CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-387

LABELING

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 (WHO Group I) in patients with NYHA Class III symptoms, to increase walk distance. (1)

----------DOSAGE AND ADMINISTRATION----------

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

----------DOSAGE FORMS AND STRENGTHS----------

Sterile solution for oral inhalation: 2.9 mL ampule containing 1.74 mg treprostinil (0.6 mg per mL). (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

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- Tyvaso dosage adjustments may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn.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

----------ADVERSE REACTIONS----------

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

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

----------DRUG INTERACTIONS----------

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

----------USE IN SPECIFIC POPULATIONS----------

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

See 17 for PATIENT COUNSELING INFORMATION.

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

Revised: [July/2009]

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

Tyvaso™ (treprostinil) inhalation solution

For Oral Inhalation Only

1 INDICATIONS AND USAGE

Tyvaso is indicated to increase walk distance in patients with WHO Group I pulmonary arterial hypertension and NYHA Class III symptoms. 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 I and nearly all NYHA Functional Class III), the most commonly reported adverse reactions on Tyvaso included: cough and throat irritation; headache, gastrointestinal effects, muscle, jaw or bone pain, flushing and syncope. Table 1 lists the adverse reactions that occurred at a rate of at least 4% and were more frequent in patients treated with Tyvaso than with placebo.

Table 1: Adverse Events in ≥ 4% of PAH Patients Receiving Tyvaso and More Frequent* than Placebo

Adverse Event	Treatment n (%)	
	Tyvaso n = 115	Placebo n = 120
Cough	62 (54)	35 (29)
Headache	47 (41)	27 (23)
Throat Irritation / Pharyngolaryngeal Pain	29 (25)	17 (14)
Nausea	22 (19)	13 (11)
Flushing	17 (15)	1 (<1)
Syncope	7 (6)	1 (<1)

*More than 3% greater than placebo

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

Adverse Events Associated with Route of Administration

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

7 DRUG INTERACTIONS

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

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

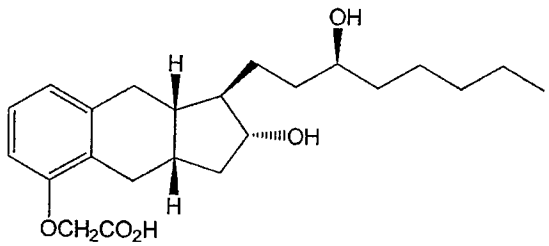
In general, symptoms of overdose with Tyvaso include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Provide general supportive care until the symptoms of overdose have resolved.

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 $C_{23}H_{34}O_5$.

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.

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 ng/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 ng/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 ng/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 μg/kg/day were administered); whereas 107 μg/kg/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 I), nearly all with NYHA Class III 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/familial (56%), secondary to collagen vascular disease (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.

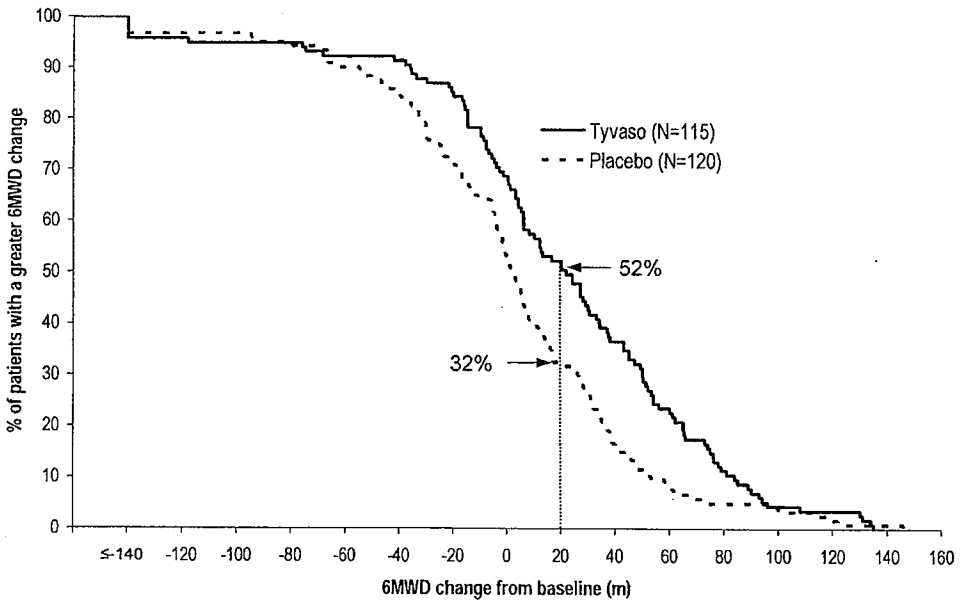


Figure 1: Distributions of 6MWD Changes from Baseline at Week 12 during Peak Plasma Concentration of Tyvaso

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).

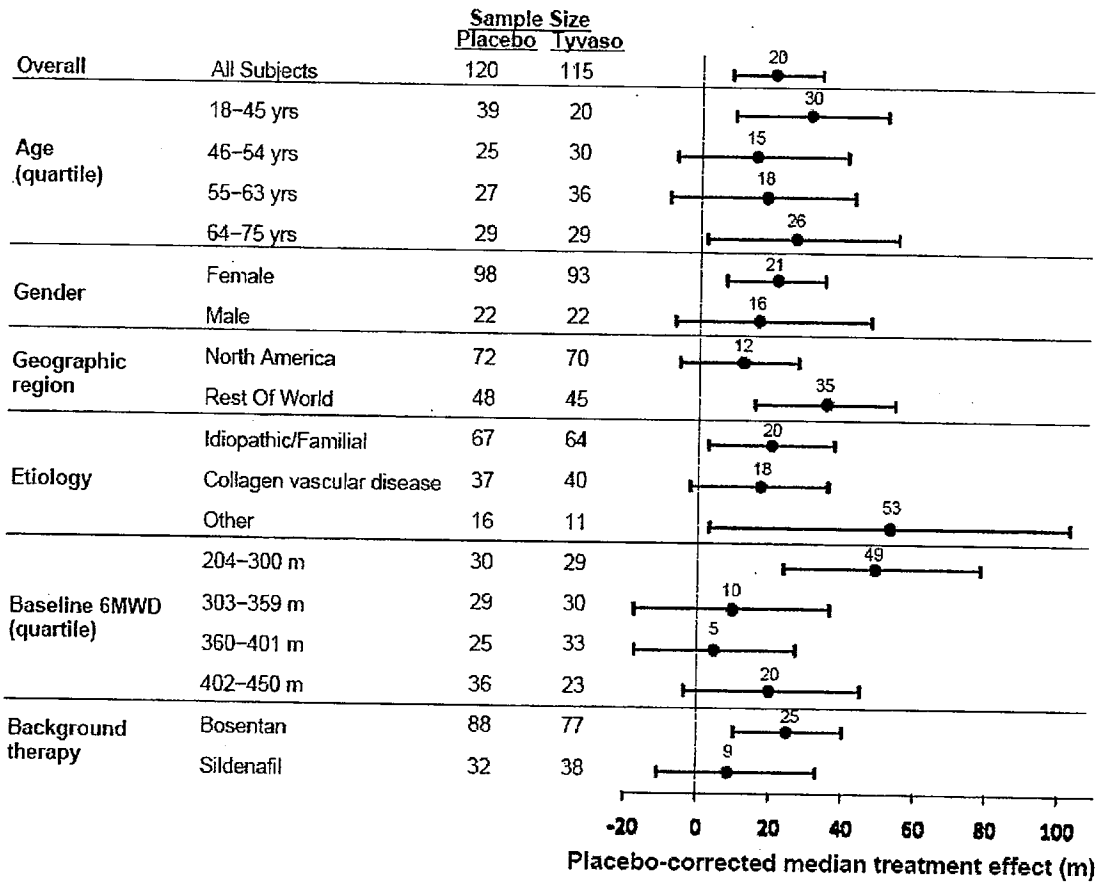


Figure 2. Placebo Corrected Median Treatment Effect (Hodges-Lehmann estimate with 95% CI) on 6MWD Change from Baseline at Week 12 During Peak Plasma Concentration of Tyvaso for Various Subgroups

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)]*.

US Patent No. 5,153,222
US Patent No. 6,765,117
US Patent No. 6,521,212
US Patent No. 6,756,033

United Therapeutics Corp.
Research Triangle Park, NC 27709

Tyvaso manufactured by:

Catalent Pharma Solutions
Woodstock, IL 60098

For United Therapeutics Corp.
Research Triangle Park, NC 27709

July 2009

PATIENT PACKAGE INSERT

Tyvaso (Tī-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 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.

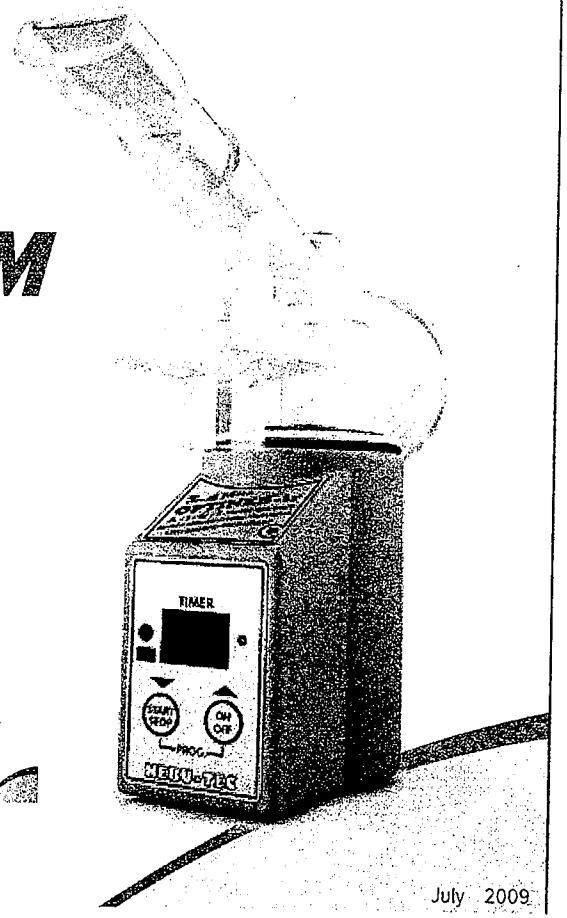
Tyvaso is jointly marketed by United Therapeutics Corporation and Lung Rx, Inc.

Literature issued July 2009

United Therapeutics Corp.
Research Triangle Park, NC 27709 USA

TYVASO™ INHALATION SYSTEM

Instructions for Use



TYVASO™ treprostinil INHALATION SOLUTION

July 2009

Table of Contents

General Instructions

The TYVASO™ Inhalation System should be handled with care.

Follow these important instructions to ensure proper use:

- Always unplug the device after each use.
- Do not immerse the device in water or other liquids.
- Do not place the device in a microwave or regular oven.
- Do not leave the device alone with a small child.
- Do not use the device near flammable liquids and materials or heated surfaces.
- Pay special attention to the instructions to help prevent damage to your TYVASO Inhalation System and help you get the best results.
- This device should only be used on the order of your doctor or licensed healthcare practitioner.

Introduction

Your doctor has prescribed TYVASO™ (treprostinil) Inhalation Solution. Please see the accompanying Patient Package Insert for important safety information on TYVASO.

TYVASO is breathed in (inhaled) using the TYVASO Inhalation System, which consists of the OPTINEB®-ir Model ON-100/7 device and its accessories.

These Instructions for Use (IFU) for the TYVASO Inhalation System provide important safety information. It is important that you read these instructions and the TYVASO Patient Package Insert (PPI) before setting up and using the TYVASO Inhalation System. If you have any questions, talk to your doctor or specialty pharmacy provider.

Before beginning treatment with TYVASO, you will receive a Patient Starter Kit containing a 28 day supply of TYVASO and 2 complete inhalation devices (all accessories and supplies included). When you refill your prescription for TYVASO each month, you will receive a Refill Kit that contains a 28 day supply of TYVASO and new accessories. You will receive a replacement device every 2 years.

IMPORTANT

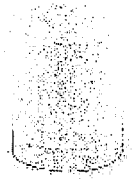
- **Do not start treatment with TYVASO until you have been trained to use the TYVASO Inhalation System. Make sure you understand all of the directions. Always ask your doctor or specialty pharmacy provider if you are unsure of anything you are taught.**
- **TYVASO is for use only with the TYVASO Inhalation System.**

Preparing for Treatment With TYVASO

Gather the following supplies before starting treatment. Note: supplies are not shown to scale.

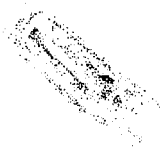
1. Inhalation device

2. Measuring cup with 45 mL of distilled water



Use only distilled water to fill your inhalation device once per day.

3. One TYVASO ampule



Use one ampule per day.

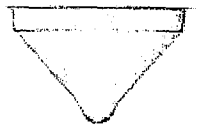
4. One of the provided power sources

AC wall plug

Rechargable battery

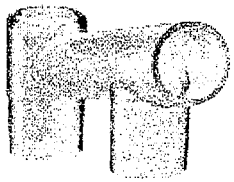
12V DC car adapter

5. Accessories

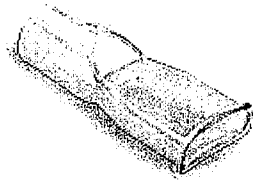


Medicine cup*

Dome assembly
with baffle plate inside*

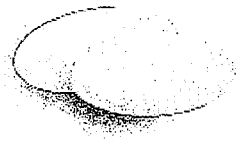


Inhalation piece*



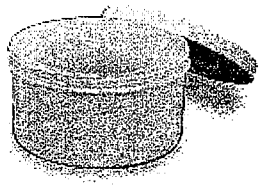
Mouthpiece*

2 Filter shells*

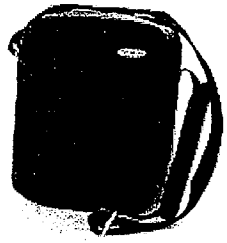


Filters (use 2 per day)*

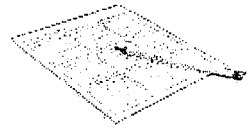
Plugs*



Storage box



Carrying case



Tracking sheet

Nose clip (optional)

Note: Supplies are not shown to scale.
* These accessories are replaced every month. Replacement accessories are included in the Monthly Refill Kit.

Using your TYVASO™ Inhalation System
Filling the Inhalation Device Chamber and Medicine Cup

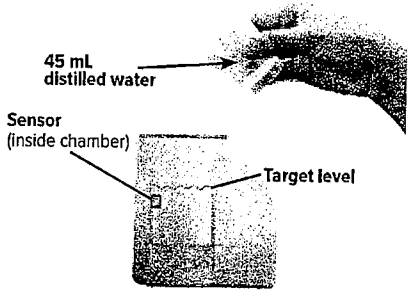
Before using the TYVASO Inhalation System, you should:

- Wash your hands

- Make sure the device is **NOT** connected to a power source
- Make sure the device is resting on a hard, flat surface during assembly

1

Fill the chamber of the device with 45 mL of distilled water (about 1.5 ounces or 3 tablespoons), using the measuring cup provided.



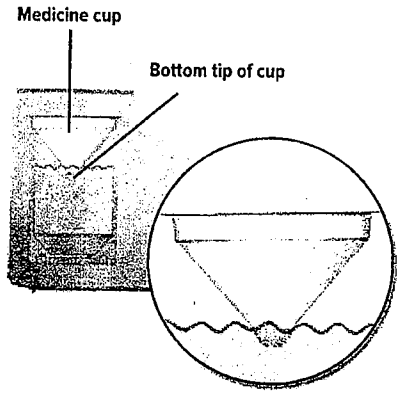
ONLY USE DISTILLED WATER in the device. Distilled water is highly purified water that can be purchased at most grocery stores and pharmacies. It is necessary for the device to function properly. If you use another type of water (such as bottled or tap water), the device may not function properly.

There is a silver sensor on the inside wall of the chamber. This sensor must be completely covered with water. However, DO NOT OVER-FILL the chamber, or the medicine cup will not fit correctly.

2

Obtain one medicine cup and inspect it for any holes, cracks, or dents. Do not use the medicine cup if it is damaged.

Insert the empty medicine cup into the chamber of the device, making sure that the cup's bottom tip is in the distilled water.



⚠CAUTION

Make sure you insert only one medicine cup. Inserting multiple cups (possibly stuck together) will prevent the flow of medicine.

3

Carefully tear or cut open the top of the foil pouch, making sure not to cut the ampules. Each pouch contains four (4) ampules.

Remove one (1) ampule of TYVASO. Keep unused ampules in the foil pouch because the TYVASO medicine is sensitive to light.

One ampule contains enough medicine for one day of treatment no matter how many breaths your doctor has prescribed.

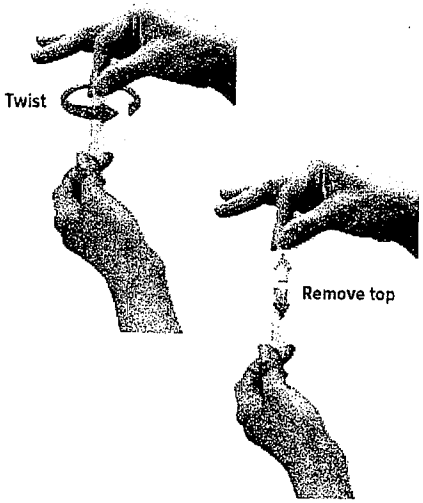
⚠ CAUTION

Ampules must be used within 7 days of opening foil pouch.

Discard any unused ampules after 7 days.

4

Gently hold the ampule and twist off its top.



⚠ CAUTION

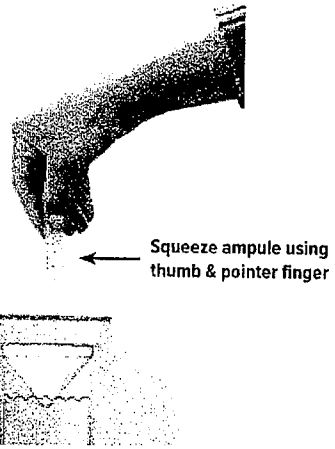
If any medicine from the ampule spills on your hands, wash your hands immediately.

Medicine contact with the skin can cause irritation.

5

Point the ampule straight down toward the medicine cup's center to avoid spills.

Gently squeeze the ampule's entire contents into the medicine cup. Squeeze repeatedly until ampule is empty.



Using your TYVASO™ Inhalation System
Assembling the Accessories of the Inhalation Device

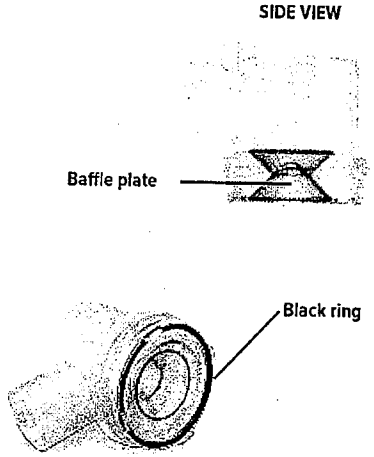
The TYVASO™ Inhalation System is made so the parts only fit together properly one way.

When the device is assembled correctly, the parts should fit together easily.
Do not force the parts together.

1

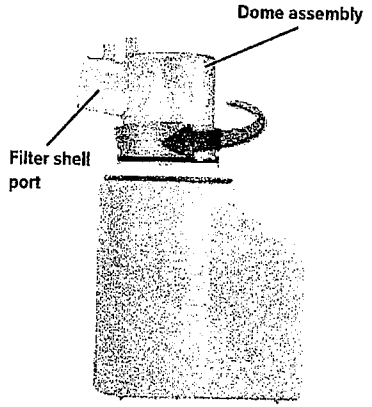
Make sure the blue plastic baffle plate and black ring are correctly placed in the center of the dome assembly. They should appear as they do in the image below.

If the baffle plate is loose or disconnected, secure it by gently pressing it into the bottom opening of the dome assembly before proceeding.



2

Screw the dome assembly onto the device clockwise (right) until you hear a click, indicating the dome assembly is fully connected to the medicine cup. Start with the filter shell port facing the back of the device.

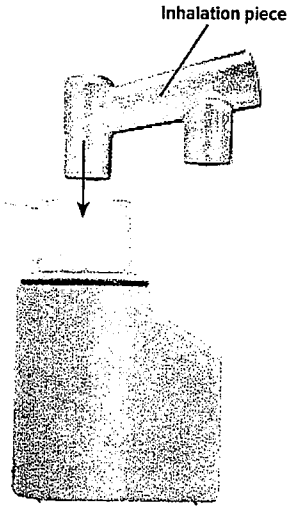


IMPORTANT

The dome assembly "clicks" only the first time it connects to the medicine cup. If you then realign the dome assembly you will not hear another click.

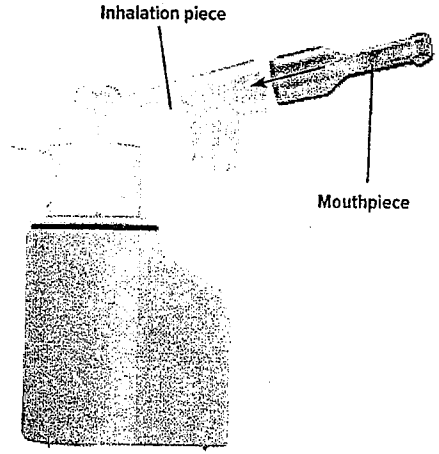
3

Insert the inhalation piece into the upper opening of the dome assembly.



4

Insert the mouthpiece into the inhalation piece.



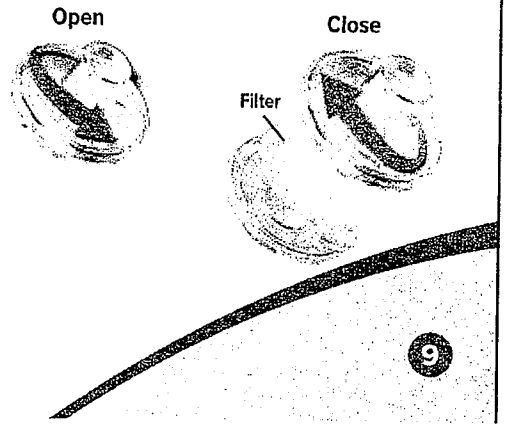
5

Each day you will need to use a new filter in each filter shell.

To install a new filter:

- Open the filter shell by unscrewing the two halves.
- Place a new filter in one of the filter shell halves.
- Close the filter shell by screwing the two halves together until you can twist no further.

Note: New filter shells come with fresh filters already installed.

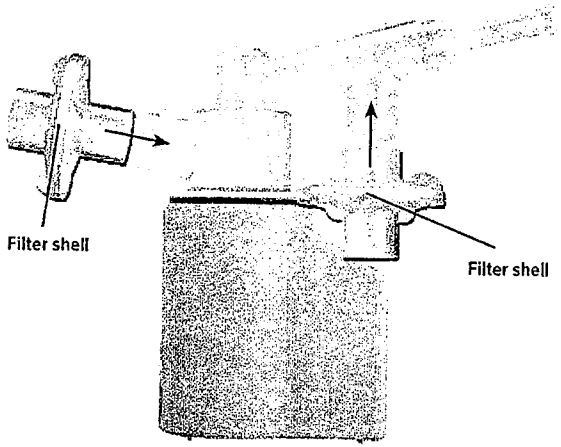


Assembling the Accessories of the Inhalation Device (continued)

6

Insert one of the filter shells into the filter shell port on the side of the dome assembly and insert the other filter shell into the port on the bottom of the inhalation piece. The two filter shells are identical and can be used in either opening.

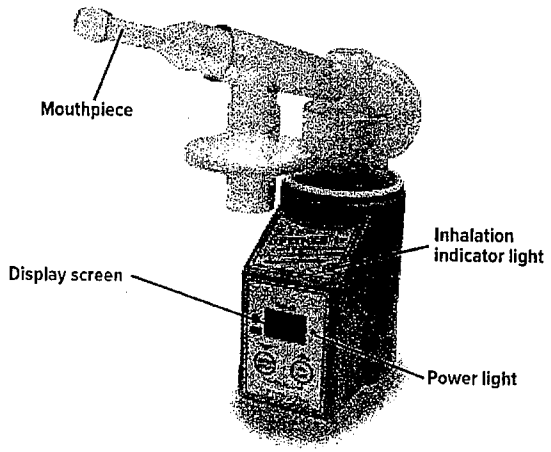
Make sure to insert the filter shells straight into their ports, rather than at an angle. If necessary, rotate the inhalation piece so you can insert the filter shell without the device getting in the way.



7

When the device is fully assembled, it should appear as it does in the photo below.

Rotate the inhalation piece so you can best see the indicator lights and display screen, which provide important prompts during your treatment.

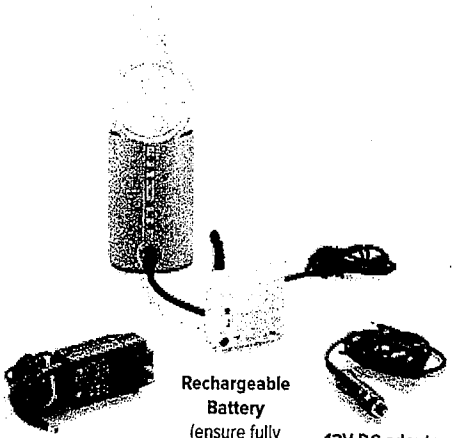


Inhaling Your Medicine, TYVASO™ (treprostinil) Inhalation Solution

You will inhale TYVASO during 4 treatment sessions each day. During each treatment session, you will take a series of breaths, called a "cycle," through the mouthpiece of the TYVASO™ Inhalation System. Each cycle equals 3 breaths of medicine.

1

Connect your device to one of the power source options by plugging one end of the power cord into the back of the inhalation device and the other end into the power source.



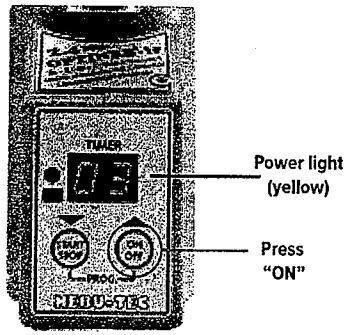
AC wall plug
(plugs into standard wall outlet)

Rechargeable Battery
(ensure fully charged)

12V DC adapter
(for use with car power source)

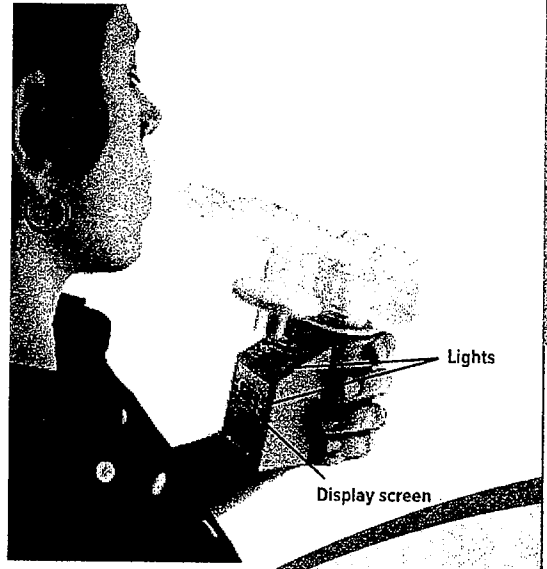
2

Turn on the device by pressing the ON/OFF button once (do not hold).
When the power is on, the display screen will show "03," and a yellow light will turn on next to the screen.



3

Hold the device as shown below, so that your hands do not cover the display screen or lights and that you can follow the visual prompts.



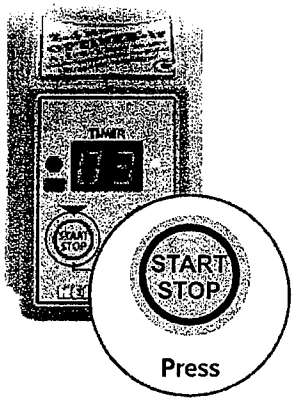
Inhaling Your Medicine, TYVASO™ (treprostinil) Inhalation Solution (continued)

4

Perform steps A-G to complete one cycle of breaths (3 breaths).
Follow the instructions exactly to make sure you receive the correct medication dose.

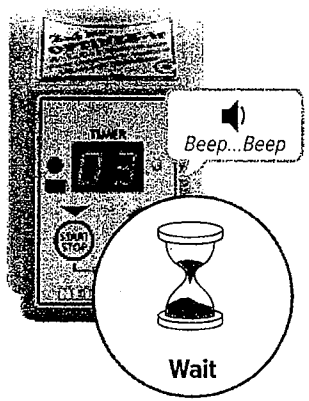
IMPORTANT
1 cycle = 3 breaths.

A



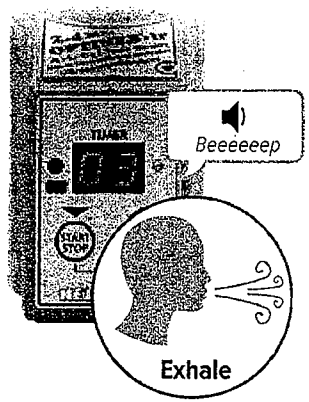
Press the START/STOP button to begin treatment.

B



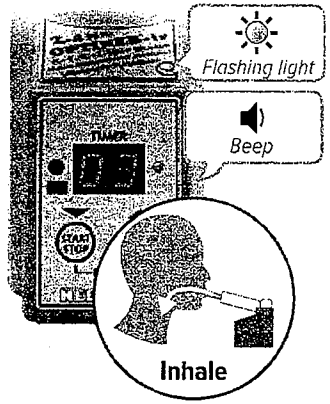
The power light turns green and the device emits two (2) short beeps.

C



While the device emits one (1) long beep, exhale completely.

D



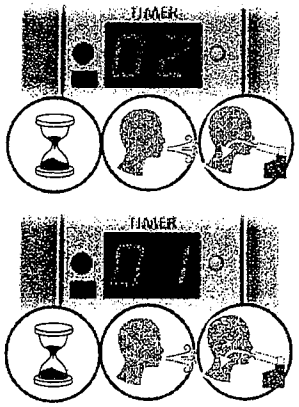
After the device emits a short beep and while the inhalation indicator light is flashing green and the device emits a beep, place your lips securely around the mouthpiece and inhale deeply.

⚠ CAUTION

If medicine is flowing you should feel or taste it in your mouth.

If you do not feel or taste any medicine, the TYVASO system might be set up incorrectly. See Troubleshooting section, pages 25-26, for details.

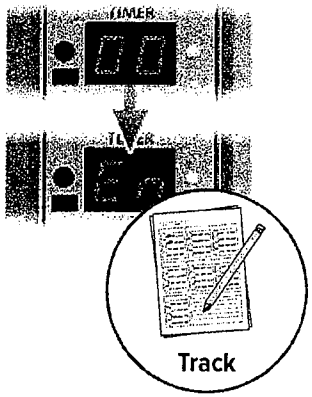
E



Repeat steps B through D two (2) more times.

The display screen will count down from "03" to "02" to "01".

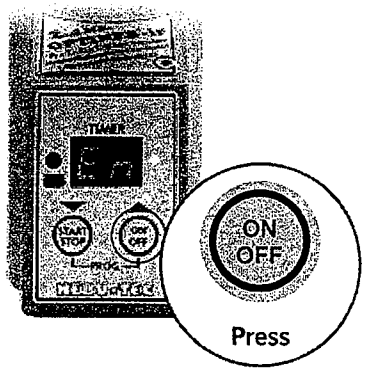
F



After the third breath of the cycle, the display screen will show "00" then "En," indicating the 3 breath cycle is complete.

Record on the tracking sheet the number of breaths you inhaled.

G



Press the "ON/OFF" button to turn off the device.

See the next page for instructions on how to take multiple cycles of breaths.

To pause the treatment between breaths during a cycle, press the START/STOP button.

The display screen will show "PA."

To resume treatment, press START/STOP again.

If treatment is interrupted for any reason (for example, a power failure), first record the number of breaths you inhaled. Second, reset the device to begin a new cycle, then inhale only the number of breaths needed to complete the interrupted cycle.

Inhaling Your Medicine, TYVASO™ (treprostinil) Inhalation Solution (continued)

If your treatment session requires more than 1 cycle of breaths (1 cycle equals 3 breaths), press the ON/OFF button at the end of a cycle of breaths to turn the device back on and take an additional cycle of breaths.

Repeat the inhalation steps (steps A through G) until you reach your prescribed number of breaths.

The recommended prescribed dose of TYVASO is up to 9 breaths (54 micrograms) per treatment session and up to 4 treatment sessions per day.

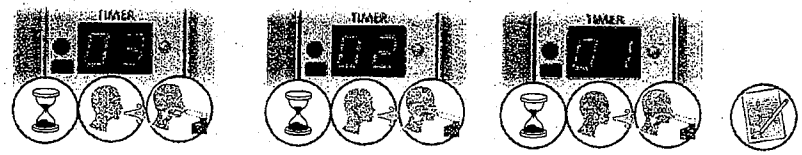
For example, if your doctor prescribed 9 breaths per treatment session, you would take 3 cycles of 3 breaths each to complete a treatment session.

IMPORTANT

After each cycle, record the number of breaths you inhaled to ensure that you receive the proper dose of medicine.

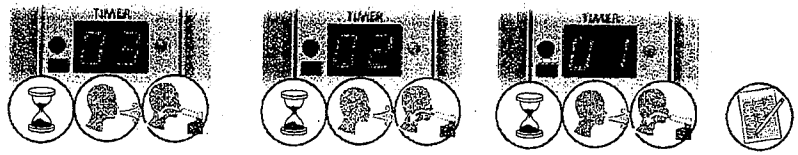
Example treatment session: 9 breaths (3 breaths = 1 cycle)

1st cycle



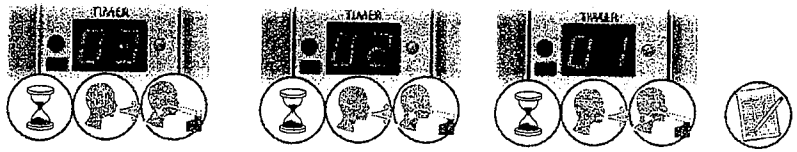
Press ON/OFF twice, then START/STOP to begin next cycle

2nd cycle



Press ON/OFF twice, then START/STOP to begin next cycle

3rd cycle



Press ON/OFF once to turn off device

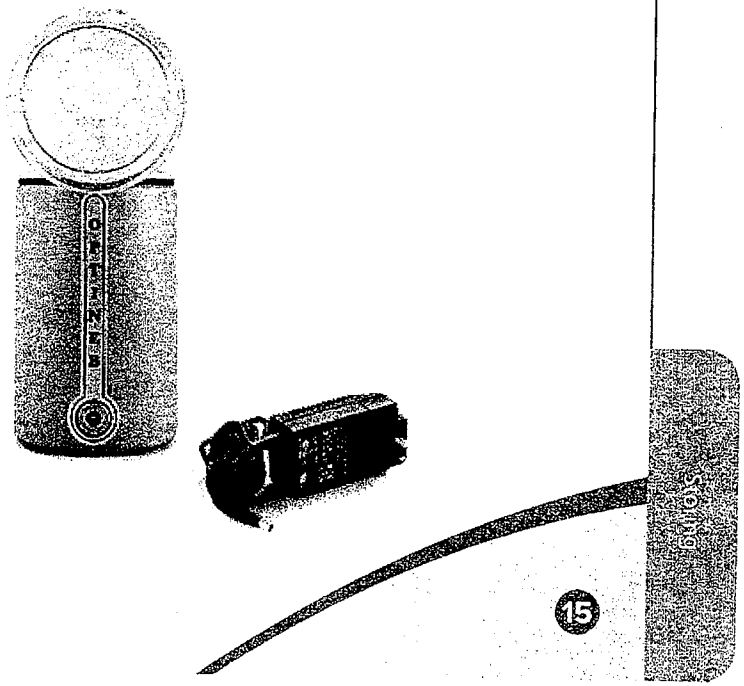
Storing the TYVASO™ Inhalation System Between Treatment Sessions

If you have more treatment sessions left in the day, perform the following steps.

If you have completed your last treatment session of the day, skip to *Cleaning and Maintenance of the TYVASO Inhalation System*.

1

Disconnect the device from its power source.

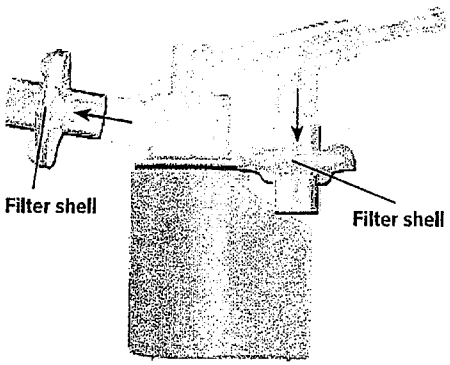


Storing the TYVASO™ Inhalation System Between Treatment Sessions (continued)

2

After finishing a treatment session, remove both filter shells.

Do NOT remove filters from filter shells until the last treatment session of the day.

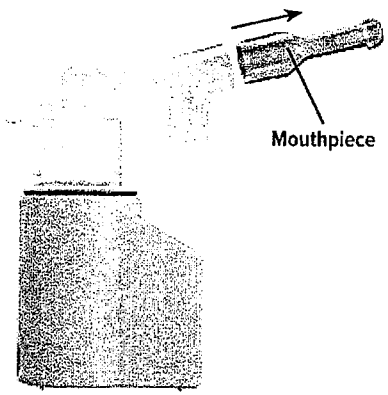


IMPORTANT

When removing accessories between treatment sessions, hold the device by its base to avoid spilling the medicine.

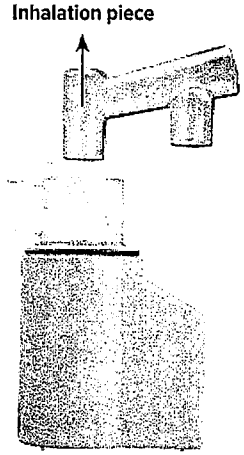
3

Remove the mouthpiece.



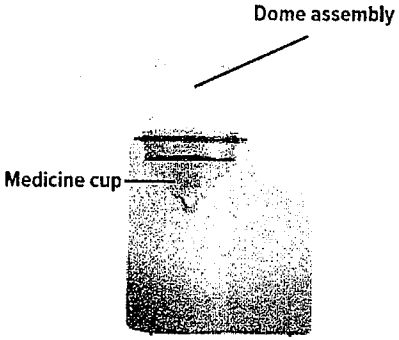
4

Remove the inhalation piece.



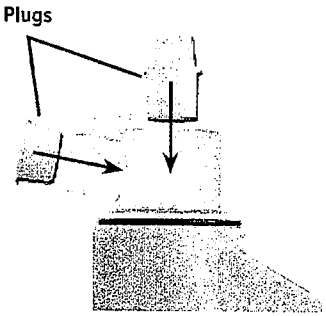
5

Leave the dome assembly and medicine cup (with the medicine still in it) connected to the device.



6

Insert a plug into each of the open holes on the dome assembly to prevent the medicine from spilling out.

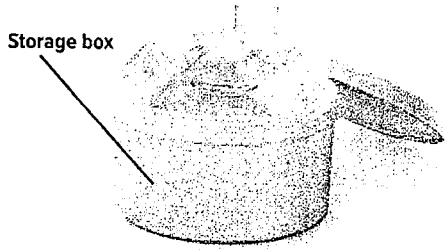


IMPORTANT

If the plugs are not in place, the medicine may spill. If you spill any medicine, start over with a new ampule. You should also replace the filters as medicine may have spilled on them.

7

Place the filter shells, inhalation piece and mouthpiece in the storage box provided to avoid losing or damaging them.



IMPORTANT

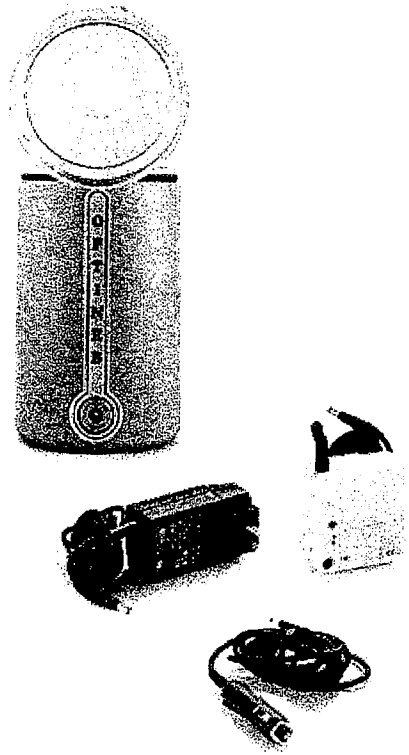
Store the inhalation device in an upright position until the next treatment session.

You can place all components of the inhalation system in the carrying case until next use.

Cleaning and Maintenance of the TYVASO™ Inhalation System
End of Day Cleaning of the Accessories

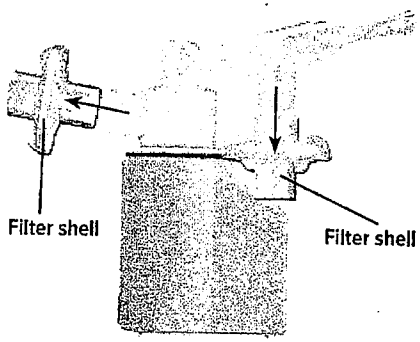
1

Disconnect the device from the power source.



2

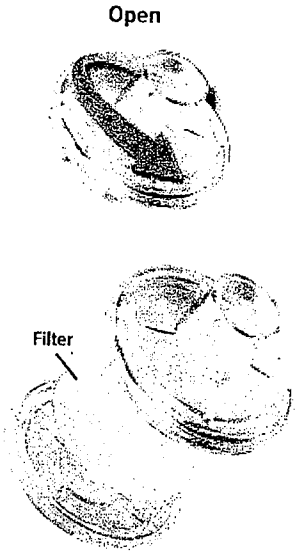
Remove both filter shells.



3

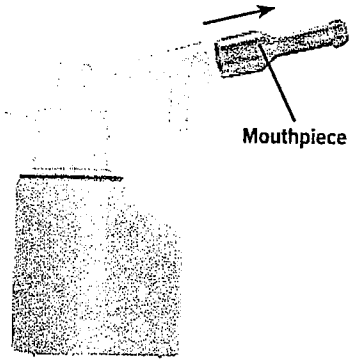
Open the filter shells by twisting in opposite directions.

Remove and discard the used filters.



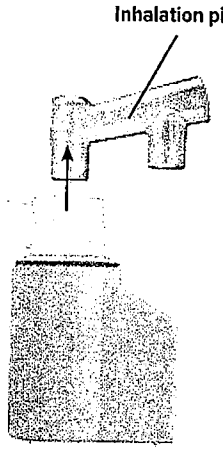
4

Remove the mouthpiece.



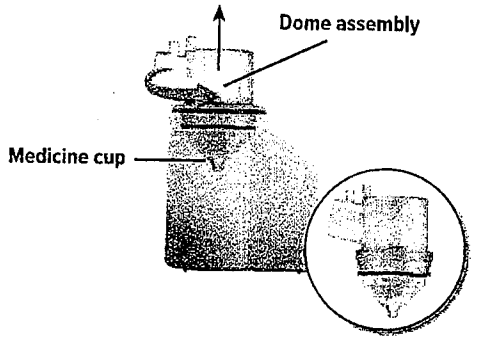
5

Remove the inhalation piece.



6

Remove the dome assembly by turning it counter- clockwise (to the left). The medicine cup will stay attached to the dome assembly.



⚠ CAUTION

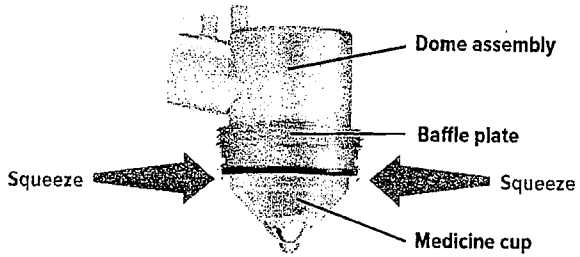
If any medicine from the medicine cup spills on your hands, wash your hands immediately.

Medicine contact with the skin can cause irritation.

End of Day Cleaning of the Accessories (continued)

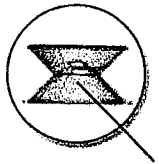
7

Remove the medicine cup by gently squeezing on the sides where it is attached to the dome assembly. Discard the medicine cup. Be careful not to spill the medicine when removing or discarding the medicine cup.



8

Remove the baffle plate by inserting a finger into the top of the dome assembly and gently pushing the baffle plate through the bottom of the dome assembly.

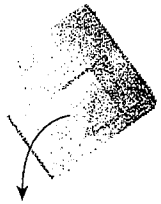


IMPORTANT

Discard the remaining TYVASO™ (treprostinil) Inhalation Solution in an appropriate waste receptacle. Throw away the plastic medicine cup. Do not reuse the medicine cup.

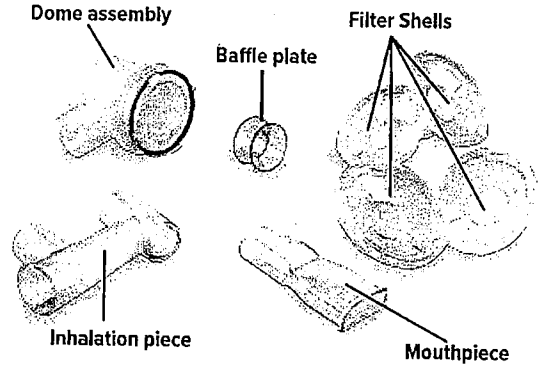
9

Empty the distilled water from the chamber and let the inhalation device air dry upside down.



10

Clean the accessories (pictured below) by hand in mild, soapy, warm water. Allow accessories to air dry.

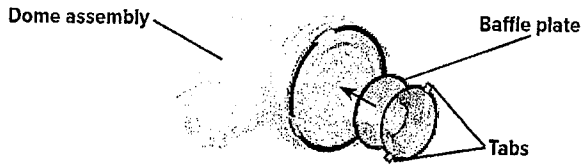


IMPORTANT

Do not place the inhalation device in water or in a dishwasher.

11

Once the accessories are dry, reinsert the baffle plate by gently pressing it into the bottom opening of the dome assembly. The baffle plate only fits in one direction, with its tabs closest to the dome assembly's bottom opening.



IMPORTANT

Make sure the baffle plate snaps completely into the dome assembly. It should sit level and centered in the dome assembly's bottom opening.

12

Store filter shells, inhalation piece, and mouthpiece in the storage box. Store the dome assembly and device in the carrying case until the next day's treatment sessions.

Weekly Cleaning

- Once a week, use a clean cloth to wipe the interior of the inhalation device chamber.

Monthly Refill Kit

- Once a month, you will receive a refill kit that will come with a new set of accessories from your specialty pharmacy provider (appropriately discard the used dome assembly, inhalation piece, mouthpiece, and 2 filter shells.)

Device Replacement

- The inhalation device should be replaced every two (2) years from your first day of use. Replacement inhalation devices will be supplied by your specialty pharmacy provider.

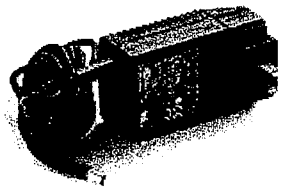
IMPORTANT

All repairs of the TYVASO™ Inhalation System must be performed by the manufacturer. Attempting to alter the device in any way voids the warranty and may cause a malfunction.

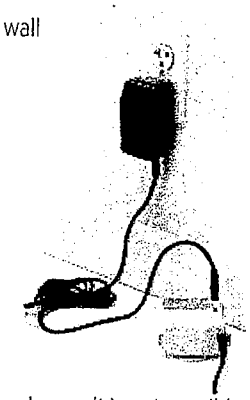
Charging Your TYVASO™ Inhalation System Rechargeable Battery

- Your TYVASO Inhalation System is supplied with a portable, rechargeable battery. Do **NOT** use other batteries.

- Your battery can only be charged using the original AC wall plug that comes with your inhalation device.

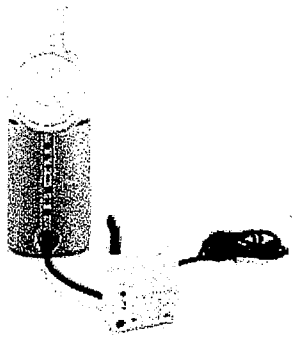


- To charge the battery, connect the AC wall plug to the battery pack and plug the AC wall plug into an outlet.



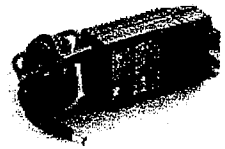
- Your battery may take up to 10 hours to charge. It is not possible to use the TYVASO Inhalation System with the battery while it is recharging.

- You should connect the charged battery to the TYVASO Inhalation System only for your treatment .

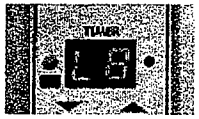


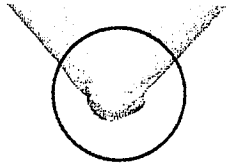
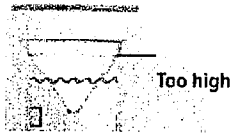
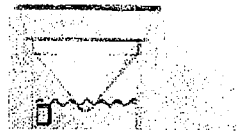
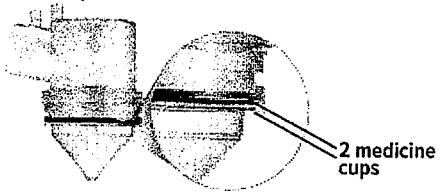
- After your treatment session is complete, remove the power plug of the battery from the device.

- Always have your AC wall plug available for backup if the battery is not charged.

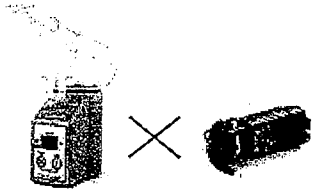
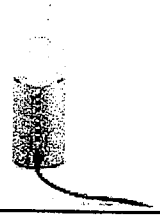
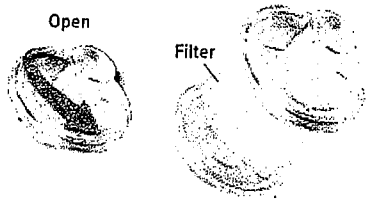


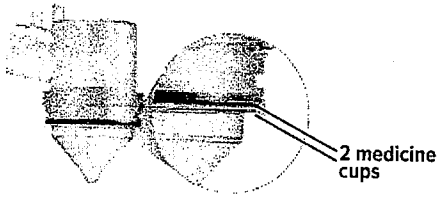
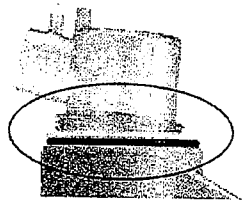
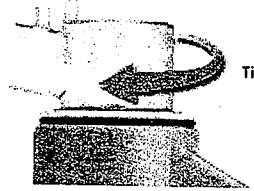
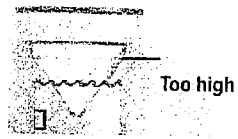
Troubleshooting the TYVASO™ Inhalation System

Problem	Possible causes	Corrective actions
Low battery (LB) 	• Low battery.	• Unplug the battery from the device. Charge the battery by attaching it to the AC wall plug and outlet.
	• Defective adapter (AC wall plug or 12V DC adapter)	• Ensure that the plug is properly connected to an outlet. • If the device is properly plugged in and still does not function, contact your specialty pharmacy provider for a replacement.
Low hydrogen (LH) 	• Distilled water level in the device chamber is too low or the device chamber is empty. 	• Unplug the device from its power source. Empty the device chamber then refill it with 45 mL of distilled water.
	• The distilled water you are using is too purified.	• Empty device chamber. Add 1 teaspoon of tap water to the measuring cup. Fill measuring cup to 45 mL line with distilled water. Pour measuring cup's contents into device chamber.

Problem	Possible causes	Corrective actions
No medicine comes out of the device during a treatment session	• Damaged medicine cup. 	• Unplug the device from its power source. Replace the medicine cup.
	• Distilled water level in the device chamber is too high. 	• Unplug the device from its power source. Empty the device chamber then refill it with 45 mL of distilled water. 
	• Multiple medicine cups attached to the dome assembly. 	• Unplug the device from its power source. Remove and dispose of all medicine cups. Insert new medicine cup into device chamber and fill with 1 ampule of TYVASO.

Troubleshooting the TYVASO™ Inhalation System (continued)

Problem	Possible causes	Corrective actions
No medicine comes out of the device during a treatment session (continued)	• No TYVASO™ (treprostinil) Inhalation Solution in the medicine cup. 	• Unplug the device from its power source. Fill medicine cup with 1 ampule of TYVASO.
	• Device not connected to a power source. 	• Connect device to a power source. 
Difficult to breathe in medicine through the mouthpiece	• Filter is clogged.	• Unplug the device from its power source. Replace filter (see page 9). 

Problem	Possible causes	Corrective actions
No "click" was heard when attaching the dome assembly	• Multiple medicine cups attached to the dome assembly.  	• Unplug the device from its power source. Remove and dispose of all medicine cups. Insert new medicine cup into device chamber and fill with 1 ampule of TYVASO.
	• Dome assembly is not securely in place. 	• Unplug the device from its power source. Screw on dome assembly until you hear a "click". 
	• Distilled water level in the device chamber is too high.  	• Unplug the device from its power source. Empty device chamber then refill device chamber with 45 mL of distilled water. 

Specifications

Inhalation Device

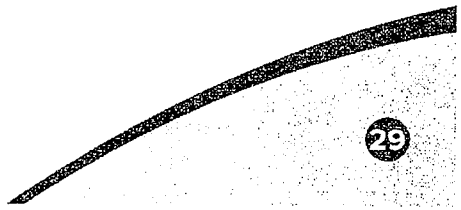
Model	**ON-100/7**
Size	**98 x 66 x 105 mm**
Weight, control unit	**280 g**
Types of power supply	**120/240V AC wall plug** **12V DC car adapter** **12V rechargeable battery**
Power supply	**12V DC, 1.5A maximum**
Operating power consumption	**18 Watt maximum**
Ultrasonic frequency	**2.4 MHz (nominal)**
Nebulization rate	**<0.6 mL/min**
MMAD (Mass Median Aerodynamic Diameter)	**2.0 µm (respirable fraction = 85%)**
1 cycle (3 breaths)	**18 micrograms treprostinil**
Medicine cup capacity	**6.0 mL**
Contact fluid chamber capacity	**approximately 45 mL**
Electric protection class	**II Type B**
Storage temperature/humidity	**-5 to 40°C/20-80% RH**
Operating temperature/humidity	**15 to 25°C/40-75% RH**

Accessories

ON-100HPA	Rechargeable battery
ON-100Z	12V DC car adapter
ON-100N-US	AC wall plug
ON-102/1	Medicine cup
ON-109	Filters
ON-115	Storage box
ON-120	Plugs
ON-118	Measuring cup
ON-101	Filter shell
ON-103/1	Dome assembly with black ring and baffle plate
ON-104	Inhalation piece
ON-105	Mouthpiece
ON-110	Black ring
ON-117B	Baffle plate (blue)
	Carrying case

Packaging Dimensions (Approximate Length x Width x Height)

Patient Starter Kit (PSK)	12.2" x 9.5" x 16"
Monthly Refill Kit (MRK)	9.5" x 6.6" x 12.1"



Glossary

Accessories: Parts of the TYVASO™ Inhalation System. See page 5.

Ampule: A sealed, lightweight clear plastic vial containing a 1 day supply of TYVASO™ (treprostinil) Inhalation Solution.

Baffle plate: A blue plastic piece that fits inside the dome assembly. The baffle plate helps create the pressure necessary to turn a liquid solution such as TYVASO into particles that are small enough to inhale.

Black ring: A round seal that fits on the bottom of the dome assembly. The seal ensures that TYVASO does not mix with the distilled water in the device chamber.

Cycle: A group of 3 breaths. Each treatment session with TYVASO contains between 1 and 4 cycles depending on the number of breaths your doctor prescribes.

Device chamber: The hollow portion in the center of the inhalation device into which distilled water and the medicine cup are placed.

Display screen: A small screen on the inhalation device that displays number and letter prompts to guide you through your treatment sessions.

Distilled water: Water that is highly purified so that it contains only essential elements.

Dome assembly: The plastic accessory that contains the baffle plate and connects the mouthpiece, inhalation piece, and filter shells to the base of the inhalation device.

Filter: The white pad that goes into the filter shells.

Filter shells: Plastic accessories that hold the filters.

Inhalation piece: The plastic accessory that connects the mouthpiece with the dome assembly.

Inhalation device: The base of the TYVASO Inhalation System to which the accessories connect. The inhalation device contains the display screen and lights.

Inhale: How you will breathe in TYVASO with the TYVASO Inhalation System.

Medicine cup: The disposable plastic cone-shaped cup into which TYVASO is poured. The medicine cup fits inside the inhalation device chamber.

Mouthpiece: The plastic part that you will breathe through (using your mouth) to inhale TYVASO.

Plugs: Plastic accessories that are inserted into the openings of the dome assembly between treatment sessions. Plugs help keep TYVASO from spilling if the inhalation device tips over.

Prompts: The audio and visual signals that help guide you through the treatment sessions.

Sensor: The silver object on the inside wall of the device chamber. The sensor must be covered with distilled water for the TYVASO Inhalation System to function properly.

Specialty pharmacy provider: A pharmacy that carries only specialized medicines and medical devices. Your specialty pharmacy provider is a good source of information about TYVASO and the TYVASO Inhalation System.

Treatment session: One of 4 daily sessions during which you will take TYVASO.

TYVASO: The prescription medicine that you will use with the TYVASO Inhalation System.

TYVASO Inhalation System: A system used to inhale the medicine, TYVASO. You may only use the TYVASO Inhalation System to take TYVASO.

To review TYVASO Inhalation System components, see *The TYVASO Inhalation System* on page 4.

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/s/

NORMAN L STOCKBRIDGE
07/30/2009