampules. Each ampule contains 1.74 mg treprostinil (0.6 mg per mL). (NDC 66302-206-03).

Tyvaso Inhalation System Institutional Starter Kit containing a 4 ampule carton of Tyvaso [one foil pouch containing four 2.9 mL ampules. Each ampule contains 1.74 mg treprostinil (0.6 mg per mL)] and the Tyvaso Inhalation System. (NDC 66302-206-04).

## 17 PATIENT COUNSELING INFORMATION

- See the FDA-approved patient labeling (Patient Package Insert and Instructions for Use).

Patients should be properly trained in the administration process for Tyvaso, including dosing, Tyvaso Inhalation System 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 Tyvaso Inhalation System 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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Tyvaso manufactured for:

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