Treprostinil (Remodulin®)

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What is treprostinil?

Treprostinil is a synthetic (not obtained from other humans or animals) analogue of prostacyclin, a medication used for the treatment of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH) which may be given subcutaneously (under the skin), intravenously (in the veins) or can be inhaled. The inhaled formulation (Tyvaso®) is discussed on a separate treatment fact sheet. Treprostinil was approved by the FDA in 2002 for subcutaneous use, and subsequently in 2004 for intravenous use for the treatment of PAH in patients with New York Heart Association Class II, III, or IV symptoms.

How does treprostinil work?

The major actions of treprostinil are vasodilatation of the pulmonary and systemic vascular beds (widening of narrowed blood vessels in the lung and other parts of the body), and inhibition of platelet clumping (aggregation). These effects appear to be similar to the effects of epoprostenol (Flolan® or Veletri®). Improved exercise capacity has been demonstrated in a 3 month study of subcutaneous treprostinil. The improvement was dose-related, meaning that those patients in the clinical trial achieving the highest doses had the greatest improvement in exercise capacity. Two longer-term (2-4 years) studies of subcutaneous treprostinil involving patients with pulmonary hypertension demonstrated continued efficacy.

Trials with intravenous treprostinil include a recently published short-term trial in group 1 PAH during which the patients had reduced symptoms and improved exercise capacity. Other small studies have transitioned patients on a stable dose of epoprostenol to treprostinil displaying maintenance of exercise capacity. The dose of treprostinil may be higher than the previous epoprostenol dose. Whether long-term intravenous treprostinil is as effective as intravenous epoprostenol is unknown as there are no long-term comparative studies.

How is treprostinil given?

Subcutaneous treprostinil is delivered via the CADD MS3 portable infusion pump. Infusion sites are placed under the skin, often in the abdominal area, and are periodically changed.

Intravenous treprostinil must be administered via a surgically placed central venous catheter. Intravenous treprostinil is delivered via the CADD Legacy pump (the same pump that is used for intravenous epoprostenol administration), the CHRONO 5 pump or the CADD MS 3 pump. Each pump system has its own benefits and complexities.

An implantable pump system (i.e. surgical placement of the pump and tubing under the skin) is currently undergoing scientific investigation as yet another way to deliver treprostinil. This system has not yet been approved for use.

Treprostinil is stable at room temperature for 48 hours when mixed with sterile solution (this means it does not have to be refrigerated or kept cold with ice while being infused).
Dosing of treprostinil

Treprostinil is usually initiated at 1.25 – 2.5 ng/kg/min and the dose is gradually increased to achieve symptomatic relief. It is not uncommon for some patients to be on a dose of 100 ng/kg/min, or higher, to achieve optimal benefit with a tolerable safety profile, however the optimal dose like other infusion agents must be individualized. The dose of treprostinil is the same for subcutaneous and intravenous delivery systems. Conversion from epoprostenol to treprostinil has been described and is included in the indications for treprostinil. The exact procedure and dosing for such a conversion would be determined by the PH provider for each specific circumstance.

How is treprostinil supplied?

Treprostinil is supplied in 20 ml vials containing 4 different concentrations of drug (1.0 mg/ml, 2.5 mg/ml, 5.0 mg/ml, and 10.0 mg/ml). A single vial should be used no more than 14 days after the initial opening and usage of the vial, provided that the proper storage procedures are followed.

How do patients obtain treprostinil?

Treprostinil must be prescribed by a physician and insurance approval must be obtained prior to starting therapy. The drug is provided directly from specialty pharmacies (Accredo Health Group, Inc., Curascript, and CVS Caremark) that provide a team of clinical pharmacists and nurses. They assist with all aspects involved in the long-term usage of Treprostinil, including insurance issues, dose titration, providing pumps and supplies, and technical troubleshooting with 24-hour hotlines.

Will insurance pay for treprostinil?

The cost of subcutaneous or intravenous treprostinil depends on the dose of medicine and patient weight and includes pump supplies. Typical estimates range from $120,000 to $160,000 per year, but may be higher depending on the dose.

It is expected that most insurance plans will pay for treprostinil prescriptions; however, co-payments may be quite substantial.

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 programs that offer 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.

How is treprostinil initiated?

Patients started on intravenous treprostinil typically require admission to the hospital for a few days similar to epoprostenol initiation. Teaching of central venous catheter (e.g. Hickman) care, CADD pump specifics, and administration of treprostinil are taught before leaving the hospital by specialty nurses. Subcutaneous treprostinil can be started either in the hospital or at home. For home initiation, pre-teaching is generally performed by specialty nurses. In addition, the specialty nurses are often present with the patient during the start-up of home drug delivery.

What are the main side effects with treprostinil?

The side effects of treprostinil are similar to those seen with epoprostenol and include headache, diarrhea, nausea, jaw pain, flushing, dizziness, swelling, itching and low systemic blood pressure.

In addition to side effects from the medicine, there may be side effects due to the infusion system or route. The major side effect with subcutaneously administered treprostinil is the development of infusion site pain which often improves after 7 to 14 days of therapy (perhaps longer) and/or redness at the site of the subcutaneous infusion. This occurs in up to 80% of patients. The occurrence of site
pain is not dose-related in most patients and often improves the longer an infusion site is left in place. There are various remedies used to treat this problem, and patients differ in their response to these remedies. Infection and bleeding can also occur at the infusion site.

The half-life of treprostinil is about four and a half hours; however, symptoms due to drug interruption can occur in less than one hour.

**What are considerations for use of treprostinil in special populations?**

There are no adequate, well-controlled studies of the potential effect of infused treprostinil in pregnant humans. Studies in pregnant rabbits of continuous subcutaneous infusions of treprostinil sodium, using doses higher than normally used in humans, has been shown to be associated with an increased incidence of fetal skeletal variations. No other fetal problems were seen. Similar studies in rats showed no effects. Infusion treprostinil currently carries an FDA grading of “B” in pregnancy. Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester. Treprostinil should only be used during pregnancy when the benefit is felt to outweigh the risk.

Safety and efficacy in pediatric patients has not been established. Treprostinil has been used in children. Clinical studies of treprostinil did not include sufficient numbers of patients 16 years of age and under to determine its safety and efficacy in children.

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

Treprostinil clearance is reduced in patients with hepatic (liver) insufficiency. The result may be increased exposure to treprostinil and decreased tolerability. In patients with mild or moderate hepatic insufficiency, the manufacturer recommends a reduction in the initial dose to 0.625 ng/kg/min ideal body weight and close monitoring. Treprostinil has not been studied in severe hepatic insufficiency.

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 treprostinil?**

There are no reports of allergies to treprostinil. It is unlikely that this would occur since prostacyclin is naturally made by the body. However, any medication can cause side effects, which are listed above. No medications are prohibited with the use of treprostinil.

**Are there other ways of administering treprostinil?**

Inhaled treprostinil (Tyvaso®) is approved and available for use in patients with pulmonary arterial hypertension. It is discussed under a separate cover.

Oral treprostinil is undergoing scientific study but is not approved or available in the United States.

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