Treprostinil (Remodulin®)

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WHAT IS TREPROSTINIL (REMODULIN®)?

Treprostinil is a medication administered either subcutaneously or intravenously approved for the treatment of pulmonary arterial hypertension (PAH) in World Health Organization (WHO) Group 1 patients. Treprostinil is a synthetic analogue of prostacyclin, a naturally occurring substance in the body, which has effects on dilating blood vessels. Treprostinil was approved for PAH by the United States Food and Drug Administration (FDA) in 2002 for subcutaneous use and in 2004 for intravenous use.

HOW DOES TREPROSTINIL (REMODULIN®) WORK?

The major actions of treprostinil appear to be similar to the effects of epoprostenol (Flolan® or Veletri®) and include 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 aggregation (clumping).

Patients receiving subcutaneous treprostinil have been shown to have increased exercise capacity as demonstrated in a three-month study. This 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 (two to four 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 this trial, 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 (REMODULIN®) GIVEN?

Subcutaneous treprostinil is delivered under the skin through a tiny tube connected to the CADD MS3 portable infusion pump. Infusion catheters 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. Treprostinil is stable at room temperature for at least 48 hours when given either subcutaneously or intravenously. This means it does not have to be refrigerated or kept cold with ice while being infused.

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.

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DOSING OF TREPROSTINIL (REMODULIN®)

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 during such a conversion would be determined by the PH provider for each specific circumstance.

HOW IS TREPROSTINIL (REMODULIN®) SUPPLIED?

Treprostinil is supplied in 20 ml vials containing four different concentrations of drug (1.0mg/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 of the vial, provided that the proper storage procedures are followed.

HOW DO PATIENTS OBTAIN TREPROSTINIL (REMODULIN®)?

Treprostinil is a limited distribution medication, which means it cannot be purchased at a local pharmacy. It 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., 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, education on pump function and central line care, providing pumps and supplies and technical troubleshooting with 24-hour hotlines.

WILL INSURANCE PAY FOR TREPROSTINIL (REMODULIN®)?

It is expected that most health insurance plans will pay part of the cost of this medication. However, some plans still leave patients with a high out-of-pocket responsibility.

Depending on your insurance type, you may be eligible for assistance from the company that manufactures your therapy or from a non-profit charitable assistance organization. For more information visit www.PHAssociation.org/Help or call 301-565-3004.

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HOW IS TREPROSTINIL (REMODULIN®) INITIATED?

Similar to epoprostenol initiation, patients started on intravenous treprostinil typically require admission to the hospital for a few days. While in the hospital, specialty nurses or pulmonary hypertension coordinators from your center teach patients central venous catheter (e.g. Hickman) care, CADD pump specifics and administration of treprostinil. 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 (REMODULIN®)?

The side effects of treprostinil are similar to those seen with all prostacyclin agents and include:

- Headache
- Diarrhea
- Nausea
- Jaw pain
- Flushing of the skin
- Dizziness
- Swelling
- Itching
- Muscle or joint pain
- Low systemic blood pressure.

In addition to side effects from the medicine, there may be side effects due to the infusion system. Infection and bleeding can occur at the infusion site.

The half-life of treprostinil is about four and a half hours. Stopping treprostinil can be fatal when done abruptly.

WHAT ARE CONSIDERATIONS FOR USE OF TREPROSTINIL (REMODULIN®) 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, have 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

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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 appears to be reduced in patients with liver insufficiency. This results in decreased tolerability. Patients with mild or moderate liver insufficiency may be started at lower initial doses and may be more sensitive to dose increases. Treprostinil has not been studied in severe liver insufficiency.

Treprostinil has not been evaluated in patients with impaired kidney function. Since treprostinil is 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 (REMODULIN®)?

This is possible, but not likely.

WHAT ARE IMPORTANT DRUG INTERACTIONS WITH TREPROSTINIL (REMODULIN®)? (PLEASE SEE PACKAGE INSERT FOR FULL DETAILS)

No medications are prohibited with the use of treprostinil.

ARE THERE OTHER WAYS OF ADMINISTERING TREPROSTINIL (REMODULIN®)?

Inhaled treprostinil (Tyvaso®) is approved and available for use in patients with pulmonary arterial hypertension. It is discussed in depth on a separate Treatment Fact Sheet.

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