

# Inhaled Treprostinil for the Treatment of Pulmonary Arterial Hypertension

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Pulmonary arterial hypertension is a progressive disease characterized by vascular proliferation and vasoconstriction of the small pulmonary arteries that eventually leads to right-sided heart failure and death. Patients often initially have symptoms such as shortness of breath, fatigue, and edema; later in the disease, presyncope and syncope are common. Patients with progressive pulmonary arterial hypertension despite oral therapy and/or with severe disease typically require treatment with a prostanoid. Inhaled treprostinil (Tyvaso) is a prostacyclin analog indicated for the treatment of pulmonary arterial hypertension to increase walk distance in patients with symptoms classified as New York Heart Association functional class III. Inhaled treprostinil was approved by the Food and Drug Administration in July 2009. This article provides a brief overview of the pathophysiology of pulmonary arterial hypertension and reviews the mechanism of action, key clinical data, and the practical management of inhaled treprostinil in patients with pulmonary arterial hypertension. (*Critical Care Nurse*. 2009;31[6]:e1-e11)

**P**ulmonary arterial hypertension (PAH) is a progressive disease characterized by vascular proliferation and vasoconstriction of the small pulmonary

arteries that eventually leads to right-sided heart failure and death.<sup>1</sup> Because of the severity of the disease and the complexity of treatment, patients often require admission to the intensive care unit when hospitalized. This article provides critical care nurses a brief overview of the pathophysiology of PAH and reviews the prostacyclin mechanism of action, key clinical data, and the practical management of inhaled treprostinil (Tyvaso) in PAH.

## Pathophysiology of PAH

The normal pulmonary vasculature is a high-flow, low-pressure

system that allows for increased blood flow as needed, such as during exercise. PAH is characterized by changes in the small pulmonary arteries, including intimal hyperplasia, medial hypertrophy, and in situ thrombosis. Additionally, excessive endothelial cell proliferation, coupled with decreased apoptosis and vasoconstriction, occurs and leads to decreased vascular luminal area. This decreased luminal area leads to increased pulmonary vascular resistance, which places an increased workload on the right ventricle.<sup>2</sup> These changes result in a low-flow, high-pressure system within the pulmonary arterial bed. Patients have progressive dyspnea and activity limitations, which become more pronounced as right ventricular function worsens. Most patients ultimately die of right ventricular failure.

Medical management is directed at lowering pulmonary pressures, increasing cardiac output, and decreasing pulmonary vascular resistance in order to slow the progression of right-sided heart failure.

## CE Continuing Education

This article has been designated for CE credit. A closed-book, multiple-choice examination follows this article, which tests your knowledge of the following objectives:

1. Identify 2 methods of classifying pulmonary artery hypertension (PAH)
2. Describe the pathophysiology of PAH
3. Discuss medication administration of treprostinil for PAH

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Patients often initially have symptoms such as shortness of breath, fatigue, and edema; later in the disease, they may have presyncope and syncope. The initial step in the evaluation of a symptomatic patient is to make the correct diagnosis. Along with a detailed medical history, multiple tests are used when evaluating patients with a suspected diagnosis of PAH, including echocardiography, chest radiography, ventilation perfusion scanning, pulmonary function testing, and serologic tests looking for connective tissue disease or infection with human immunodeficiency virus (HIV).<sup>3</sup>

Assessment of oxygenation, at rest and with exertion, is also important to determine if supplemental oxygen is necessary because chronic hypoxemia can lead to elevated pulmonary artery pressures. A right-sided heart catheterization is required to confirm the diagnosis of PAH. Specifically, PAH is defined as a mean pulmonary artery pressure of 25 mm Hg or greater with a normal pulmonary capillary wedge pressure of less than or equal to 15 mm Hg.<sup>4</sup>

Pulmonary hypertension is categorized into 5 World Health Organization (WHO) groups, of which PAH is categorized as WHO group 1.

This group includes idiopathic (formerly primary) PAH, as well as PAH associated with other conditions or exposures, such as connective tissue disease, congenital heart disease, liver disease, HIV infection, exposure to anorexic drugs, and exposure to methamphetamine.

The Registry to Evaluate Early And Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL) is the largest cohort of patients with PAH proven by right-sided heart catheterization in the world. The registry was established to collect demographic, clinical, and disease management data on patients with PAH (WHO group 1) with the goal of improving diagnosis, treatment, and management of this cohort. A total of 2967 consecutive patients were enrolled in this registry from March 1, 2006, through September 30, 2007, with an additional 500 newly diagnosed patients enrolled thereafter. Patients with idiopathic PAH constitute 46.2% of patients enrolled; the largest group of patients was those with PAH due to connective tissue disease (49.9%).<sup>1</sup>

Scleroderma is by far the most common connective tissue disease among patients with PAH. Mortality in this group can be as high as

25% to 50% at 2 years after diagnosis. Scleroderma itself is associated with significant inflammation and vasculopathy, and PAH is a manifestation of this process.<sup>5</sup> PAH occurs in patients with scleroderma because of direct involvement of the pulmonary vasculature with development of intimal proliferation and medial hypertrophy, very similar to idiopathic PAH.

Patients with scleroderma who are at the highest risk for development of PAH include those who first had low diffusing capacity of the lung for carbon monoxide (<50%) and patients with prior echocardiographic abnormalities.<sup>6</sup> The remaining 4 WHO groups (Table 1) are not discussed here because they are diseases that cause elevated pulmonary pressures for other reasons, such as left-sided heart failure, sleep apnea, lung disease, and chronic thromboembolic disease,<sup>7</sup> among others. Currently, all therapies for PAH approved by the Food and Drug Administration (FDA) are labeled only for WHO group 1.

In addition to the cause of the PAH, patients' functional abilities are used to classify the disease. The WHO functional classification or the New York Heart Association (NYHA) functional classification are used for this purpose. Early in the disease, patients may have no activity limitations, but as the disease advances, their symptoms progress to the point that they are short of breath at rest and may have edema and syncope. Patients are categorized by functional class along a spectrum from no symptoms (functional class I) and symptoms at rest (functional class IV; Table 2).<sup>8</sup>

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**Table 1** World Health Organization classification of pulmonary hypertension<sup>a</sup>

Group	Main classification	Diseases included
1	Pulmonary arterial hypertension (PAH)	PAH: Idiopathic, familial, associated with connective tissue disease, associated with congenital heart disease, associated with HIV infection, associated with drugs or toxins
2	Pulmonary hypertension due to left-sided heart disease	Systolic dysfunction, diastolic dysfunction, valvular disease
3	Pulmonary hypertension due to lung disease and/or hypoxia	Chronic obstructive pulmonary disease, interstitial lung disease, mixed restrictive and obstructive pattern, sleep disordered breathing, alveolar hypoventilation disorders, chronic exposure to high altitude, developmental abnormalities
4	Chronic thromboembolic pulmonary hypertension	Chronic thromboembolic disease
5	Pulmonary hypertension with unclear multifactorial mechanisms	Hematologic disorders: myeloproliferative disorders, splenectomy; systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis; lymphangioleiomyomatosis, neurofibromatosis, vasculitis; metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders; others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

<sup>a</sup> Revisions made at the 4th World Symposium on Pulmonary Hypertension held at Dana Point, California, in 2008.

**Table 2** World Health Organization and New York Heart Association functional classification in patients with pulmonary hypertension

Class	A. New York Heart Association functional classification
I	No symptoms with ordinary physical activity
II	Symptoms with ordinary activity; slight limitation of activity
III	Symptoms with less than ordinary activity; marked limitation of activity
IV	Symptoms with any activity or even at rest
	B. World Health Organization functional assessment classification
I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right-sided heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Although PAH has no cure, survival rates have improved with the advent of new targeted therapies specifically for PAH. Data were collected by the National Institutes of Health in cases of idiopathic PAH between 1981 and 1985, before any medical therapies for the disease had been approved, and at that time, 1-year survival was 68%.<sup>9</sup>

Today 9 therapies for PAH have been approved in the United States, and the mean survival rate at 1 year after diagnosis is 91%.<sup>10</sup>

### Pharmacology

#### *Mechanism of Action of Prostacyclin*

Prostacyclin, through the action of cyclooxygenase-2, is released from the endothelial cells, leading to platelet

aggregation and vasodilatation.<sup>11</sup> Prostacyclin is derived from arachidonic acid and is a major metabolite in the vascular endothelium, causing potent vasodilatation of both systemic and pulmonary arteries. Prostacyclin has antiproliferative activity, as demonstrated by its inhibition of growth of smooth muscle cells. It causes these effects

by stimulating cyclic adenosine monophosphate, a key cellular second messenger.<sup>12</sup>

In patients with PAH, the dysfunctional endothelial cells produce less prostacyclin and nitric oxide while the levels of thromboxane and endothelin-1 increase. These imbalances between vasodilators and vasoconstrictors are hallmark observations in PAH and contribute to vasoconstriction and vascular remodeling in pulmonary blood vessels. Prostacyclin inhibits endothelin-1 production, presumably through stimulation of guanylate cyclase and reduction of endothelin-1 release.<sup>13</sup>

Three prostanoid medications for the treatment of PAH have been approved by the FDA: epoprostenol, treprostinil, and iloprost. These medications replace deficits in endogenous prostacyclin observed in patients with PAH. Parenteral prostanoids are considered the most potent of the PAH medications and are a mainstay of treatment of patients with advanced disease.<sup>12</sup> Currently no oral forms of prostacyclin have been approved by the FDA, although several are under investigation. Thus, these medications are delivered long term via infusion, either intravenously (epoprostenol, treprostinil) or subcutaneously (treprostinil), or intermittently by inhalation (treprostinil, iloprost). Prostacyclin-related side effects, found across all routes of delivery, can be significant and include nausea, flushing, diarrhea, jaw discomfort, musculoskeletal pain, headache, rash and thrombocytopenia. Route-related side effects also may occur, such as cough with inhaled delivery and site pain with the subcutaneous route.

### *Treatment With Inhaled Prostanoids: Differentiation and Potential Benefits of Inhaled Over Parenteral Prostanoid Therapy*

Patients with progressive PAH despite oral therapy with endothelin receptor antagonists and/or inhibitors of phosphodiesterase type 5 and patients with severe disease typically require the addition of a prostanoid. Inhaled prostanoids generally are added to oral therapy for patients with early symptoms of NYHA functional class III or in patients who are not candidates for parenteral therapy. They can be added to the medication regimen of PAH patients whose condition is declining or patients who are not improving with oral therapy.

The advantage of inhaled prostanoid therapy is the delivery of medication directly to the lungs, which results in less systemic absorption, and potentially, less severe systemic side effects. Additionally, the inhaled approach offers an alternative for some patients who are unable to manage or tolerate parenteral therapy, which requires an infusion pump and carries a risk for blood stream infections or infusion site reactions. However, if patients treated with inhaled prostanoids experience worsening symptoms; a significant decrease in 6-minute walking distance (6MWD); a decline in right ventricular function; or worsening hemodynamics, oxygenation, or functional class, they may benefit from a parenteral prostacyclin. Those patients with more severe disease (late functional class III or IV) should be treated with a parenteral prostanoid when-ever possible.

### **Trial Data**

#### *Addition of Inhaled Treprostinil to Oral Therapy for PAH (TRIUMPH) Clinical Trial Data*

Inhaled treprostinil (Tyvaso) is a prostacyclin analogue indicated to increase walk distance when treating PAH in patients with NYHA functional class III symptoms. It was approved by the FDA in July 2009 on the basis of data from the pivotal clinical trial TRIUMPH, in which inhaled treprostinil was added to stable doses of either bosentan or sildenafil background therapy in patients with PAH.

As PAH is a rare disease, clinical trials often study smaller numbers of patients than do trials that involve more common diseases. In the study, 235 patients with PAH were randomized to receive up to 54 µg (9 breaths) of inhaled treprostinil or placebo 4 times a day via the Optinex inhalation device (Nebu-Tec, Elsenfeld, Germany). The primary end point was change in peak 6MWD at 12 weeks. Titration of inhaled treprostinil was determined by the investigator with the initiation of therapy starting at 3 breaths 4 times a day. Dosing was then increased as tolerated, to 9 breaths 4 times a day. Seventy-two percent of the patients in the inhaled treprostinil arm of the study received the maximum dose of 9 breaths 4 times a day after 3 weeks.

The Hodges-Lehman placebo-corrected change from baseline in peak 6MWD was 19 m at week 6 ( $P < .001$ ) and 20 m at week 12 ( $P < .001$ ). Further evaluation of 6MWD results showed that 32% of patients receiving inhaled treprostinil had an improvement in 6MWD of 50 m or more at the end of the

12-week period. Week 12 placebo-corrected trough 6MWD improved by 14 m ( $P=.004$ ), with trough being defined as 4 hours or more after the dose of treprostinil.

Improvements were seen in both quality of life and level of N-terminal pro-B-type natriuretic peptide for patients on active therapy. Adverse events were related to the route of administration (cough: 54% on inhaled treprostinil and 29% on placebo) and prostacyclin-like side effects (headache: 41% on inhaled treprostinil vs 23% on placebo; nausea: 19% vs 11%, inhaled treprostinil vs placebo, respectively).<sup>14</sup>

### *Long-Term Data*

The open label portion of the TRIUMPH clinical trial followed patients who were all on active therapy and was designed to assess the effects of long-term treatment with inhaled treprostinil. Two hundred six patients entered the open-label extension study, and approximately 64% of patients completed the study after 2 years. Maintenance of improvements in 6MWD was evident through the 2-year period, with a survival rate of 93% for the patients who continued treatment with inhaled treprostinil. Sixty-eight percent of patients remained clinically stable without the need for additional PAH therapy, and more than 90% of patients maintained or improved their NYHA functional class from baseline.<sup>15</sup>

### *Safety and Tolerability*

Caution is necessary in patients with concomitant pulmonary disease (eg, asthma, chronic obstructive

pulmonary disease, and interstitial lung disease) because safety and efficacy have not been established in this population of patients.<sup>16</sup>

Symptoms may worsen and patients' overall functional status may decline. Patients with acute pulmonary infections require close monitoring to detect both worsening disease and ineffective drug delivery, as evidenced by lack of clinical improvement. Because inhaled treprostinil is a systemic and pulmonary vasodilator, patients with baseline hypotension may experience untoward symptoms from a further reduction in systemic blood pressure.

### *Special Populations*

Treprostinil is classified as a pregnancy category B drug and has not been adequately studied in pregnant women. It should be used in this population only at the discretion of an experienced physician who specializes in the care of patients with PAH. It is unknown if inhaled treprostinil is excreted in human milk; therefore, caution should be exercised if inhaled treprostinil is administered to women who are nursing. As no data exist in patients with hepatic and renal insufficiency, cautious use of inhaled treprostinil with slow titration is recommended.

The age inclusion criterion for the TRIUMPH study was 18 to 75 years. Insufficient numbers of pediatric and geriatric patients precluded determination of response to treprostinil in those populations. In general, the geriatric population has a greater frequency of comorbid conditions; therefore, dosing of treprostinil should be cautious and carefully monitored.

## **Practical Aspects of Medication Administration**

### *Dosing of Inhaled Treprostinil*

Inhaled treprostinil is dosed in breaths (1 breath = 6 µg treprostinil) with the target goal of 9 breaths 4 times a day.<sup>16</sup> Patients should begin dosing at 3 breaths 4 times a day and then titrate up to 9 breaths 4 times a day as long as significant, dose-limiting side effects do not develop. Dose increases are individualized for patients depending on their overall condition and medication tolerance. Dose escalation can be as slow as increasing by 1 breath 4 times a day every 3 to 5 days or as rapid as increasing by 1 breath 4 times a day daily to the maximum recommended dose of 9 breaths 4 times a day. More aggressive dose escalation could be considered in some patients in a monitored medical setting. Titration of the dose up to 12 breaths 4 times a day has been done by some clinicians, and although it was not studied in a randomized fashion, it was evaluated and tolerated by some patients in the open-label extension of the TRIUMPH study.

Treatment times are brief, lasting approximately 2 to 3 minutes, allowing for rapid medication delivery, with 4 times a day dosing. Visual and auditory prompts in the Optibea device are available to encourage accurate timing of each breath for administration of the medication (Figures 1-4). Thorough education by health care providers trained to use the device is essential for maximum efficacy. This education includes medication preparation, proper breathing technique, operation of the device, and medication side effects. Periodic review



**Figure 1** Optineb device used to administer inhaled treprostinil.

Courtesy United Therapeutics Corp, Durham, North Carolina.

of technique is recommended to ensure that the patient is inhaling the medication correctly and to maintain compliance with therapy. Critical care nurses should be educated on the basic operation of the nebulizer but, in most cases, respiratory therapists will administer the treatments and maintain the equipment for patients in

the intensive care unit. Specialty pharmacy personnel are highly trained on the device and administration of inhaled treprostinil and are readily available to provide on-site education for nursing staff. The patient or the patient's family member will know and provide contact information for the specialty pharmacy that services them.

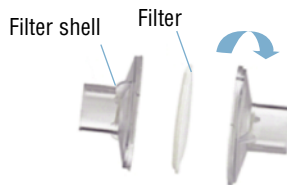
Circumstances such as surgery, anesthesia, sedation, physical limitations, and mental status changes for extended periods may result in interruptions in therapy. It is important to stress the need for patients or family members to contact their health care team should these circumstances occur. Close monitoring may be required to prevent clinical deterioration. In some cases, alternative PAH therapies, such as intravenous or subcutaneous prostacyclin, may be used.

#### Assembling Accessories

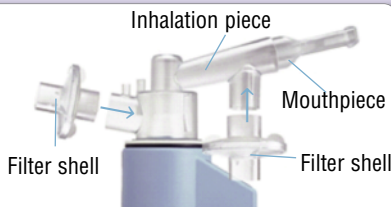
**Insert inhalation piece into top of dome assembly  
Connect the mouthpiece to the inhalation piece**



**Assemble filters in shells**



**Connect filter shells to the dome assembly and inhalation piece**



**Figure 2** Assembling inhalation device.

Courtesy United Therapeutics Corp, Durham, North Carolina.

#### Device for Inhalation

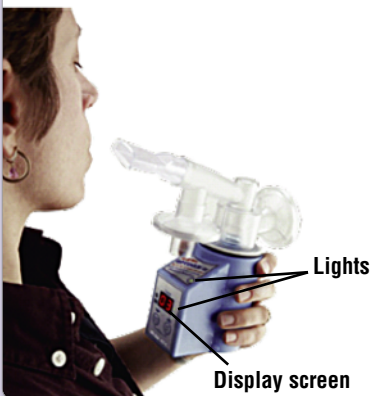
The Optineb ultrasonic nebulizer was used in the pivotal clinical trial and thus is the only device approved by the FDA for the administration of inhaled treprostinil. The medication was approved by the FDA as a bundled kit including the administration device, parts to assemble, and medication. The cost of the device and medication are billable to Medicare and other payers. Several financial assistance foundations are available for all PAH therapies to qualified patients who are uninsured, underinsured, or have high co-payments.

The other FDA-approved inhaled prostacyclin, iloprost, was approved for use with a different device called the I-neb (Actelion Pharmaceuticals, San Francisco, California). Efforts are currently underway to create an improved version of the Optineb.

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.



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



Press the START/STOP button to begin treatment.



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



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



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.



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

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



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.



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

**Figure 3** Device operation.

Courtesy United Therapeutics Corp, Durham, North Carolina.



**Figure 4** Correct positioning of the device.

Courtesy United Therapeutics Corp, Durham, North Carolina.

The instructions for operation of the Optineb hand-held device must be followed closely, and failure to do so may result in inadequate drug delivery and/or adverse reactions. The device can be connected to 3 different power sources: alternating current wall power, a car adapter, or a rechargeable battery pack. These options enable the patient to be fully mobile to administer treatments. It is important to use distilled or demineralized water with the device, because failure to do so will eventually lead to corrosion of the Optineb.

The device consists of 10 lightweight, easy-to-assemble, accessory pieces that fit together in only 1 configuration, which eliminates potential errors during the setup process. The pieces can be stored in a small plastic container when not in use during the day and can be quickly assembled for the next treatment session.

device with warm, soapy water is required to maintain proper working order. Once a month, the plastic components are discarded and replaced with new ones. The device's ease of use, quick cleanup, and short treatment time provide optimal convenience for patients.

#### *Management of Adverse Events*

Most adverse events associated with treprostinil administration are similar to those typically observed with prostacyclin use: headache; gastrointestinal side effects; muscle, jaw, or bone pain; flushing; and syncope. Two of the most common adverse events, cough and throat irritation, are most likely related to the inhalation route of administration.

*Management of Cough.* Cough associated with treprostinil use ranges from mild to intractable, the latter sometimes leading to discontinuation of therapy. It is important to review proper technique of

One treprostinil ampule is sufficient for a full day of therapy and is easily stored between treatments inside the capped Optineb. At the end of the day, all leftover medication is discarded to reduce the risk of contamination through growth of microorganisms. Daily cleaning of the

medication administration and to try to relieve or decrease the intensity of cough, in order to continue the treatment. Incorrect technique, such as incorrect placement of the mouthpiece or not holding the Optineb level, has been associated with cough and can easily be corrected with basic retraining. Other interventions that have been noted to reduce or eliminate cough in clinical practice are listed in Table 3.

*Management of Headache.* Forty-one percent of patients in the inhaled treprostinil arm in the TRIUMPH trial experienced headache, as opposed to 23% of patients receiving placebo. Treatment of headache with acetaminophen can be beneficial, if not otherwise contraindicated. Slower titration may also help to lessen the degree of headache. Reassuring the patient that the headaches will most likely resolve over time helps with compliance during the titration phase. Nausea, a less common side effect, can often be resolved by having the patient rinse the mouth and spit after each treatment. This process prevents the patient from swallowing any residual drug that may be in the oral cavity. Other interventions that may help to decrease nausea include slower titration or eating a small meal before the treatment. If these simple measures do not relieve adverse events, patients should contact their health care provider or specialty pharmacy personnel for further assistance. See Table 4 for possible side effects and interventions to alleviate them.

#### *Instructions for Patients*

Patients may have many questions about treatment with inhaled

**Table 3** Interventions for cough relief

Intervention for cough	Rationale
Inhaled anticholinergics	Relief of bronchospasm
Inhaled steroids	Reduce inflammation
Oral phenol-based analgesic sprays (eg, Chloraseptic), administered before treatments	Reduce throat irritation by numbing the throat
Cough medicine over the counter or prescribed cough preparations (eg, Tessalon Perles) but avoiding cough drops to decrease the risk of aspiration	Reduce incidence or intensity of cough
Drink very cold or warm water before a treatment	Cold for numbing effect; warm for soothing and relaxing effect
Maintain normal breathing pattern (aerosol is “waiting” for the patient during the green light and they just need to breathe it in)	Improves administration and distribution of medication
Do not hold breath once medication is inhaled	Not needed for medication administration
Use the pause button between breaths if needed	When learning, this reduces anxiety associated with the breathing treatment pattern
Reduce the number of breaths per treatment and/or titrate slower; (eg, by 1 breath 4 times a day)	Allows the patient to adapt to the medicine and increases tolerance

**Table 4** Nursing considerations for administration of inhaled treprostinil

Nursing considerations	Intervention	Rationale
Dosing goal of inhaled treprostinil is 9 breaths 4 times a day with starting dose usually at 3 breaths 4 times a day		Dose is titrated up as per physician's order with final dose based on that studied in clinical trial
Titration varies from patient to patient		Side effect profile may slow titration with administration of this vasodilator
1 ampule of inhaled treprostinil used daily		Enough medication in ampule to last the entire day whether 3 to 9 breaths 4 times a day
Keep extra ampules of medication in the foil pouch to protect from light		Medication is sensitive to light
Discard any leftover medication every evening after last dose of the day		To reduce the possible risk of contamination through microorganism growth
Wash plastic parts with soap and water nightly and let air dry		To keep the parts clean
Charge the battery pack nightly		To keep the battery pack charged
Potential side effects		
Cough	See Table 3	Relieve cough
Headaches	Acetaminophen, short-term ibuprofen, aspirin, temporarily decrease by 1 breath 4 times a day	Alleviate headache
Nausea	Swish and spit after each treatment session, temporarily decrease by 1 breath 4 times a day	Relieve nausea
Flushing	If severe, can decrease by 1 breath 4 times a day and then increase again when symptom improved	Relieve flushing
Throat irritation	Oral phenol-based analgesic sprays (eg, Chloraseptic), administered before treatments	Reduce throat irritation by numbing the throat
Decreased blood pressure in some patients	Decrease by 1 breath 4 times a day if patient symptomatic	If decrease in blood pressure related to medication, decrease in dose of medication should help resolve

treprostinil, which often are focused on potential for improvement of symptoms and the impact on patients' quality of life, specifically how much time they will spend taking treatments. Critical care nurses can educate patients on dosing requirements and overall goals of this therapy, most importantly that quality of life improves as symptoms of PAH improve.

Questions related to the method of delivery are common as well. Two devices are provided when patients begin therapy. These devices should be rotated monthly, with the monthly medication shipment, to ensure that both remain operational. The portable battery in the Optineb will last up to 4½ days (200 inhalations) when completely charged. The battery does not need to be depleted before it is recharged. Initial charging of the battery may take up to 40 hours. Inhaled treprostinil is supplied in foil pouches, and the unused ampules must be kept in these pouches to maintain potency, since the medication is sensitive to light. Once the foil pouch is opened, the medication must be used within 7 days. Patients should be encouraged to date the foil pouch when they open it to ensure that the medication is used within the specified time frame. If admitted to the hospital, patients must bring their Optineb device so that accurate dosing of the inhaled treprostinil can be ensured.

## Conclusions

Treprostinil is safe, effective, well tolerated, and easy to administer. The placebo-controlled study, TRI-UMPH, showed a statistically significant improvement in 6MWD when inhaled treprostinil was added to

oral PAH therapy. Prostacyclin therapy has been, and remains, critically important in the treatment of PAH. Inhaled prostanoid therapy directly targets the pulmonary circulation, with less severe side effects than intravenous or subcutaneous routes of administration, and uses a convenient delivery system.

Inhaled treprostinil therapy is not a substitute for parenteral prostacyclin, which remains the reference standard of care for patients with advanced disease or rapidly worsening symptoms. Transition from parenteral prostacyclin therapy to inhaled treprostinil therapy should be considered only in select patients under the direct supervision of a pulmonary hypertension specialist. Few patients are suitable candidates for this type of transition. Studies are currently in progress to help better define this population.

With multiple PAH therapies currently available, patients with suboptimal response or failure to improve with initial treatment have more treatment options. Critical care nurses are likely to encounter them when such patients are hospitalized for worsening PAH. Evaluating response to therapy and escalating therapy should be undertaken by expert practitioners in the PAH field so as to provide optimal care, better quality of life, and ultimately improved survival for patients with PAH. **CCN**

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## Financial Disclosures

Both authors have received honoraria from United Therapeutics Inc, Gilead Inc, and Actelion LTD, companies that manufacture or distribute medications for pulmonary arterial hypertension.

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## CE Test Test ID C1163: Inhaled Treprostinil for the Treatment of Pulmonary Arterial Hypertension

**Learning objectives:** 1. Identify 2 methods of classifying pulmonary artery hypertension 2. Describe the pathophysiology of pulmonary artery hypertension 3. Discuss medication administration of treprostinil for pulmonary artery hypertension

**1. Which of the following describes the pulmonary vascular system?**

- a. High-flow, low-pressure system
- b. Low-flow, low-pressure system
- c. High-flow, high-pressure system
- d. Low-flow, high-pressure system

**2. Treatment goals for patients with pulmonary artery hypertension (PAH) include which of the following?**

- a. Increased pulmonary pressure
- b. Decreased cardiac output
- c. Decreased pulmonary vascular resistance
- d. Decreased right ventricular function

**3. Which of the following diagnostic tests is required for a PAH diagnosis?**

- a. Echocardiogram
- b. Ventilation/Perfusion scan
- c. Oxygenation assessment
- d. Right-sided heart catheterization

**4. Which of the following defines PAH?**

- a. Mean pulmonary artery pressure (PAP) is >25 mm Hg and pulmonary capillary wedge pressure (PCWP) is <15 mm Hg
- b. Mean PAP is <25 mm Hg and PCWP is <15 mm Hg
- c. Mean PAP is >25 mm Hg and PCWP is >15 mm Hg
- d. Mean PAP is <25 mm Hg and PCWP is >15 mm Hg

**5. PAH is common in patients with scleroderma because of which of the following?**

- a. Decreased proliferation of the intimal cells
- b. Direct involvement of the pulmonary vasculature
- c. Decreased inflammation of vasculature
- d. Increased diffusion capacity of carbon dioxide by the lungs

**6. Which of the following are associated with the dysfunctional epithelial cells in patients with PAH?**

- a. Increased prostacyclin production
- b. Increased nitric oxide production
- c. Increased thromboxane levels
- d. Decreased endothelial-1 production

**7. Which PAH medication is administered subcutaneously?**

- a. Epoprostenol
- b. Treprostinil
- c. Iloprost

**8. Which of the following is considered an advantage of inhaled PAH medication therapy?**

- a. It requires a pump
- b. It increases systemic absorption
- c. It has decreased risk of side effects
- d. It has a longer onset of action

**9. What is the most common adverse affect associated with inhaled PAH medications?**

- a. Cough
- b. Headache
- c. Nausea
- d. Hiccoughs

**10. Which of the following is true regarding the care and cleaning of the Optineb?**

- a. Medication can be stored in a capped Optineb for 3 days therapy
- b. The Optineb should be cleaned daily with warm, soapy water
- c. The chamber in the Optineb should be discarded after each treatment
- d. The Optineb should be disinfected with bleach once a month

**11. Which treprostinil side effects are associated with inhalation administration?**

- a. Headaches and gastrointestinal upsets
- b. Muscle and bone pain
- c. Flushing and syncope
- d. Cough and throat irritation

**12. A patient is unable to get out of bed without exhibiting symptoms of PAH. What classification is this?**

- a. New York Heart Association I
- b. New York Heart Association IV
- c. World Health Organization II
- d. World Health Organization I

**Test answers:** Mark only one box for your answer to each question. You may photocopy this form.

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