Treprostinil Inhaled (Tyvaso®)

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What is inhaled treprostinil?

Inhaled treprostinil (Tyvaso®) is an inhaled prostacyclin medication indicated for the treatment of pulmonary arterial hypertension (PAH) in World Health Organization (WHO) Group 1 patients 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 disease (33%).

Inhaled treprostinil is marketed as Tyvaso® for PAH and was approved by the Food and Drug Administration (FDA) in 2009.

The controlled clinical experience with inhaled treprostinil is over 12 weeks as additional therapy on a background of either oral bosentan (an endothelin receptor antagonist) and/or sildenafil (a phosphodiesterase-5 inhibitor).

It is a synthetic (not obtained from other humans or animals) analog of prostacyclin.

How does inhaled treprostinil work?

The major action of inhaled treprostinil is direct vasodilatation of the pulmonary vascular bed or relaxation and opening of narrowed blood vessels (arteries) in the lungs. It may also inhibit platelets from clumping together (aggregating). Relaxing and widening of the blood vessels in the lungs makes it easier for the heart to pump blood through the lungs. This reduces blood pressure in the lungs that should lead to improvement in physical activity level and well being.

Inhaled treprostinil showed clinical improvement as defined by increased ability to exercise measured by the 6-minute walk test in a multi-center, short-term (12 week) randomized study conducted in 235 patients.

How is inhaled treprostinil given (Please see package insert for full details)?

The effects of inhaled treprostinil diminish over the minimum dosing interval of 4 hours. The medication is inhaled using the Tyvaso Inhalation System® which consists of the Optineb-ir Model ON-100/7® (an ultrasonic, pulsed delivery device that delivers medication to your lungs).

Inhaled treprostinil is dose in 4 separate, equally spaced treatment sessions during the day (i.e. during waking hours). The treatment sessions should be approximately 4 hours apart.

Therapy should begin with 3 breaths of inhaled treprostinil (18 mcg of treprostinil) per treatment session. Dosing is increased by an additional 3 breaths generally at 1 to 2 week intervals until a target dose of 9 breaths (54 mcg treprostinil) per session is achieved.

If a treatment session is missed or interrupted, therapy should be resumed as soon as possible at the usual dose.
How is inhaled treprostinil supplied (Please see package insert for full details)?
Inhaled treprostinil comes in 2.9 mL polyethylene vials (ampules) containing 1.74 mg treprostinil (0.6 mg per mL).

Each ampule of the solution also contains 18.9 mg sodium chloride, 18.3 mg sodium citrate, 0.58 mg sodium hydroxide, 11.7 mg 1 N hydrochloric acid (for pH adjustment to between 6.0 and 7.2) in water.

Inhaled treprostinil system starter and refill kits contain 28 ampules packaged as 7 foil pouches each containing four 2.9 mL ampules.

Ampules of inhaled treprostinil are stable when stored in the unopened foil pouch at room temperature. Once the foil pouch has been opened, the ampule should be used within 7 days.

How can a patient obtain inhaled treprostinil?
Inhaled treprostinil must be prescribed by a physician and insurance approval must be obtained prior to starting therapy. Once approved by insurance, inhaled treprostinil is then sent directly to patients by one of the following specialty pharmacies: Accredo Health Group, Inc., Curascript, and CVS Caremark.

Will insurance pay for inhaled treprostinil?
The cost of inhaled treprostinil is about $46,912 per year.

It is expected that most insurance plans will pay for inhaled treprostinil prescriptions; however, plans with a set co-payment may result in additional cost to the patient.

Medicaid and most state-run insurance plans will pay for inhaled treprostinil. Medicare will also cover inhaled treprostinil in most cases under the part D component of that program.

There are a number of patient assistance program offers options to cover either partial or full drug costs for any patient with qualifying financial circumstances. To find the most appropriate program United Therapeutics® has created ASSIST (877-864-8437). Caring Voice Coalition (888-267-1440), an organization that provides grants to assist with drug cost for patients with chronic illnesses, may also provide coverage if the patient qualifies for such assistance.

What are frequent side effects of inhaled treprostinil?
The most common side effects include increased cough and throat irritation; headache; gastrointestinal effects (e.g. nausea); muscle, jaw or bone pain; flushing; and passing out (syncope). Other side effects may include decreased systemic blood pressure (hypotension), nosebleeding (epistaxis), coughing blood (hemoptyisis), and wheezing. The cough and throat irritation may decrease over time.

Inhaled treprostinil solution can also irritate the eyes and skin. If inhaled treprostinil comes in contact with the skin or eyes, rinse immediately with water.

How are side effects of inhaled treprostinil monitored?
While not required by the manufacturer, vital signs may be monitored by the specialty pharmacy staff when initiating inhaled treprostinil.

If you experience any of the symptoms mentioned in the previous section, you should promptly notify your physician.

What are considerations for use of inhaled treprostinil in special populations?
There are no adequate, well-controlled studies of the potential effect of inhaled treprostinil in either pregnant humans or animals. Studies in pregnant rabbits of continuous subcutaneous infusions of
treprostinil sodium, using doses higher than normally used in humans, has been shown to cause damage to the fetus (i.e. teratogenic). It is not known whether inhaled treprostinil is excreted in breast milk of nursing mothers.

Inhaled treprostinil should be used in pregnant or nursing mothers only if the potential benefit justifies the risk to the fetus or infant.

Safety and efficacy in pediatric patients has not been established.

Clinical studies did not include a sufficient number of patients over age 65 to determine either safety or efficacy.

Inhaled treprostinil has not been evaluated in patients with impaired liver (hepatic) function; however, plasma clearance of treprostinil when administered by subcutaneous infusion is reduced by up to 80% in patients with mild-to-moderate hepatic impairment. The result may be increased exposure to treprostinil and decreased tolerability.

Inhaled treprostinil has not been evaluated in patients with impaired kidney (renal) function. Since treprostinil and its metabolites are mainly excreted through the kidney, reduced drug clearance may potentially result in increased exposure to treprostinil and decreased tolerability.

Likewise, the effect of dialysis is unknown.

**Could a patient be allergic to inhaled treprostinil?**

This is unlikely. An ampule of inhaled treprostinil does not contain preservatives or sulfites. However, any medication can cause side effects or sensitivities and patients should check with their doctor if they experience a problem.

**What are important drug interactions with inhaled treprostinil (Please see package insert for full details)?**

Inhaled treprostinil and other medicines may potentially affect each other, causing side effects.

There is potential risk when inhaled treprostinil is used with medicines used to treat systemic high blood pressure or heart problems of low systemic blood pressure and passing out (syncope).

Inhaled treprostinil has the potential to increase risk of bleeding, particularly in patients maintained on anticoagulants or platelet inhibitors (e.g. heparin, warfarin, clopidogrel, dabigatran).

Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor, such as gemfibrozil, may increase exposure to treprostinil. Conversely, co-administration of a cytochrome P450 (CYP) 2C8 enzyme inducer, such as rifampin, may decrease exposure to treprostinil. Increased exposure may result in increased adverse effects and decreased exposure may reduce clinical effectiveness.

No pharmacokinetic interactions have been observed in human studies of co-administration of treprostinil with either bosentan or sildenafil.

**Can inhaled treprostinil be taken with other medications?**

Inhaled treprostinil is safe to take with most medications but can cause side effects that interfere with or require changes in other medications. Check all medications with your doctor.

As noted above, it appears safe to take treprostinil with either bosentan or sildenafil based on prior human studies.

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