

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 per session 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)
- Tyvaso may cause symptomatic hypotension. (5.2)
- Tyvaso inhibits platelet aggregation and increases the risk of bleeding. (5.4)
- Tyvaso dosage adjustments may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn. (5.5, 7.3)
- 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 FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

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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 an ultrasonic, pulsed delivery device and its accessories.

Tyvaso is dosed in 4 separate, equally spaced treatment sessions per day, during waking hours. Each treatment session will take 2 to 3 minutes. 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 per treatment session at approximately 1- to 2-week intervals, if tolerated, until the target dose of 9 breaths (54 mcg of treprostinil) is reached, 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* (7.3) 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, dizziness, 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 $\geq 4\%$ 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 2.3 years, with a maximum exposure of 5.4 years. Eighty-nine percent (89%) of patients achieved the target dose of nine breaths, four times daily. Forty-two percent (42%) 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 vs. 10.9 per 100 patient-years), throat irritation (4.5 vs. 1.2 per 100 pt-years), nasal discomfort (2.6 vs. 1.3 per 100 pt-years), and hemoptysis (2.5 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 post-approval 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

7.1 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.

7.2 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.

7.3 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)*].

7.4 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

Risk Summary

Limited case reports of treprostinil use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. However, there are risks to the mother and the fetus associated with pulmonary arterial hypertension (see *Clinical Considerations*). In animal studies, no adverse reproductive and developmental effects were seen for treprostinil at ≥ 9 and ≥ 145 times the human exposure when based on C_{max} and AUC following a single treprostinil dose of 54 mcg, respectively.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and embryo-fetal risk

Pulmonary arterial hypertension is associated with an increased risk of maternal and fetal mortality.

Data

Animal reproduction studies have been conducted with treprostinil via continuous subcutaneous administration and with treprostinil diolamine administered orally. In pregnant rats, continuous subcutaneous infusions of treprostinil during organogenesis and late gestational development, at doses as high as 900 ng treprostinil/kg/min (about 117 times the starting human subcutaneous infusion rate, on a ng/m² basis and about 16 times the average rate achieved in clinical trials), resulted in no evidence of harm to the fetus. In pregnant rabbits, effects of continuous subcutaneous infusions of treprostinil during organogenesis were limited to an increased incidence of fetal skeletal variations (bilateral full rib or right rudimentary rib on lumbar 1) associated with maternal toxicity (reduction in body weight and food consumption) at a dose of 150 ng treprostinil/kg/min (about 41 times the starting human subcutaneous infusion rate, on a ng/m² basis, and 5 times the average rate used in clinical trials). In rats, continuous subcutaneous infusion of treprostinil from implantation to the end of lactation, at doses of up to 450 ng treprostinil/kg/min, did not affect the growth and development of offspring. In studies with orally administered 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 Tyvaso 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 Tyvaso dose of 54 mcg, respectively. No treprostinil treatment-related effects on labor and delivery were seen in animal studies. Animal reproduction studies are not always predictive of human response.

8.2 Lactation

Risk Summary

There are no data on the presence of treprostinil in human milk, the effects on the breastfed infant, or the effects on milk production.

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

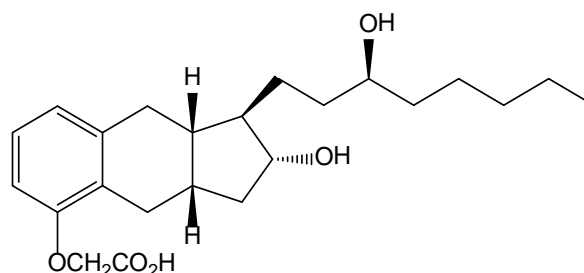
In general, symptoms of overdose with Tyvaso include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Provide general supportive care until the symptoms of overdose have resolved.

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 390.52 and a molecular formula of C₂₃H₃₄O₅.

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-hydroxyloctyl 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.

Specific 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/m² 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.

13.4 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 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.

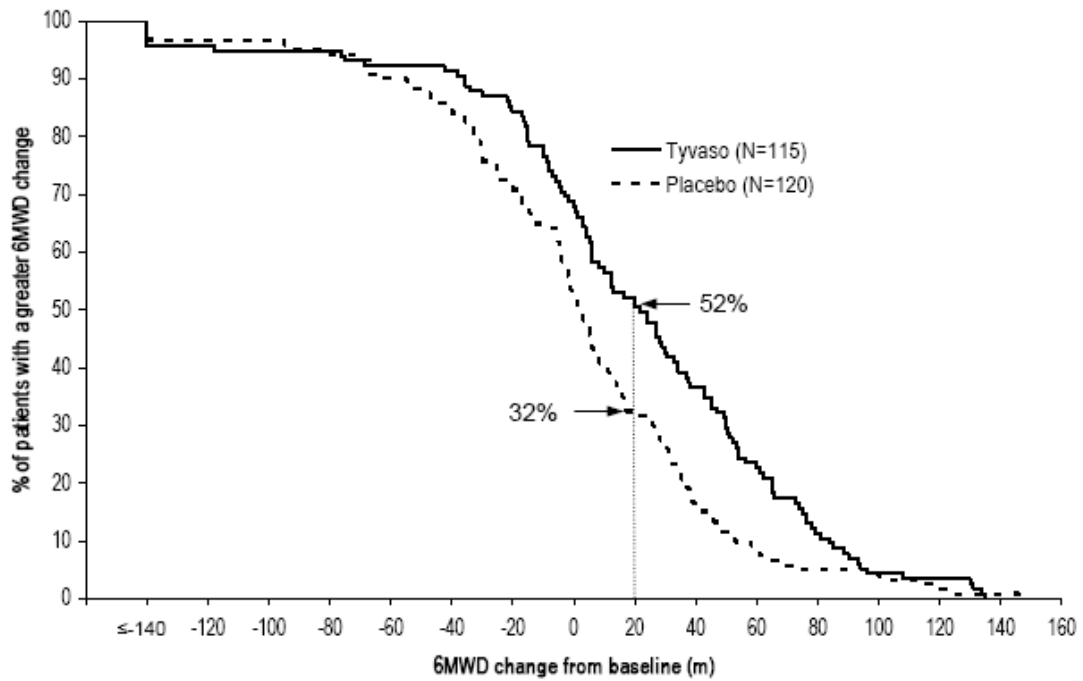


Figure 1: Distributions of 6MWD Changes from Baseline at Week 12 during Peak Plasma Concentration of Tyvaso

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).

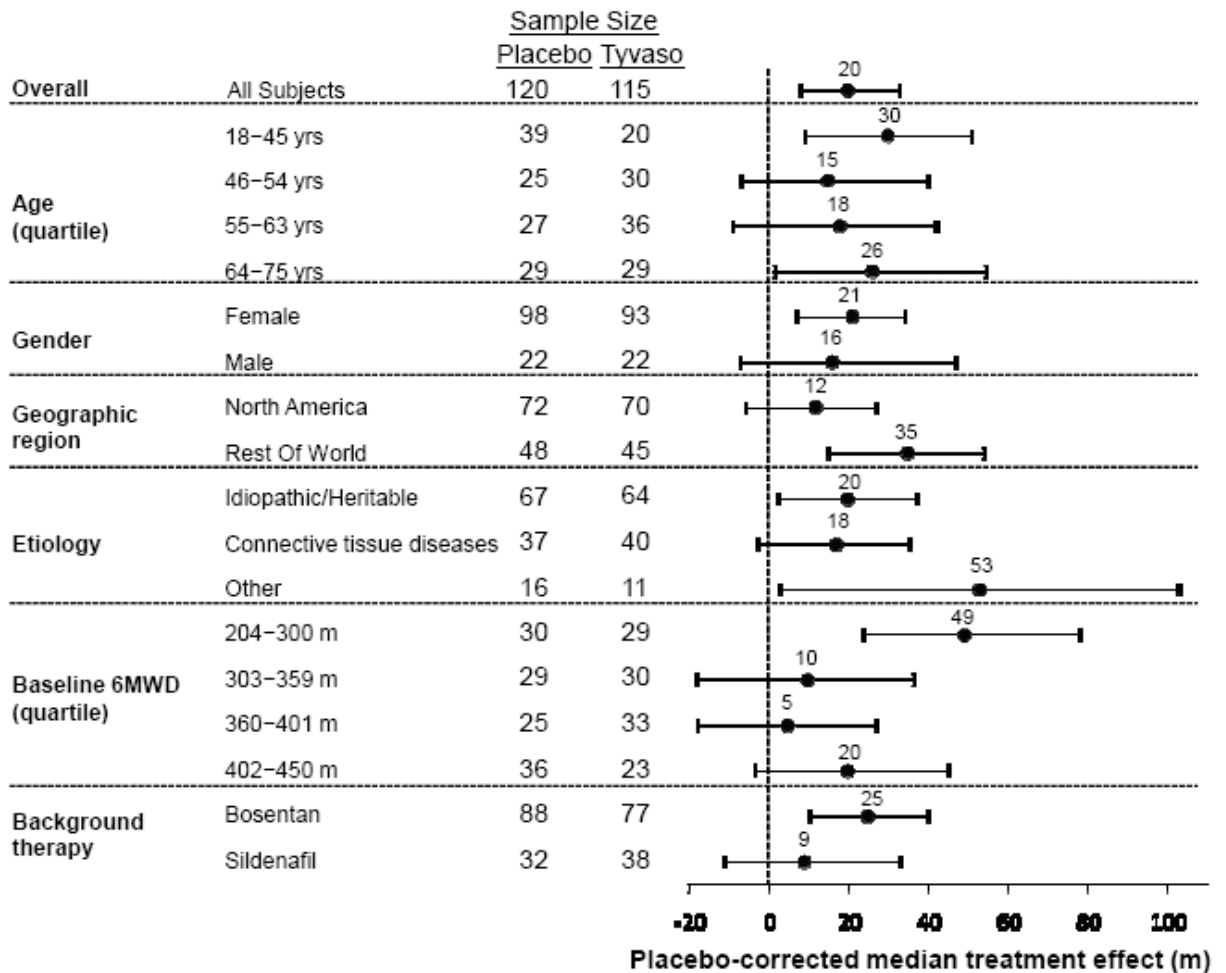


Figure 2. Placebo Corrected Median Treatment Effect (Hodges-Lehmann estimate with 95% CI) on 6MWD Change from Baseline at Week 12 During Peak Plasma Concentration of Tyvaso for Various Subgroups

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

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Train patients 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, resume therapy as soon as possible [*see Dosage and Administration (2.1)*].

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:

United Therapeutics Corp.
Research Triangle Park, NC 27709

PATIENT INFORMATION

**Tyvaso (Ti-vāsō)
(treprostinil)
inhalation solution**

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 exercise. Your ability to exercise decreases 4 hours after treatment with Tyvaso.

It is not known if Tyvaso is safe and effective in children under 18 years of age.

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
- have bleeding problems
- are pregnant or plan to become pregnant. It is not known if Tyvaso will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Tyvaso passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with Tyvaso.

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

Especially tell your healthcare provider if you take:

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

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?

- **See the detailed “Instructions for Use Manual” that comes with your Tyvaso Inhalation System for instructions on how to take Tyvaso the right way.**
- Tyvaso must be used only with the Tyvaso Inhalation System.
- Do not mix Tyvaso with other medicines in the Tyvaso Inhalation System.
- Take Tyvaso exactly as your healthcare provider tells you to. Your healthcare provider may change your dose if needed.
- Do not swallow Tyvaso inhalation solution.
- Tyvaso is breathed in (inhaled) through your mouth into your lungs. Tyvaso is taken in 4 separate treatment sessions every day during waking hours. The sessions should be at about 4 hours apart.
- Each treatment session will take 2 to 3 minutes.
- Avoid getting Tyvaso solution in your eyes or onto your skin. If you get Tyvaso in your eyes or on your skin, rinse your skin or eyes right away with water.
- If you miss a dose of Tyvaso, take your usual dose as soon as possible.
- If you take too much Tyvaso, call your healthcare provider or go to the nearest hospital emergency room right away.
- To avoid a possible delay in your Tyvaso treatment, you should always have access to a back-up Tyvaso Inhalation System device.

What are the possible side effects of Tyvaso?

Tyvaso can cause serious side effects, including:

- **Low blood pressure (symptomatic hypotension).** If you have low blood pressure, Tyvaso may lower your blood pressure more.
- **Bleeding problems.** Tyvaso may increase the risk of bleeding in people who take blood thinners (anticoagulants).

The most common side effects of Tyvaso include:

- | | |
|------------------------------|--|
| • cough | • headache |
| • nausea | • reddening of your face and neck (flushing) |
| • dizziness | • diarrhea |
| • throat irritation and pain | • fainting or loss of consciousness |

These are not all the possible side effects of Tyvaso.

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

How should I store Tyvaso?

- Store at 25°C (77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
- Store Tyvaso ampules in the unopened foil pouch and out of the light until you are ready to use them.
- If unopened and stored in the foil pouch, Tyvaso ampules can be used until the expiration date printed on the pouch. Do not use Tyvaso ampules past the expiration date printed on the pouch.
- Tyvaso ampules should be used within 7 days after opening the foil pouch.
- Tyvaso can be kept in the Tyvaso Inhalation System medicine cup for no more than 1 day. Throw away any remaining Tyvaso that is left in the medicine cup at the end of the day.

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 purposes other than those listed 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. You can ask your healthcare provider or specialty pharmacist for information about Tyvaso that is written for health professionals.

What are the ingredients in Tyvaso?

Active ingredient: treprostinil

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

Manufactured by: United Therapeutics Corp., Research Triangle Park, NC 27709 USA

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For more information, go to www.tyvaso.com or call 1-877-864-8437.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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