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RESEARCH**

APPLICATION NUMBER:

21-272

APPROVED LABELING

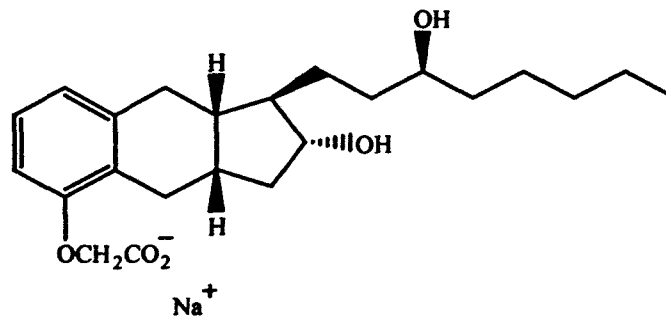
PRODUCT INFORMATION**REMODYLIN™ (treprostinil sodium) Injection****DESCRIPTION**

Remodulin (treprostinil sodium) Injection is a sterile sodium salt formulated for subcutaneous administration. Remodulin is supplied in 20 mL multi-use vials in four strengths, containing 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL or 10.0 mg/mL of treprostinil. Each mL also contains 5.3 mg sodium chloride (except for the 10.0 mg/mL strength which contains 4.0 mg sodium chloride), 3.0 mg metacresol, 6.3 mg sodium citrate, and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2.

Treprostinil is chemically stable at room temperature and neutral pH.

Treprostinil sodium is (1R,2R,3aS,9aS)-[[2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]acetic acid monosodium salt. Treprostinil sodium has a molecular weight of 412.49 and a molecular formula of $C_{23}H_{33}NaO_5$.

The structural formula of treprostinil sodium is:

**CLINICAL PHARMACOLOGY**

General: 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. Other studies have shown that treprostinil causes a dose-related negative inotropic and lusitropic effect. No major effects on cardiac conduction have been observed.

Pharmacokinetics

The pharmacokinetics of continuous subcutaneous Remodulin are linear over the dose range of 1.25 to 22.5 ng/kg/min (corresponding to plasma concentrations of about 0.03 to 8 µg/L) and can be described by a two-compartment model. Dose proportionality at infusion rates greater than 22.5 ng/kg/min has not been studied.

Absorption: Remodulin is relatively rapidly and completely absorbed after subcutaneous infusion, with an absolute bioavailability approximating 100%. Steady-state concentrations occurred in approximately 10 hours. Concentrations in patients treated with an average dose of 9.3 ng/kg/min were approximately 2 µg/L.

Distribution: The volume of distribution of the drug in the central compartment is approximately 14L/70 kg ideal body weight. Remodulin at in vitro concentrations ranging from 330-10,000 µg/L was 91% bound to human plasma protein.

Metabolism: Remodulin is substantially metabolized by the liver, but the precise enzymes responsible are unknown. Five metabolites have been described (HU1 through HU5). The biological activity and metabolic fate of these metabolites are unknown. The chemical structure of HU1 is unknown. HU5 is the glucuronide conjugate of treprostinil. The other metabolites are formed by oxidation of the 3-hydroxyoctyl side chain (HU2) and subsequent additional oxidation (HU3) or

dehydration (HU4). Based on the results of in vitro human hepatic cytochrome P450 studies, Remodulin does not inhibit CYP-1A2, 2C9, 2C19, 2D6, 2E1, or 3A. Whether Remodulin induces these enzymes has not been studied.

Excretion: The elimination of Remodulin is biphasic, with a terminal half-life of approximately 2-4 hours. Approximately 79% of an administered dose is excreted in the urine as unchanged drug (4%) and as the identified metabolites (64%). Approximately 13% of a dose is excreted in the feces. Systemic clearance is approximately 30 liters/hr for a 70 kg ideal body weight person.

Special Populations

Hepatic Insufficiency: In patients with portopulmonary hypertension and mild (n=4) or moderate (n=5) hepatic insufficiency, Remodulin at a subcutaneous dose of 10 ng/kg/min for 150 minutes had a C_{max} that was increased 2-fold and 4-fold, respectively, and $AUC_{0-\infty}$ was increased 3-fold and 5-fold, respectively, compared to healthy subjects. Clearance in patients with hepatic insufficiency was reduced by up to 80% compared to healthy adults.

In patients with mild or moderate hepatic insufficiency, the initial dose of Remodulin should be decreased to 0.625 ng/kg/min ideal body weight and should be increased cautiously. Remodulin has not been studied in patients with severe hepatic insufficiency.

Renal Insufficiency: No studies have been performed in patients with renal insufficiency, so no specific advice about dosing in such patients can be given. Although only 4% of the administered dose is excreted unchanged in the urine, the five identified metabolites are all excreted in the urine.

Effect of Other Drugs on Remodulin: *In vitro* studies: Remodulin did not significantly affect the plasma protein binding of normally observed concentrations of digoxin or warfarin.

In vivo studies: Acetaminophen - Analgesic doses of acetaminophen, 1000 mg every 6 hours for seven doses, did not affect the pharmacokinetics of Remodulin, at a subcutaneous infusion rate of 15 ng/kg/min.

Clinical Trials in Pulmonary Arterial Hypertension (PAH)

Two 12-week, multicenter, randomized, double-blind studies compared Remodulin to placebo in a total of 470 patients with NYHA Class II-IV pulmonary arterial hypertension (PAH). PAH was primary in 58% of patients, associated with collagen vascular disease in 19%, and the result of congenital left to right shunts in 23%. The mean age was 45 (range 9 to 75 years). About 81% were female and 84% were Caucasian. Pulmonary hypertension had been diagnosed for a mean of 3.8 years. The primary endpoint of the studies was change in 6-minute walking distance, a standard measure of exercise capacity. There were many assessments of symptoms related to heart failure, but local discomfort and pain associated with Remodulin may have substantially unblinded those assessments. The 6-minute walking distance and an associated subjective measurement of shortness of breath during the walk (Borg dyspnea score) were administered by a person not participating in other aspects of the study. Remodulin was administered as a subcutaneous infusion, described in DOSAGE AND ADMINISTRATION, and the dose averaged 9.3 ng/kg/min at Week 12. Few subjects received doses > 40 ng/kg/min. Background therapy, determined by the investigators, could include anticoagulants, oral vasodilators, diuretics, digoxin, and oxygen but not an endothelin receptor antagonist or epoprostenol. The two studies were identical in design and conducted simultaneously, and the results were analyzed both pooled and individually.

Hemodynamic Effects

As shown in Table 1, chronic therapy with Remodulin resulted in small hemodynamic changes consistent with pulmonary and systemic vasodilation.

Table 1: Hemodynamics During Chronic Administration of Remodulin in Patients with PAH

Hemodynamic Parameter	Baseline		Mean change from baseline at Week 12	
	Remodulin (N=204-231)	Placebo (N=215-235)	Remodulin (N=163-199)	Placebo (N=182-215)
CI (L/min/m ²)	2.4 ± 0.88	2.2 ± 0.74	+0.12 ± 0.58*	-0.06 ± 0.55
PAPm (mmHg)	62 ± 17.6	60 ± 14.8	-2.3 ± 7.3*	+0.7 ± 8.5
RAPm (mmHg)	10 ± 5.7	10 ± 5.9	-0.5 ± 5.0*	+1.4 ± 4.8
PVRI (mmHg/L/min/m ²)	26 ± 13	25 ± 13	-3.5 ± 8.2*	+1.2 ± 7.9
SVRI (mmHg/L/min/m ²)	38 ± 15	39 ± 15	-3.5 ± 12*	-0.80 ± 12
SvO ₂ (%)	62 ± 100	60 ± 11	+2.0 ± 10*	-1.4 ± 8.8
SAPm (mmHg)	90 ± 14	91 ± 14	-1.7 ± 12	-1.0 ± 13
HR (bpm)	82 ± 13	82 ± 15	-0.5 ± 11	-0.8 ± 11

*Denotes statistically significant difference between Remodulin and placebo, p<0.05.

CI = cardiac index; PAPm = mean pulmonary arterial pressure; PVRI = pulmonary vascular resistance indexed; RAPm = mean right atrial pressure; SAPm = mean systemic arterial pressure; SVRI = systemic vascular resistance indexed; SvO₂ = mixed venous oxygen saturation; HR = heart rate.

Clinical Effects

The effect of Remodulin on 6-minute walk, the primary end point of the studies, was small and did not achieve conventional levels of statistical significance. For the combined populations, the median change from baseline on Remodulin was 10 meters and the median change from baseline on placebo was 0 meters. Although it was not the primary endpoint of the study, the Borg dyspnea score was significantly improved by Remodulin during the 6-minute walk, and Remodulin also had a significant effect, compared with placebo, on an assessment that combined walking distance with the Borg dyspnea score. Remodulin also consistently improved indices of dyspnea, fatigue and signs and symptoms of pulmonary hypertension, but these indices were difficult to interpret in the context of incomplete blinding to treatment assignment resulting from infusion site symptoms.

INDICATIONS AND USAGE

Remodulin™ is indicated as a continuous subcutaneous infusion for the treatment of pulmonary arterial hypertension in patients with NYHA Class II-IV symptoms (see CLINICAL PHARMACOLOGY: Clinical Effects) to diminish symptoms associated with exercise.

CONTRAINDICATIONS

Remodulin is contraindicated in patients with known hypersensitivity to the drug or to structurally related compounds.

WARNINGS

Remodulin is indicated for subcutaneous use only.

PRECAUTIONS

General

Remodulin should be used only by clinicians experienced in the diagnosis and treatment of PAH.

Remodulin is a potent pulmonary and systemic vasodilator. Initiation of Remodulin must be performed in a setting with adequate personnel and equipment for physiological monitoring and emergency care. Subcutaneous therapy with Remodulin may be used for prolonged periods, and the patient's ability to administer Remodulin and care for an infusion system should be carefully considered.

Dose should be increased for lack of improvement in, or worsening of, symptoms and it should be decreased for excessive pharmacological effects or for unacceptable infusion site symptoms (see **DOSAGE AND ADMINISTRATION**).

Abrupt withdrawal or sudden large reductions in dosage of Remodulin may result in worsening of PAH symptoms and should be avoided.

Information for Patients

Patients receiving Remodulin should be given the following information: Remodulin is infused continuously through a subcutaneous catheter, via an infusion pump. Therapy with Remodulin will be needed for prolonged periods, possibly years, and the patient's ability to accept, place, and care for a subcutaneous catheter and to use an infusion pump should be carefully considered. Additionally, patients should be aware that subsequent disease management may require the initiation of an intravenous therapy.

Drug Interactions

Reduction in blood pressure caused by Remodulin may be exacerbated by drugs that by themselves alter blood pressure, such as diuretics, antihypertensive agents, or vasodilators. Since Remodulin inhibits platelet aggregation, there is also a potential for increased risk of bleeding, particularly among patients maintained on anticoagulants. During clinical trials, Remodulin was used concurrently with anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, antipyretics, nonsteroidal anti-inflammatories, opioids, corticosteroids, and other medications.

Effect of Other Drugs on Remodulin

In vitro studies: Remodulin did not significantly affect the plasma protein binding of normally observed concentrations of digoxin or warfarin.

In vivo studies: Acetaminophen - Analgesic doses of acetaminophen, 1000 mg every 6 hours for seven doses, did not affect the pharmacokinetics of Remodulin, at a subcutaneous infusion rate of 15 ng/kg/min.

Remodulin has not been studied in conjunction with Flolan® (epoprostenol sodium) or Tracleer™ (bosentan).

Effect of Remodulin on Other Drugs

In vivo studies: Warfarin - Remodulin does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S- warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous Remodulin at an infusion rate of 10 ng/kg/min.

Hepatic and Renal Impairment

Caution should be used in patients with hepatic or renal impairment (see **SPECIAL POPULATIONS**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies have not been performed to evaluate the carcinogenic potential of treprostinil. *In vitro* and *in vivo* mutagenicity studies did not demonstrate any mutagenic or clastogenic effects of treprostinil. Treprostinil sodium did not affect fertility or mating performance of male or female rats given continuous subcutaneous infusion at rates of up to 450 ng treprostinil/kg/min [about 59 times the recommended starting human rate of infusion (1.25 ng/kg/min) and about 8 times the average rate (9.3 ng/kg/min) achieved in clinical trials, on a ng/m² basis]. In this study, males were dosed from 10 weeks prior to mating and through the 2-week mating period. Females were dosed from 2 weeks prior to mating until gestational day 6.

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