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REPRINT

REMODULIN® (TREPROSTINIL SODIUM) INJECTION THERAPY FOR PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION

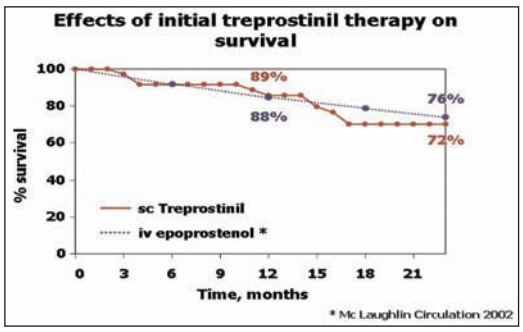
Remodulin® (treprostinil sodium) Injection, developed by **United Therapeutics Corporation** (Silver Spring, MD), is indicated as a continuous subcutaneous infusion for the treatment of pulmonary arterial hypertension (PAH) in patients with New York Heart Association (NYHA) Class II, III, and IV symptoms to diminish symptoms associated with exercise. Remodulin is the only FDA-approved treatment for NYHA Class II PAH, and is an approved therapy for Medicare and Medicaid programs.

Remodulin is a stable prostacyclin analog which is in solution and does not require additional extemporaneous mixing. It is stable at room temperature with no need for the use of external refrigerants to keep the drug at lower than room temperature. Continuous subcutaneous infusion of Remodulin is administered via a self-inserted subcutaneous catheter, using an infusion pump designed for subcutaneous drug delivery. The ambulatory infusion pump used to administer Remodulin should: (1) be small and lightweight; (2) be adjustable to approximately 0.002 mL/hour; (3) have occlusion/no delivery, low battery, programming error, and motor malfunction alarms; (4) have delivery accuracy of plus or minus 6 percent or better; and (5) be positive pressure-driven.

The half-life of subcutaneous Remodulin is four hours, which is significantly longer than intravenous prostacyclin, epoprostenol, which has a half-life of approximately 2-7 minutes. Remodulin thus poses less of a safety risk to the patient, should an unexpected interruption of therapy occur. In addition, Remodulin can be safely administered to patients with underlying hepatic diseases (a secondary cause of PAH), with some dosage adjustments, and it can also be used in patients with connective-tissue diseases, such as scleroderma.

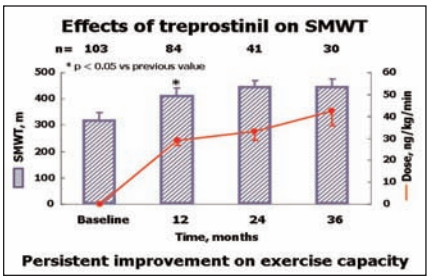
The major pharmacological actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. In animals, the vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. It has been shown that treprostinil causes a dose-related negative inotropic and lusitropic effect, with no major effects on cardiac conduction observed.

Recent long-term data on treprostinil was presented at the American College of Cardiology 53rd Annual Scientific Sessions in New Orleans, LA by Dr. Jean-Luc Vachiery, Associate Professor of Cardiology at the Erasme Hospital in Brussels, Belgium. Dr. Vachiery's presentation showed persistent clinical improvements and prolonged survival in a multicenter cohort of 112 pulmonary arterial hypertension patients treated with Remodulin for up to 57 months.

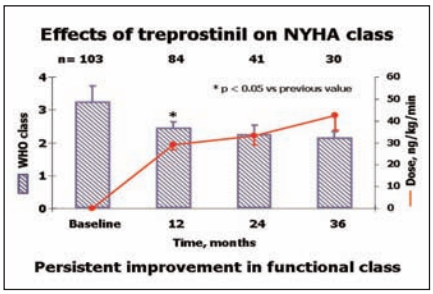


"These multicenter data provide further confirmation that treprostinil therapy offers long-term symptomatic and survival benefit to patients with pulmonary hypertension. In our experience, such data, along with the obvious safety advantages of treprostinil over intravenous epoprostenol, clearly signify that treprostinil can be used as a first-line prostacyclin therapy for the treatment of PAH in the ever-increasing number of patients who are failing oral therapies," said Dr. Vachiery.

Dr. Vachiery also feels treprostinil dosing should be aggressive, "Our experience shows infusion pain, which dissipates over time, is not a limiting factor in the vast majority of patients; yet the treatment benefit, as with intravenous epoprostenol, is dose-dependent." said Dr Vachiery. Also reported was the effect of treprostinil on the Six Minute Walk Test (SMWT), in which patients showed an improvement of more than 150 meters over the duration of the study.



Finally, Dr. Vachiery provided data demonstrating persistent improvement in patient's functional NYHA classification of PAH by more than 35% over baseline.



Remodulin is supplied in 20-mL/vials in concentrations of 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL, and 10.0 mg/mL. The infusion rate is initiated at 1.25 ng/kg/min; if not tolerated, it can be reduced to 0.625 ng/kg/min; or, if needed, increased in increments by no more than 1.25 ng/kg/min per week.

Clinical Trials with Remodulin in Patients with PAH

Remodulin was compared with placebo in two 12-week, multicenter, randomized, double-blind studies in 470 patients, mean age of 45 years (range 9 to 75 years), with NYHA Class II-IV PAH. The condition was primary in 58% of the patients, associated with collagen vascular disease in 19% of the patients, and the result of congenital left to right shunts in 23% of the patients. The primary endpoint of the studies was change in 6-minute walking distance, a standard measure of exercise capacity. The dose of Remodulin averaged 9.3 ng/kg/min at Week 12. Background therapy, determined by the investigators, could include anticoagulants, oral vasodilators, diuretics, digoxin, and oxygen, but not an endothelin receptor antagonist or epoprostenol. Remodulin therapy resulted in small hemodynamic changes consistent with pulmonary and systemic vasodilation. Although the effect of Remodulin on the 6-minute walk was small, the Borg dyspnea score (a subjective measurement of shortness of breath) was significantly improved by Remodulin during the 6-minute walk. Remodulin also had a significant effect, compared with placebo, on an assessment that combined walking distance with the Borg dyspnea score (*1*). The medication consistently improved indices of dyspnea, fatigue, and signs of pulmonary hypertension.

Patients receiving Remodulin report a wide range of adverse events, many related to the underlying disease (dyspnea, fatigue, chest pain, right ventricular heart failure, and pallor). Infusion site pain and reaction are the most common adverse events reported with Remodulin therapy. Infusion site reaction is defined as any local adverse event other than pain or bleeding/bruising at the infusion site, and includes symptoms such as erythema, induration, or rash.

Remodulin is approved for use in the United States, Canada, and Israel; is pending its final approval in Australia and Switzerland; and is awaiting approval in France, Poland, Hungary, and the Czech Republic. Currently there are over 700 Remodulin patients worldwide, some of whom received Remodulin for over 5 years.

Remodulin is available through United Therapeutics' U.S. distributors, Priority Healthcare Corporation, Accredo Therapeutics, Inc, and Caremark Rx, Inc. For more information concerning Remodulin (treprostinil sodium) Injection, you may call Priority Healthcare at 1-866-4PHTEAM, Accredo Therapeutics Inc. at 1-866-FIGHTPH, or Caremark Rx, Inc. at 1-877-356-5261, or visit the product Web site at www.remodulin.com.

Reference:

1. Data on file.