

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-272/S-002

Trade Name: Remodulin

Generic Name: treprostinil sodium

Sponsor: United Therapeutics Corporation

Approval Date: November 24, 2004

Purpose: Adding the infusion of Remodulin (treprostinil sodium) 1, 2.5, 5 & 10 mg/ml Injection via an indwelling central venous catheter to the labeling

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APPLICATION NUMBER:

21-272/S-002

APPROVAL LETTER



NDA 21-272/S-002

United Therapeutics Corporation
Attention: Mr. Dean Bunce
One Park Drive
Research Triangle Park, NC 27709

Dear Mr. Bunce:

Please refer to your supplemental new drug application dated January 30, 2004, received January 30, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Remodulin (treprostinil sodium) 1, 2.5, 5 & 10 mg/mL Subcutaneous and Intravenous Injection.

We acknowledge receipt of your submissions dated March 5 and 15; April 5, May 4, 6 and 20; July 21; August 26; September 17; and November 11 and 18, 2004.

This supplemental new drug application provides for adding the infusion of Remodulin (treprostinil sodium) 1, 2.5, 5 & 10 mg/mL Injection via an indwelling central venous catheter to the labeling.

We have completed the review of this supplemental application, as amended, according to the regulations for accelerated approval, and have concluded that adequate information has been presented to approve Remodulin (treprostinil sodium) 1, 2.5, 5 & 10 mg/mL Subcutaneous and Intravenous Injection for use as recommended in the enclosed labeling text. Accordingly, the application is approved under 21 CFR 314 Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert, and immediate container and carton labels submitted on November 12, 2004 (email attachment). Please submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – NDAs* (January 1999) as soon as it is available, in no case more than 30 days after it is printed. Alternatively, you may submit 20 paper copies of the FPL, ten of which are individually mounted on heavy-weight paper or similar material. For administrative purposes, this submission should be designated “**FPL for approved NDA 21-272/S-002.**” Approval of this submission by FDA is not required before the labeling is used.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your post marketing study (Subpart H Phase 4 commitments) specified in our letter dated August 18, 2003.

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are exempting the pediatric study requirement for this application because Remodulin (treprostinil sodium) indicated for the treatment of pulmonary arterial hypertension received Orphan Drug designation on November 2, 1999.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Project Manager
(301) 594-5332

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Norman Stockbridge
11/24/04 12:30:25 PM

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APPLICATION NUMBER:

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LABELING

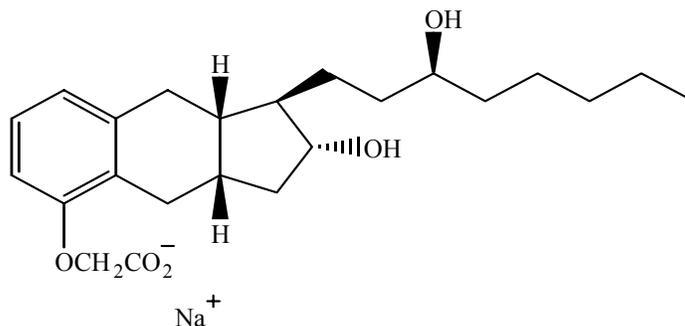
PRODUCT INFORMATION**REMODULIN[®] (Trepstinil sodium) Injection****DESCRIPTION**

Remodulin[®] (trepstinil sodium) Injection is a sterile sodium salt formulated for subcutaneous or intravenous administration. Remodulin is supplied in 20 mL multi-use vials in four strengths, containing 1 mg/mL, 2.5 mg/mL, 5 mg/mL or 10 mg/mL of trepstinil. Each mL also contains 5.3 mg sodium chloride (except for the 10 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.

Trepstinil is chemically stable at room temperature and neutral pH.

Trepstinil 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. Trepstinil sodium has a molecular weight of 412.49 and a molecular formula of C₂₃H₃₃NaO₅.

The structural formula of trepstinil sodium is:

**CLINICAL PHARMACOLOGY**

General: The major pharmacologic actions of trepstinil 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 trepstinil 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 mcg/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.

Subcutaneous and intravenous administration of Remodulin demonstrated bioequivalence at steady state at a dose of 10 ng/kg/min.

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 mcg/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 mcg/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 trepstinil. 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 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 an $AUC_{0-\infty}$ that 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 continuous subcutaneous infusion of 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 or intravenous infusion (for those not able to tolerate a 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 or intravenous 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. 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 pharmacologic 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 or surgically placed indwelling central venous catheter, via an infusion pump. Therapy with Remodulin will be needed for prolonged periods, possibly years, and the patient's ability to accept and care for a catheter and to use an infusion pump should be carefully considered. In order to reduce the risk of infection, aseptic technique must be used in the preparation and administration of Remodulin. Additionally, patients should be aware that subsequent disease management may require the initiation of an alternative intravenous prostacyclin therapy, Flolan[®] (epoprostenol sodium).

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.

Remodulin has not been studied in conjunction with Flolan or Tracleer[®] (bosentan).

Effect of Other Drugs on Remodulin

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.

Effect of Remodulin on Other Drugs

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

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* genetic toxicology 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 infusions 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.

Pregnancy

Pregnancy Category B - In pregnant rats, continuous subcutaneous infusions of treprostinil sodium during organogenesis and late gestational development, at rates as high as 900 ng treprostinil/kg/min (about 117 times the starting human rate of infusion, on a ng/m² basis and about 16 times the average rate achieved in clinical trials), resulted in no evidence of harm to the fetus. In pregnant rabbits, effects of continuous subcutaneous infusions of treprostinil during organogenesis were limited to an increased incidence of fetal skeletal variations (bilateral full rib or right rudimentary rib on lumbar 1) associated with maternal toxicity (reduction in body weight and food consumption) at an infusion rate of 150 ng treprostinil/kg/min (about 41 times the starting human rate of infusion, on a ng/m² basis, and 5 times the average rate used in clinical trials). In rats, continuous subcutaneous infusion of treprostinil from implantation to the end of lactation, at rates of up to 450 ng treprostinil/kg/min, did not affect the growth and development of offspring. Because animal reproduction studies are not always predictive of human response, Remodulin should be used during pregnancy only if clearly needed.

Labor and delivery

No treprostinil sodium treatment-related effects on labor and delivery were seen in animal studies. The effect of treprostinil sodium on labor and delivery in humans is unknown.

Nursing mothers

It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, caution should be exercised when Remodulin is administered to nursing women.

Pediatric use

Safety and effectiveness in pediatric patients have not been established. Clinical studies of Remodulin did not include sufficient numbers of patients aged ≤16 years to determine whether they respond differently from older patients. In general, dose selection should be cautious.

Geriatric use

Clinical studies of Remodulin did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Patients receiving Remodulin as a subcutaneous infusion reported a wide range of adverse events, many potentially related to the underlying disease (dyspnea, fatigue, chest pain, right ventricular heart failure, and pallor). During clinical trials with subcutaneous infusion of Remodulin, infusion site pain and reaction were the most common adverse events among those treated with Remodulin. Infusion site reaction was defined as any local adverse event other than pain or bleeding/bruising at the infusion site and included symptoms such as erythema, induration or rash. Infusion site reactions were sometimes severe and could lead to discontinuation of treatment.

Table 2. Percentages of subjects reporting subcutaneous infusion site adverse events

	Reaction		Pain	
	Placebo	Remodulin	Placebo	Remodulin
Severe	1	38	2	39
Requiring narcotics*	NA**	NA**	1	32
Leading to discontinuation	0	3	0	7

* based on prescriptions for narcotics, not actual use

**medications used to treat infusion site pain were not distinguished from those used to treat site reactions

Other adverse events included diarrhea, jaw pain, edema, vasodilatation and nausea, and these are generally considered to be related to the pharmacologic effects of Remodulin, whether administered subcutaneously or intravenously.

Adverse Events During Chronic Dosing

Table 3 lists adverse events that occurred at a rate of at least 3% and were more frequent in patients treated with subcutaneous Remodulin than with placebo in controlled trials in PAH.

Table 3: Adverse Events in Controlled Studies of Patients with PAH, Occurring with at Least 3% Incidence and More Common on Subcutaneous Remodulin than on Placebo.

Adverse Event	Remodulin (N=236) Percent of Patients	Placebo (N=233) Percent of Patients
Infusion Site Pain	85	27
Infusion Site Reaction	83	27
Headache	27	23
Diarrhea	25	16
Nausea	22	18
Rash	14	11
Jaw Pain	13	5
Vasodilatation	11	5
Dizziness	9	8
Edema	9	3
Pruritus	8	6
Hypotension	4	2

Reported adverse events (at least 3%) are included except those too general to be informative, and those not plausibly attributable to the use of the drug, because they were associated with the condition being treated or are very common in the treated population.

Adverse Events Attributable to the Drug Delivery System

In controlled studies of Remodulin administered subcutaneously, there were no reports of infection related to the drug delivery system. There were 187 infusion system complications reported in 28% of patients (23% Remodulin, 33% placebo); 173 (93%) were pump related and 14 (7%) related to the infusion set. Eight of these patients (4 Remodulin, 4 Placebo) reported non-serious adverse events resulting from infusion system complications. Adverse events resulting from problems with the delivery systems were typically related to either symptoms of excess Remodulin (e.g., nausea) or return of PAH symptoms (e.g., dyspnea). These events were generally resolved by correcting the delivery system pump or infusion set problem such as replacing the syringe or battery, reprogramming the pump, straightening a crimped infusion line. Adverse events resulting from problems with the delivery system did not lead to clinical instability or rapid deterioration.

There are no controlled clinical studies with Remodulin administered intravenously. Among the subjects (n=38) treated for 12-weeks in an open-label study, 2 patients had either line infections or sepsis. Other events potentially related to the mode of infusion include arm swelling, paresthesias, hematoma and pain.

OVERDOSAGE

Signs and symptoms of overdose with Remodulin during clinical trials are extensions of its dose-limiting pharmacologic effects and include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Most events were self-limiting and resolved with reduction or withholding of Remodulin.

In controlled clinical trials, seven patients received some level of overdose and in open-label follow-on treatment seven additional patients received an overdose; these occurrences resulted from accidental bolus administration of Remodulin, errors in pump programmed rate of administration, and prescription of an incorrect dose. In only two cases did excess delivery of Remodulin produce an event of substantial hemodynamic concern (hypotension, near-syncope).

DOSAGE AND ADMINISTRATION

Remodulin® is supplied in 20 mL vials in concentrations of 1 mg/mL, 2.5 mg/mL, 5 mg/mL and 10 mg/mL. Remodulin can be administered as supplied or diluted for intravenous infusion with Sterile Water for Injection or 0.9% Sodium Chloride Injection prior to administration.

Initial Dose

Remodulin is administered by continuous infusion. Remodulin is preferably infused subcutaneously, but can be administered by a central intravenous line if the subcutaneous route is not tolerated, because of severe site pain or reaction. The infusion rate is initiated at 1.25 ng/kg/min. If this initial dose cannot be tolerated because of systemic effects, the infusion rate should be reduced to 0.625 ng/kg/min.

Dosage Adjustments

The goal of chronic dosage adjustments is to establish a dose at which PAH symptoms are improved, while minimizing excessive pharmacologic effects of Remodulin (headache, nausea, emesis, restlessness, anxiety and infusion site pain or reaction).

The infusion rate should be increased in increments of no more than 1.25 ng/kg/min per week for the first four weeks and then no more than 2.5 ng/kg/min per week for the remaining duration of infusion, depending on clinical response. There is little experience with doses >40 ng/kg/min. Abrupt cessation of infusion should be avoided (see **PRECAUTIONS**).

Administration

Subcutaneous Infusion

Remodulin is administered subcutaneously by continuous infusion, via a self-inserted subcutaneous catheter, using an infusion pump designed for subcutaneous drug delivery. To avoid potential interruptions in drug delivery, the patient must have immediate access to a backup infusion pump and subcutaneous infusion sets. The ambulatory infusion pump used to administer Remodulin should: (1) be small and lightweight, (2) be adjustable to approximately 0.002 mL/hr, (3) have occlusion/no delivery, low battery, programming error and motor malfunction alarms, (4) have delivery accuracy of ±6% or better and (5) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass.

For subcutaneous infusion, Remodulin is **delivered without further dilution** at a calculated Subcutaneous Infusion Rate (mL/hr) based on a patient's Dose (ng/kg/min), Weight (kg), and the Vial Strength (mg/mL) of Remodulin being used. During use, a single reservoir (syringe) of undiluted Remodulin can be administered up to 72 hours at 37°C. The Subcutaneous Infusion rate is calculated using the following formula:

$$\text{Subcutaneous Infusion Rate (mL/hr)} = \frac{\text{Dose (ng/kg/min)} \times \text{Weight (kg)} \times 0.00006^*}{\text{Remodulin Vial Strength (mg/mL)}}$$

*Conversion factor of 0.00006 = 60 min/hour x 0.000001 mg/ng

Example calculations for *Subcutaneous Infusion* are as follows:

Example 1:

For a 60 kg person at the recommended initial dose of 1.25 ng/kg/min using the 1 mg/mL Remodulin Vial Strength, the infusion rate would be calculated as follows:

$$\begin{array}{l} \text{Subcutaneous} \\ \text{Infusion Rate} \\ \text{(mL/hr)} \end{array} = \frac{1.25 \text{ ng/kg/min} \quad \times \quad 60 \text{ kg} \quad \times \quad 0.00006}{1 \text{ mg/mL}} = 0.005 \text{ mL/hr}$$

Example 2:

For a 65 kg person at a dose of 40 ng/kg/min using the 5 mg/mL Remodulin Vial Strength, the infusion rate would be calculated as follows:

$$\begin{array}{l} \text{Subcutaneous} \\ \text{Infusion Rate} \\ \text{(mL/hr)} \end{array} = \frac{40 \text{ ng/kg/min} \quad \times \quad 65 \text{ kg} \quad \times \quad 0.00006}{5 \text{ mg/mL}} = 0.031 \text{ mL/hr}$$

Intravenous Infusion

Remodulin must be diluted with either Sterile Water for Injection or 0.9% Sodium Chloride Injection and is administered intravenously by continuous infusion, via a surgically placed indwelling central venous catheter, using an infusion pump designed for intravenous drug delivery. To avoid potential interruptions in drug delivery, the patient must have immediate access to a backup infusion pump and infusion sets. The ambulatory infusion pump used to administer Remodulin should: (1) be small and lightweight, (2) have occlusion/no delivery, low battery, programming error and motor malfunction alarms, (3) have delivery accuracy of $\pm 6\%$ or better of the hourly dose, and (4) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass.

Diluted Remodulin has been shown to be stable at ambient temperature for up to 48 hours at concentrations as low as 0.004 mg/mL (4,000 ng/mL).

When using an appropriate infusion pump and reservoir, a predetermined intravenous infusion rate should first be selected to allow for a desired infusion period length of up to 48 hours between system changeovers. Typical intravenous infusion system reservoirs have volumes of 50 or 100 mL. With this selected Intravenous Infusion Rate (mL/hr) and the patient's Dose (ng/kg/min) and Weight (kg), the Diluted Intravenous Remodulin Concentration (mg/mL) can be calculated using the following formula:

$$\begin{array}{l} \text{Step 1} \\ \text{Diluted} \\ \text{Intravenous} \\ \text{Remodulin} \\ \text{Concentration} \\ \text{(mg/mL)} \end{array} = \frac{\begin{array}{l} \text{Dose} \\ \text{(ng/kg/min)} \end{array} \quad \times \quad \begin{array}{l} \text{Weight} \\ \text{(kg)} \end{array} \quad \times \quad 0.00006}{\begin{array}{l} \text{Intravenous Infusion Rate} \\ \text{(mL/hr)} \end{array}}$$

The Amount of Remodulin Injection needed to make the required Diluted Intravenous Remodulin Concentration for the given reservoir size can then be calculated using the following formula:

Step 2 Amount of Remodulin Injection (mL)	=	Diluted Intravenous Remodulin Concentration (mg/mL)	x	Total Volume of Diluted Remodulin Solution in Reservoir (mL)
		Remodulin Vial Strength (mg/mL)		

The calculated amount of Remodulin Injection is then added to the reservoir along with the sufficient volume of diluent (Sterile Water for Injection or 0.9% Sodium Chloride Injection) to achieve the desired total volume in the reservoir.

Example calculations for *Intravenous Infusion* are as follows:

Example 3:

For a 60 kg person at a dose of 5 ng/kg/min, with a predetermined intravenous infusion rate of 1 mL/hr and a reservoir of 50 mL, the Diluted Intravenous Remodulin Solution Concentration would be calculated as follows:

Step 1
Diluted Intravenous Remodulin Concentration
(mg/mL)

$$= \frac{5 \text{ ng/kg/min} \times 60 \text{ kg} \times 0.00006}{1 \text{ mL/hr}} = 0.018 \text{ mg/mL} \quad (18,000 \text{ ng/mL})$$

The Amount of Remodulin Injection (using 1 mg/mL Vial Strength) needed for a total Diluted Remodulin Concentration of 0.018 mg/mL and a total volume of 50 mL would be calculated as follows:

Step 2 Amount of Remodulin Injection (mL)	=	0.018 mg/mL	x 50 mL = 0.9 mL
		1 mg/mL	

The Diluted Intravenous Remodulin Concentration for the person in Example 3 would thus be prepared by adding 0.9 mL of 1 mg/mL Remodulin Injection to a suitable reservoir along with a sufficient volume of diluent to achieve a total volume of 50 mL in the reservoir. The pump flow rate for this example would be set at 1 mL/hr.

Example 4:

For a 75 kg person at a dose of 30 ng/kg/min, with a predetermined intravenous infusion rate of 2 mL/hr, and a reservoir of 100 mL, the Diluted Intravenous Remodulin Solution Concentration would be calculated as follows:

Step 1
Diluted Intravenous Remodulin Concentration
(mg/mL)

$$= \frac{30 \text{ ng/kg/min} \times 75 \text{ kg} \times \frac{0.00006}{6}}{2 \text{ mL/hr}} = 0.0675 \text{ mg/mL} \quad (67,500 \text{ ng/mL})$$

The Amount of Remodulin Injection (using 2.5 mg/mL Vial Strength) needed for a total Diluted Remodulin Concentration of 0.0675 mg/mL and a total volume of 100 mL would be calculated as follows:

Step 2 Amount of Remodulin Injection (mL)	=	0.0675 mg/mL	x 100 mL = 2.7 mL
		2.5 mg/mL	

The Diluted Intravenous Remodulin Concentration for the person in Example 4 would thus be prepared by adding 2.7 mL of 2.5 mg/mL Remodulin Injection to a suitable reservoir along with a sufficient volume of diluent to achieve a total volume of 100 mL in the reservoir. The pump flow rate for this example would be set at 2 mL/hr.

HOW SUPPLIED

Remodulin® is supplied in 20 mL multi-use vials at concentrations of 1mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL treprostiniL, as sterile solutions in water for injection, individually packaged in a carton. Each mL contains treprostiniL sodium equivalent to 1mg/mL, 2.5 mg/mL, 5 mg/mL, or 10 mg/mL treprostiniL. Unopened vials of Remodulin are stable until the date indicated when stored at 15 to 25°C (59 to 77°F). Store at 25°C (77°F), with excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

During use, a single reservoir (syringe) of undiluted Remodulin can be administered up to 72 hours at 37°C. Diluted Remodulin Solution can be administered up to 48 hours at 37°C when diluted to concentrations as low as 0.004 mg/mL in Sterile Water for Injection or 0.9% Sodium Chloride Injection. A single vial of Remodulin should be used for no more than 30 days after the initial introduction into the vial.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If either particulate matter or discoloration is noted, Remodulin should not be administered.

20-mL vial containing treprostiniL sodium equivalent to 1 mg treprostiniL per mL, carton of 1 (NDC 66302-101-01).

20-mL vial containing treprostiniL sodium equivalent to 2.5 mg treprostiniL per mL, carton of 1 (NDC 66302-102-01).

20-mL vial containing treprostiniL sodium equivalent to 5 mg treprostiniL per mL, carton of 1 (NDC 66302-105-01).

20-mL vial containing treprostiniL sodium equivalent to 10mg treprostiniL per mL, carton of 1 (NDC 66302-110-01).

US Patent No. 5,153,222 (Use Patent)

United Therapeutics Corp.
Research Triangle Park, NC 27709

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REMODULIN manufactured by:

Baxter Pharmaceutical Solutions LLC
Bloomington, IN 47403

NDA 21-272/S-002

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For United Therapeutics Corp.
Research Triangle Park, NC 27709

Rx only

November 2004

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-272/S-002

MEDICAL REVIEW(S)



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Divisional Memorandum

NDA: 21-272 (Remodulin; treprostinil for pulmonary hypertension)
Sponsor: United Therapeutics
Submission: SE3-002 (30 January 2004): a request to approve Remodulin for IV use in pulmonary hypertension.

Review date: 24 November 2004

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Comments here are based on reviews by Drs. Karkowsky (medical), Beasley (biopharmaceutics), Joseph (pharmacology), and Advani (chemistry).

The chemistry review recommends that 5% dextrose not be used as a diluent, since this use results in accelerated degradation.

The sponsor submitted 13-week toxicology studies in rats and dogs, the review of which uncovered no novel concerns.

The sponsor performed a crossover comparison of pharmacokinetics in 51 normal volunteers administered Remodulin by SC and IV routes at 10 ng/kg/min for 24 hours. AUC and C_{max} were within conventional limits for acceptable bioequivalence. Plasma levels are most easily distinguished at offset, where the terminal phase with SC is somewhat slower. No clinical implication of this difference is expected.

The sponsor also, at the Division's request, submitted complete case report forms for an ongoing investigator-initiated study of patients being switched from IV Flolan to IV Remodulin (n=24) or initiated on IV Remodulin (n=14) and followed for up to 12 weeks. The clinical review identified numerous apparently line-related adverse events (infection or pain), but no novel safety findings. Dr. Karkowsky's review stops short of a recommendation on approval, but he does recommend that the IV route be reserved for use in patients not able to tolerate pain associated with the SC route, although no study demonstrated that the IV route is superior in this regard. The safety concern is amply supported by a post-marketing safety review of (again) presumed line-related events with Flolan. And certainly, there are inadequate data to support exchange of Remodulin for Flolan.

The sponsor has categorically denied inappropriate financial arrangements with investigators per 21CFR 54.2(a), (b), or (f).

The Division has waived pediatric studies with Remodulin.

The original approval of Remodulin was under Subpart H, and the sponsor has not met its post-marketing commitments. Approval of Remodulin by this new route will continue to be subject to the original commitments.

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/s/

Norman Stockbridge
11/24/04 10:41:55 AM
MEDICAL OFFICER

Division of Cardio-Renal Drug Products
 Medical Officer Review

NDA 21,272

Name of Drug: Treprostinil, Remodulin, UT-15.

Date of Submission Aug 27, 2004 and Sept 20, 2004

Type of Review and Summary:

This review is the sponsor's response to the deficiencies and request for information in the letters of 22 June 2004 and 15 September 2004. There is also a minimal set of data among patients who were newly initiated on Treprostinil. Approximately 2/3 of these patients were transitioned from Flolan to Treprostinil. To the extent that this data is interpretable, the results show no clinical deterioration (NYHA class change, or walk distance from baseline) for those not discontinuing the study. The preliminary data, however, did show worsened hemodynamics.

This submission attempts to address the following two previously noted deficiencies.

- 1) The effect of the intravenous route of administration on the safety profile of UT-15 when compared to the subcutaneous route. Since the steady-state concentrations when administered either by the subcutaneous or intravenous routes are the same, the safety issue is limited to the infusion site reactions.

- 2) Compatibility with blood with respect to flocculation or hemolysis was studied with higher concentrations of Treprostinil than in the previously performed studies. In those studies, the concentrations of Treprostinil was higher (approximately 100 ug/ml) when compared to previous studies (198 ng/ml). The results of the compatibility studies are shown below.

	Concentration of UT-15	Blood from Men (n=3)	Blood from women (N=3)
Plasma Hemoglobin Concentration g/dL	0	0.3 + 0.1	0.2 + 0.1
	5 ug/ml	0.2 + 0.1	0.2 = 0.1
	25 ug/ml	0.2 + 0.1	0.2 + 0.0
	50 ug/ml	0.2 + 0.1	0.2 + 0.1
	100 ug/ml	0.2 + 0.0	0.2 + 0.1
Plasma Potassium Concentration mEq/L	0	3.74 + 0.02	3.40 + 0.13
	5 ug/ml	3.66 + 0.01	3.25 + 0.08
	25 ug/ml	3.64 + 0.03	3.24 + 0.10
	50 ug/ml	3.63 + 0.04	3.27 + 0.11
	100 ug/ml	3.80 + 0.04	3.46 + 0.14
Plasma Visual Hemolysis	0	None for all	None for all
	5 ug/ml		
	25 ug/ml		
	50 ug/ml		
	100 ug/ml		
Plasma Visual Flocculation	0	None for all	None for all
	5 ug/ml		
	25 ug/ml		
	50 ug/ml		
	100 ug/ml		

There were small increases in potassium concentrations in the high concentrations in both men and women. There, however, is no convincing dose-response effect. None of the other parameters suggest significant hemolysis or flocculation at the modest doses employed in the study.

Other submitted data:

The sponsor submits an interim report on 38 patients out of the planned 50 patients who were enrolled in an intravenous Remodulin protocol. This population consisted of 24 patients who had been treated with intravenous Flolan and have been switched to Remodulin and 14 de novo patients. The duration of exposure in this study was 12-weeks. A 1-year follow up safety experience was also planned.

The study does, however, allow some insight into the consequence of switching Flolan patients the intravenous route of Remodulin infusion. Based on the reading of the case report forms and summaries supplied by the sponsor there were several patients who were transitioned to Remodulin from Flolan but were symptomatic from their pulmonary hypertension and were switched back to Flolan.

Since the sponsor's report is preliminary in nature, and since the only available data reflect a change in the parameter at 6 and 12 weeks compared to baseline, no conclusion with regards to efficacy can be made. Nevertheless, the available paired baseline and on-therapy measurements limited to those not discontinuing therapy does not suggest that Remodulin should be routinely substituted for Flolan.

The symptomatic measurements include 6 minute walk, Naughton protocol, and hemodynamics. With respect to the de novo patients (n=14) there were increases over baseline measurements in week 6 (n=12) and 12 weeks (n=9) in the 6-minute walk; and in the Naughton protocol at 6 weeks (N=13) and 12 weeks (N=9). Hemodynamics in the de novo population showed an increase in CI and a decrease in PVRI, positive hemodynamic responses. For the population transitioning from Flolan (n=24), there were no differences in the 6-minute walk at 6-weeks (n= 16) and 12 weeks (n=11) or Naughton protocol at 6-weeks (n=16) and 12-weeks (n=11). At 12-weeks, there were worsening of hemodynamic parameters as indicated by a decrease in CI and an increase in PVRI and PAPm. Since there were no concurrent controls remaining on Flolan, it is impossible to determine if these changes reflect the natural course of the disease or the worsening in status based on the change in therapy.

I examined the case report forms for adverse events for those who were enrolled in the 12-week portion of the study. The specific adverse events possibly related to the infusion method and site is shown in the Table below. Since the site of the intravenous line is not specified in the case report form, and causality to the intravenous route was not elicited, it is unclear how these events were truly site related.

Patient ID	Event	Specifics
Patient (b) (6)	50y/o W/F NYHA IV,	Hickman catheter infection of moderate severity treated with Keflex after 6 months
Patient (b) (6)	29 y/o W/F, NYA III	Right arm hematoma swelling of severe intensity (patient appears to be the index case of the original review.)
Patient (b) (6)	55 y/o W/M NYHA III	Swelling of hands of mild/moderate intensity.
Patient (b) (6)	58 y/o Asian/F NYHA III	Left upper arm swelling and painful swelling in fingers, shoulder aches all mild in intensity
Patient (b) (6)	28 y/o W/F, NYHA II	Right arm pain of mild intensity
Patient (b) (6)	57 y/o W/M NYHA III	Paresthesias both arms of moderate intensity
Patient (b) (6)	52 y/o W/F, NYHA II	Bilateral arm pain, muscle pain.
Patient (b) (6)	46 y/o Hispanic/, NYHA II	Line sepsis, moderate intensity
Patient (b) (6)	54 y/o W/F; NYHA II	Bilateral underarm pain of moderate intensity.

There were a total of 9 of the 38 patients who had some adverse event that in this reviewer's opinion may have been related to the route of infusion.

Conclusion:

Should the application be approved, the intravenous route of Remodulin infusion should be limited to those not tolerating subcutaneous infusion. The additional risk attendant to the use of an indwelling intravenous line, would make the intravenous route of administration inherently more risky. I would discourage switching from intravenous Flolan to intravenous Remodulin. There is inadequate information that efficacy of Remodulin is equivalent between the effect of Flolan.

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/s/

Abraham Karkowsky
10/25/04 11:45:53 AM
MEDICAL OFFICER

Clinical Review Cover Sheet

Clinical Review for NDA 21-272

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Executive Summary

Division of Cardio-Renal Drug Products
Medical Officer Review

NDA 21-272 (SE3)

Name of Drug Remodulin (Trepstinil sodium, UT-15)

Date of Submission: Jan 30, 2004; Document room received Feb 2, 2004

Date of Review: July 6, 2004

Introduction: This amendment proposes for the inclusion in labeling of an additional route for the administration of UT-15, and that the INSTRUCTIONS FOR USE section should be expanded to allow for the administration of UT-15 either by a SC (currently approved) or an intravenous route via a centrally dwelling intravenous catheter. No clinical trials were submitted that demonstrating a clinical benefit of UT-15 when it was administered by the intravenous (central catheter) route. Efficacy is based on equivalence of serum concentrations of UT-15 in normals, when comparing UT-15 as administered by the intravenous route (at a dose of 10-ug/kg/min) to the approved subcutaneous route for 72 hours.

A summary of the comparative PK parameters is shown below. Please see the review by Dr. Beasley (Nguyen) for additional discussion. The two routes of administration appear to yield equivalent concentrations and pharmacokinetic parameters, although, the coefficient of variation is greater by the intravenous route compared to the subcutaneous route. Consequently, the anticipated effect and safety profile of UT-15 via the subcutaneous route and intravenous route should be the same. The only additional information necessary is the consequence of higher concentrations of UT-15 at the site of introduction into blood, as well as the effect of UT-15 on inflammatory responses at the new site of administration.

Table 1. PK parameters in all 51 subjects – primary analysis

Parameter	Geometric LS Mean (CV %)		Comparison ¹
	IV	SC	
AUC _{ss} (ng • hr/mL)	25.7 (22.0)	27.6 (16.2)	92.9 (89.8, 96.1)
C _{max ss} (ng/mL)	1.5 (37.5)	1.4 (16.1)	106.0 (99.4, 113.0)

1. Comparisons are based on a general linear model for a two period crossover design fit using PROC GLM or MIXED, SAS ver 8.0. Number is ratio of geometric LS means with 90 % CI

With respect to the effect of high concentration of UT-15 on blood components, the sponsor submits safety data which includes hemolysis and flocculation studies. The hemolysis study was carried out with washed human blood (a 50% suspension of washed erythrocytes in saline) at a concentration of UT-15 of 198-ng/ml. The amount of free hemoglobin generated was equivalent when UT-15 was incubated with the erythrocytes as when saline control or citrate buffer was used as a control. Similar results were obtained when canine erythrocytes were incubated with UT-15. Flocculation studies at the same concentration of UT-15 as above with human or canine plasma did not lead to increased turbidity relative to saline or citrate controls. No positive controls were included.

[Comment: The flocculation and hemolysis studies did not use adequate concentrations of UT-15 to assess the ability of the solution to induce flocculation or hemolysis. The concentration of UT-15 employed to detect flocculation or hemolysis, was approximately 198-ng/ml, approximating the concentrations observed at C_{max} for high

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infusion rates. The current labeling for UT-15 has instructions for infusion rates based on a concentration of an infusion solution of 10 mg/ml. For those requiring large infusion rates (e.g., 50 ng/kg/min, for a 70 kg subject) this concentration can be diluted approximately 1:50 in the infusion reservoir so that infusion rates of approximately 1 cc/hr can be administered. The concentration of UT-15 in the reservoir could be approximately 200 ug/ml, three orders of magnitude greater than the concentration employed in the flocculation and hemolysis studies. .

With respect to animal studies and the effect of UT-15 at the site of the infusion, the sponsor has completed and submitted (b) (4)

(b) (4)

(b) (4)

Dr. Joseph, the FDA pharmacologist, has not yet completed the review of these studies, with respect to the effect of short-term study on infusion site pathology.

(b) (4) has been submitted (with (b) (4) the study has not yet been reviewed.

There is limited experience in humans receiving UT-15 by the intravenous route. During the crossover pharmacokinetic study 55 subjects received UT-15 by the intravenous route for 72 hours. Of the 55 subjects, 45 had adverse events attributable to the infusion site (e.g., edema, erythema, pain, reaction, induration or pruritis). In 12 subjects one or more of these events was classified with a severity of “moderate”. The other adverse events were classified with an intensity of ‘mild’.

There were an additional 5 studies during which patients received UT-15 intravenously for periods of up to 150 minutes. There were a total of 75 subjects or patients with PPH or CHF.

The sponsor indicates that as part of an ongoing study, 14 subjects (50 patients are planned), so far, have been treated with UT-15 by a central route of administration. Among those who completed 12-weeks intravenous therapy, the average dose was approximately 33-ng/kg/min. There was one serious adverse event among the 14 subjects related to the site of infusion. The adverse event is described below. The MedWatch report is appended.

REM_00047_2003 concerns a 28-year old female with SLE and pulmonary hypertension. Additional history includes pulmonary embolism, DVT, with IVC filter placement, recurrent UTI, arthritis, arthralgia, urticaria, diffuse hair thinning, photosensitivity, positive FANA 1:640 (homogenous speckled, positive Ro antibody, depressed complement, elevated anti-DNA antibody), lupus nephritis with Class IV biopsy, lupus hypercoagulable state, rectal bleeding, allergy to penicillin and sulfa, transient diplopia, ORSA bacteremia, CMV esophagitis, vocal cord paralysis, past history of exploratory laparotomy and acute renal failure secondary to contrast.

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The patient had an episode of urosepsis or catheter related sepsis. She was apparently receiving medication via the Hickman catheter (Remodulin?). The Hickman catheter was removed and a PICC line placed for Remodulin infusion. After a little more than 2 weeks, the PICC line was removed and a new Hickman catheter placed. The platelet count was 68K at the time of discharge.

Five days after discharge she complained of swelling under her right arm diagnosed as a hematoma. Approximately 2 weeks later, she complained of swelling which encompassed the entire right arm up to the wrist, including the dorsum of the hand. An ultrasound was performed showing a fluid collection and a hematoma. A chest CT showed a large right axillary hematoma. There was a suggestion of stenosis of the right proximal subclavian vein, however this may be artifactual and no evidence of pulmonary embolism. Her coumadin was withheld.

The patient was admitted to an outside hospital approximately 6 weeks after the initial sepsis episode for worsening dyspnea. She died the next day.

An autopsy report revealed the patient died of severe pulmonary hypertension with plexogenic changes and diffuse proliferative glomerulonephritis due to lupus (grade IV changes).

In summary, there was one serious adverse event associated with the infusion site. The full study report for those treated with UT-15 by the central intravenous route has not yet been submitted.

APPEARS THIS WAY ON ORIGINAL

CLINICAL REVIEW

Clinical Review Section

MEDWATCH Report

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U.S. Department of Health and Human Services

UNITED THERAPEUTICS CORP.

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

Form Approved OMB No. 0910-0291 Expires 04/30/05
 Please Forward Facsimile Mfr report # REM 00047_2003
 LFDist report #
 FDA Use Only

Page 1 of 5

Patient information			
1. Patient identifier (b) (6)	2. Age at time of event: 28 yrs or Date of birth: (b) (6)	3. Sex <input type="checkbox"/> female <input type="checkbox"/> male	4. Weight 165 lbs or kgs

B. Adverse event or product problem	
1. Adverse event and/or Product problem (e.g., defects/malfunctions)	
2. Outcomes attributed to adverse event (check all that apply)	<input type="checkbox"/> death <input type="checkbox"/> life-threatening <input type="checkbox"/> hospitalization - initial or prolonged <input type="checkbox"/> disability <input type="checkbox"/> congenital anomaly <input type="checkbox"/> required intervention to prevent permanent impairment/damage <input type="checkbox"/> other:
3. Date of event (month/year) 11/13/2003	4. Date of this report (month/year) 03/30/2004

5. Describe event or problem

A pulmonologist reported that a patient in an investigator driven study experienced sepsis/urosepsis, thrombocytopenia, hematoma, and right arm swelling. The patient is a 28 year old, 165 lb female with secondary pulmonary hypertension who has been receiving intravenous Remodulin for 3 months. The patient has a history of systemic lupus erythematosus, pulmonary embolism, right lower extremity DVT with IVC filter placement, recurrent urinary tract infections, arthritis, arthralgias, urticaria, diffuse hair thinning due to prednisone, vasomotor instability without true Raynaud's, photosensitivity, serologic abnormalities (positive FANA 1:640 homogenous and speckled, positive RO *

6. Relevant tests/laboratory data, including dates
Platelets 20 Nov 2003: (b) (6) 22 Nov 2003: 27 Nov 2003: 28 Nov 2003: 01 Dec 2003: *

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepato/renal dysfunction, etc.)
Secondary Pulmonary Hypertension Right Heart Failure Systemic Lupus Erythematosus Pulmonary Embolism: 02 Mar 2002 Right lower extremity DVT with IVC filter *

C. Suspect medication(s)			
1. Name (give labeled strength & mfr/labeler, if known)			
#1 REMODULIN	/USA/		
2. Dose, frequency & route used			
#1 *	3. Therapy dates (if unknown, give duration) (month or best estimate) #1 19-AUG-2003, continuing		
4. Diagnosis for use (indication)			
#1 *	5. Event abated after use stopped or dose reduced		
#2	#1	yes	no
		doesn't apply	
6. Lot # (if known)			
#1 NI	7. Exp. date (if known)		
#2	#1 NI		
8. Event reappeared after reintroduction			
		#1	yes
		#2	yes
		no	
		doesn't apply	
9. NDC # - for product problems only (if known)			
#1 NI		#2	
10. Concomitant medical products and therapy dates (exclude treatment of event)			
Name: LOVENOX Dates: NI, not continuing Name: argatroban Dates: NI, not continuing Name: Prednisone Dates: NI, continuing *			

G. All manufacturers	
1. Contact office - name/address (& mfg site for devices)	2. Phone number
UNITED THERAPEUTICS CORP. 1 Park Drive P.O. Box 14186 Research Triangle Park, NC 27709	1 919 485 8350
4. Date received by manufacturer (month/year) 01/05/2004	3. Report source (check all that apply)
6. If IND, protocol #	<input type="checkbox"/> foreign <input type="checkbox"/> study <input type="checkbox"/> literature <input type="checkbox"/> consumer <input type="checkbox"/> health professional <input type="checkbox"/> user facility <input type="checkbox"/> company representative <input type="checkbox"/> distributor <input type="checkbox"/> other:
7. Type of report (check all that apply)	5. (A)NDA # 21-272
5-day	IND #
10-day	PLA #
Initial	pre-1938 <input type="checkbox"/> yes
follow-up # 2	OTC product <input type="checkbox"/> yes
8. Adverse event term(s)	9. Mfr. report number
SEPSIS, UROSEPSIS, THROMBOCYTOPENIA, OEDEMA, PERIPHERAL, HAEMATOMA, CATHETER SITE ECCHYMOSIS, AXILLARY VEIN THROMBOSIS, SUBCLAVIAN VEIN *	REM_00047_2003

E. Initial reporter	
(b) (6)	



Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.
 * Item completed on continuation pages.

2. Health professional? yes no	3. Occupation PHYSICIAN	4. Initial reporter also sent report to FDA yes no unk
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CLINICAL REVIEW

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B.5. Describe event or problem

[continuation:] antibody, depressed complement, elevated anti-DNA antibody), lupus nephritis with Class IV biopsy, lupus hyper-coagulable state, rectal bleeding, allergy to penicillin and sulfa, transient diplopia, ORSA bacteremia, CMV esophagitis, left total vocal cord paralysis, exploratory laparotomy, and acute renal failure secondary to IV contrast dye.

On (b) (6), the patient was transferred to (b) (6) from an outside hospital for sepsis presumed to be related to central venous catheter and/or urosepsis. The Hickman catheter was removed and a peripherally inserted central catheter (PICC) placed for infusion of treprostinil. The patient also developed thrombocytopenia (platelet count 24,000). The cause of thrombocytopenia was not entirely clear. The differential diagnoses included sepsis mediated destruction of platelets, idiopathic thrombocytopenia (ITP) possibly related to systemic lupus erythematosus or heparin-induced thrombocytopenia (HIT) from Lovenox (heparin fraction sodium salt). The patient was initially anticoagulated with argatroban, and HIT panels were sent but results did not reveal evidence of HIT. The PF4 ELISA revealed values of 0.13, 0.175, and 0.159, less than the 0.4 diagnostic value. The patient was seen by the hematology staff and it was thought that she may have ITP; she received six doses of IV immune globulin and was started on prednisone. Tapering of the prednisone resulted in a drop in the platelet count again and thus the patient was discharged on prednisone. Her platelet count prior to discharge was 68,000. The Hickman catheter was replaced and the PICC line removed on (b) (6). The patient was discharged (b) (6).

Days following discharge on (b) (6), the patient complained of swelling under her right axilla which appeared related to a hematoma per evaluation by her local physician. She presented to clinic on (b) (6) with a marked increase in swelling over the past several weeks since discharge associated with a fairly extensive hematoma accompanied by right arm swelling down to the wrist and even including the back of the hand. There was ecchymosis of the right lateral chest wall as well. In view of the patient's platelet count of 57,000, the extensive hematoma and the possibility of axillary/subclavian/brachial vein thrombosis, the patient was hospitalized for further evaluation. There may have been complications related to the PICC line removal and the thrombocytopenia. The question was also raised whether the treprostinil infiltrated local tissue inducing inflammation. The patient had an ultrasound that showed a fluid collection and a hematoma. A chest CT scan showed a large right axillary hematoma as described above. There was a suggestion of stenosis of the right proximal subclavian vein, however, this may be artifactual and no evidence of pulmonary embolism. Her Coumadin (warfarin) was held.

The patient developed suprapubic pain reminiscent of previous urinary tract infections. The pain was treated with Vicodin (hydrocodone bitartrate, acetaminophen) and oxycodone. Given the severity of this pain, aztreonam and Cipro (ciprofloxacin) were empirically started. The aztreonam was discontinued when the cultures were negative.

In the pulmonologist's opinion, the Hickman catheter placement and PICC line removal on (b) (6) together with the thrombocytopenia was the likely cause of the hematoma and right arm swelling. Her platelet count prior to discharge on (b) (6) was 59,000.

Dec 2003 the patient was contacted and reported resolution of bruising on her right thorax *

CLINICAL REVIEW

Clinical Review Section

B.5. Describe event or problem

[continuation:] but continued to have swelling and a hematoma of the right axilla and arm. It was unchanged from hospital discharge. She reported increased dyspnea on exertion, but had concomitant bronchitis diagnosed by her local physician. The patient was placed on a 7 day course of Tequin (gatifloxacin), prednisone taper, and albuterol inhaler. She denied any edema, chest discomfort, palpitations, or syncopal symptoms. On 22 Dec 2003, the thrombocytopenia had not completely recovered and a hematology consult thought this was representative of ITP. Coumadin (warfarin sodium) was restarted on 25 Dec 2003 at 2mg QD with an INR value of 1.7 after five days, as reported by the patient.

On 30 Dec 2003, the patient reported that her arm was still swollen and that there was still evidence of a hematoma. She also reported that the ecchymosis of right lateral chest wall was almost completely gone. She was down to 10mg QD of prednisone for the thrombocytopenia. The Coumadin (warfarin sodium) dose was not increased and the patient was scheduled to be seen in clinic at (b)(6). The patient was instructed to seek medical attention prior to that time if symptoms worsened.

Concomitant medications include prednisone 20mg QD, Lasix (furosemide) 40mg QD, Lovenox (heparin-fraction sodium salt), and argatroban. The patient received Remodulin (treprostinil) from (b)(6) via continuous intravenous infusion with a dose of 32 ng/kg/min at the time of the events. No medication was taken with Remodulin in management of these events.

FOLLOW UP INFORMATION:

On (b)(6) the patient was again admitted to an outside hospital with increased dyspnea. On (b)(6) the patient became restless and was treated with Valium (diazepam). She arrested shortly afterwards. The patient died the following day. In the pulmonologist's opinion, the patient most likely experienced pulmonary embolism or sudden death from pulmonary hypertension and bronchitis. An autopsy was performed. Results are pending.

FOLLOW UP INFORMATION RECEIVED ON 24 MAR 2004:

The autopsy report revealed the patient died of severe pulmonary hypertension with plexogenic changes and diffuse proliferative glomerulonephritis due to lupus (grade IV changes).

prednisone
immune globulin IV X 6
Vicodin (hydrocodone bitartrate, acetaminophen) PO Q4h PRN: (b)(6)
oxycodone 10 mg PO Q8h PRN: 17 Dec 2003 - (b)(6)
Colace (docusate sodium) 100 mg PO BID PRN: 17 Dec 2003 - 31 Dec 2003
Cipro (ciprofloxacin) 750 mg Q12h: 16 Dec 2003 - 26 Dec 2003
aztreonam: 16 Dec 2003 - 19 Dec 2003
Zofran (ondansetron hydrochloride) 4 mg PO PRN: 16 Dec 2003 - 31 Dec 2003
Tequin (gatifloxacin)
albuterol INH
(b)(6)um (diazepam) PO: 02 Jan 2003 *

CLINICAL REVIEW

B.6. Relevant tests/laboratory data (including dates)

[continuation:] 16 Dec 2003: 57,000

19 Dec 2003: 59,000

Urine culture negative: 19 Dec 2003

Ultrasound, CT scan - large right axillary hematoma and stenosis of right proximal subclavian vein:
Dec 2003

B.7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

[continuation:] placement: Mar 2002

Recurrent Urinary Tract Infections

Arthritis, Arthralgias

Urticaria

Diffuse hair thinning due to prednisone

Vasomotor instability without true Raynaud's

Photosensitivity

Serologic abnormalities: positive FANA 1:640 homogenous and

speckled, positive RO antibody, depressed complement, elevated anti-DNA

body

Glomerulonephritis with Class IV biopsy: Jan 2001

Deep hyper-coaguable state

Rectal bleeding

Allergy to penicillin, sulfa

Transient diplopia of uncertain etiology

ORSA bacteremia

CMV esophagitis

Left total vocal cord paralysis

Exploratory laparotomy: 18 Jan 2002

Acute renal failure secondary to IV contrast dye

Concomitant disease(s): Malar rash

Bronchitis

Race: CAUCASIAN

Pregnant: UNK

C.2. Dose, frequency & route used(Suspect #1)

32 NG/KG/MIN CONTINUOUS IV

C.4. Diagnosis for use (indication)(Suspect #1)

Secondary Pulmonary Hypertension

C.10. Concomitant medical products and therapy dates (exclude treatment of event)

[continuation:] Name: LASIX Dates: NI, continuing

Coumadin Dates: NI, continuing

CLINICAL REVIEW

Clinical Review Section

I. Recommendations

A. Recommendation on Approvability

I do not recommend approval of the intravenous route for administration of UT-15. Aside from an abstract and an adverse event, we do not have data when UT-15 is administered by a central route of administration. Once the data and safety of those treated by this route has been submitted for review, the issue of safety by this route can be reconsidered. Flocculation and hemolysis studies using adequate concentrations should be performed.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

Not applicable.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

There were no clinical studies performed. A single biopharmaceutical study demonstrated the equivalence in pharmacokinetic parameters comparing subcutaneous to intravenous routes of administration. The only safety information is derived from the biopharmaceutical study and preliminary data on 14 subjects who received the intravenous route of administration. One serious adverse event was reported.

B. Efficacy

Efficacy can be inferred from the equivalence of UT-15 parameters when comparing the concentrations in normals generated by the intravenous to the subcutaneous route.

C. Safety

Safety for most aspects of UT-15 can be inferred by the biopharmaceutical equivalence of UT-15 as administered by the intravenous compared to the SC route. The most common adverse event observed adverse events for the SC route are site pain, which are likely mitigated by the change in the route of administration. The consequence of site related irritation for the intravenous route of UT-15 administration is unclear.

D. Dosing

No new dosing recommendations result from this supplement. I cannot recommend that the central route can be considered as an alternative to the subcutaneous route. Since there are inherent additional risks to an indwelling central catheter in addition to the other risks of the use of UT-15, and should additional information satisfy the concern about the route of administration, the intravenous route should be considered only if the subcutaneous route is unusable.

E. Special Populations

No data on special populations are included.

CLINICAL REVIEW

Clinical Review Section

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

No new data was submitted.

B. State of Armamentarium for Indication(s)

UT-15 is currently approved to diminish symptoms associated with exercise in NYHA class II-IV pulmonary hypertension patients. No new clinical data were supplied.

C. Important Milestones in Product Development

The Division met with United Therapeutics on 15 December 2003.

D. Other Relevant Information

Not applicable

E. Important Issues with Pharmacologically Related Agents

Not applicable

A. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

See review by Dr. Nguyen (Beasley). The two routes of administration appear to yield similar kinetic constants (see Table 1).

B. Pharmacodynamics

No pharmacodynamic data were supplied.

CLINICAL REVIEW

Clinical Review Section

IV. Description of Clinical Data and Sources

A. Overall Data

One biopharmaceutical study was supplied that demonstrated equivalence of UT-15 as administered subcutaneously compared to intravenously administered drug.

B. Tables Listing the Clinical Trials

No clinical trials were submitted. One biopharmaceutical trial was, however, included in the submission.

C. Postmarketing Experience

The sponsor refers to a small series of patients who received UT-15 by the proposed route of administration

D. Literature Review

None performed

V. Clinical Review Methods

A. How the Review was Conducted

The review was limited to the submitted information.

B. Overview of Materials Consulted in Review

The submitted data include [REDACTED] (b) (4)
[REDACTED] (b) (4) was recently submitted to the pharmacology reviewer but has not yet been reviewed. A flocculation and hemolysis study was submitted.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Not applicable

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Not applicable

E. Evaluation of Financial Disclosure

CLINICAL REVIEW

Clinical Review Section

Not applicable

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Not applicable.

B. General Approach to Review of the Efficacy of the Drug Not applicable

No clinical data were available for review.

C. Detailed Review of Trials by Indication

None submitted.

D. Efficacy Conclusions

Not applicable.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

There is inadequate information to assure the safety when a centrally placed catheter for intravenous dosing administers UT-15. Both the flocculation and hemolysis studies used inadequate exposure to UT-15 to assure safety. There is limited experience in human subjects on the use of UT-15 by the proposed route of administration. There was one serious event associated with the intravenous route of administration. The safety of this route based on analogous compounds (Flolan) is of unclear utility. The sponsor has not yet submitted the safety of UT-15 as a central infusion as a full study.

B. Description of Patient Exposure

The biopharmaceutic study exposed normals for 72 hours at a dose of 10 ng/kg/min. The exposure in a cohort who received UT-15 by the central route is unclear.

C. Methods and Specific Findings of Safety Review

The concentration of UT-15 employed in the flocculation and hemolysis assays were only 198 ng/ml. The concentrations at the interface between the infusion media and blood are likely to be much higher.

CLINICAL REVIEW

Clinical Review Section

D. Adequacy of Safety Testing

There is minimal experience.

E. Summary of Critical Safety Findings and Limitations of Data

There is inadequate experience related to safety for the intravenous route of administration, particularly those adverse events related to the site of infusion. The hemolysis and flocculation studies were performed with inadequate concentrations of UT-15.

VIII. Dosing, Regimen, and Administration Issues

The only issue for this supplement is the route of administration. The data is reviewed under the executive summary section.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

None performed

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Not applicable.

C. Evaluation of Pediatric Program

There were a few subjects < 16 included in the original NDA. No new subjects within the pediatric age group were included in this submission.

D. Comments on Data Available or Needed in Other Populations

X. Conclusions and Recommendations

A. Conclusions

No clinical data were supplied. Data for safety for the use of UT-15 intravenously has not yet been submitted for review. Blood compatibility studies at a higher dose should be performed.

B. Recommendations

CLINICAL REVIEW

Clinical Review Section

XI. Appendix

A. Other Relevant Materials

Not applicable.

B. Individual More Detailed Study Reviews (If performed)

Not applicable.

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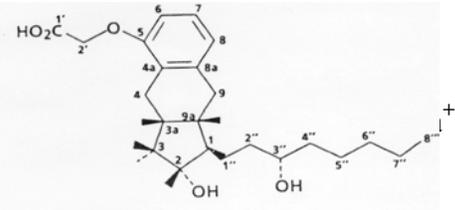
Abraham Karkowsky
7/6/04 01:27:03 PM
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-272/S-002

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 21-272
3. Name and Address of Applicant (City & State) United Therapeutics Corporation P.O. Box 14186, One Park Drive Research Triangle Park, NC 27709		4. Supplement(s) Number(s) Date(s) SE3-002 01-30-04
5. Drug Name Remodulin	6. Nonproprietary Name treprostinil sodium injection	7. Amendments & Other (reports, etc) - Dates
1. Supplement Provides For: A new intravenous route of administration and labeling revisions for the infusion of Remodulin via an indwelling central venous catheter. This is a Labeling Changes Efficacy Supplement		
9. Pharmacological Category New IV route for treatment of Pulmonary Arterial Hypertension (PAH)	10. How Dispensed <input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Injection	13. Potencies 1, 2.5, 5, 10 mg/mL	
14. Chemical Name and Structure  [[[(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. <u>Molecular Formula</u> C ₂₃ H ₃₃ NaO ₅ <u>Molecular weight</u> 412.49		15. Records/Reports Current <input type="checkbox"/> Yes <input type="checkbox"/> No Reviewed <input type="checkbox"/> Yes <input type="checkbox"/> No
16. Comments: In support of labeling changes associated with the intravenous (IV) use, firm has provided the following data 1) Stability study of Remodulin diluted in common IV diluents. Stability studies indicate that 5% dextrose in Injection should not be used. 2) The results of in-use stability study to support the extension of the shelf life of punctured vials. And proposed labeling revisions and revised vial and carton labeling. Microbiologist Stephen Langille also informally reviewed the antimicrobial testing data, and results are satisfactory (continued)		
17. Conclusions and Recommendations Claim for categorical exclusion from Environmental assessment is satisfactory. As revisions to chemistry section of draft package insert, we recommend that the labeling explicitly state that 5% dextrose should not be used as a diluent. Revised changes to vial and carton labels are acceptable. This supplement is satisfactory as far as chemistry and micro data is concerned. Supplement may be approved from CMC perspective.		

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/s/

J. V. Advani
7/23/04 02:15:10 PM
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Kasturi Srinivasachar
8/2/04 02:10:09 PM
CHEMIST

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-272/S-002

PHARMACOLOGY REVIEW(S)

NDA 21-272 SE3

REVIEW AND EVALUATION OF TOXICOLOGY DATA

**Xavier Joseph, D.V.M.
August 30, 2004**

NDA SUPPLEMENT 002 DATED: January 30, 2004
CENTER RECEIPT DATE: January 30, 2004
REVIEWER RECEIPT DATE: February 5, 2004

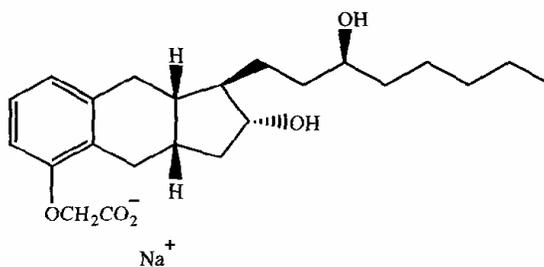
NDA SUPPLEMENT AMENDMENT DATED: May 4, 2004
CENTER RECEIPT DATE: May 5, 2004
REVIEWER RECEIPT DATE: May 06, 2004

NDA SUPPLEMENT AMENDMENT DATED: July 21, 2004
CENTER RECEIPT DATE: July 22, 2004
REVIEWER RECEIPT DATE: July 27, 2004

SPONSOR: United Therapeutics Corp., One Park Drive
P.O.Box 14186, Research Triangle Park, NC 27709

DRUG PRODUCT: Remodulin[®] Injection

DRUG: Generic name – Treprostinil sodium
Code names – UT-15, 15AU81 and LRX-15



M.W. 412.49

FORMULATION: Remodulin Injection is a sterile sodium salt solution supplied in 20 ml multi-use vials containing 1.0, 2.5, 5.0 or 10.0 mg/ml of treprostinil. Each ml of the formulation also contains 5.3 mg sodium chloride (except for the 10.0 mg/ml concentration 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 are added to adjust the pH between 6.0 and 7.2.

PHARMACOLOGICAL CLASS: Prostacyclin (PGI₂) analog

PROPOSED INDICATION: Treatment of pulmonary arterial hypertension (PAH)

PROPOSED DOSAGE REGIMEN: [Remodulin was approved earlier for continuous subcutaneous infusion for the treatment of PAH. With this supplemental NDA submission, the sponsor is requesting approval for a new route of administration (intravenous)]. Remodulin is administered by continuous subcutaneous or intravenous infusion at an initial infusion rate of 1.25 ng/kg/min, with [REDACTED] (b) (4) adjustments based on PAH symptoms and drug-related adverse effects. It is recommended that increments not to exceed 1.25 ng/kg/min per week for the first four weeks and 2.5 ng/kg/min per week for the remaining duration of infusion.

INDs UNDER WHICH CLINICAL TRIALS WERE CONDUCTED: IND 36,704 and IND 67, 561

DISCLAIMER: Tables and graphs are from sponsor’s submission unless stated otherwise.

TABLE OF CONTENTS

Pharmacology/Toxicology studies conducted with treprostinil sodium (Remodulin) were reviewed earlier (Original NDA Review dated March 12, 2001). Two additional toxicology studies, to support the new iv route of administration, were submitted with the May 4th amendment to the NDA supplement and are the subject of this review.

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INTRAVENOUS INFUSION TOXICITY STUDIES	
13-Week Continuous iv Infusion Toxicity Study in the Rat -----	3
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13-Week Continuous Intravenous Infusion Toxicity Study of Treprostinil Sodium in the Rat with a 4-Week Recovery Period

Key Study Findings: Continuous iv administration of treprostinil sodium at 0, 50, 300 and 900 ng/kg/min for 13 weeks produced dose-related reductions in platelet counts in treated males and females. Infusion site lesions were observed in both control and treated animals of both sexes. The infusion site lesions are considered to be associated with the test article delivery system (catheter).

Project Number: 500218

Location of Data: Amendments dated May 4, 2004 & July 21, 2004

Conducting Laboratory: (b) (4)

Date of Treatment Initiation: September 22, 2003

GLP Compliance: yes

QA Report: yes

Drug Lot # : 802324; purity - 99%

Formulation: Treprostinil sodium injection (1 mg/ml) was diluted daily to appropriate concentrations with the vehicle (containing citric acid, sodium citrate, sodium chloride and metacresol dissolved in sterile water, with a final pH of 6.0 to 7.2). The dose formulations were stored at room temperature, protected from light, prior to use. Dose formulations were determined to be stable for 48 hr at 40° C.

Methods**Animals**

Species/Strain: Rat/Sprague-Dawley CD (CrI:CD SD BR). Rats were obtained from (b) (4).

No./Sex/Group: 15 for main study, 5 for reversibility (control and high dose only), and 5 for toxicokinetics

Age: 10-11 weeks

Weight: males – 268 to 334 g; females – 190 to 253 g

Animals were housed individually in stainless steel wire mesh-bottomed cages equipped with an automatic watering valve and/or water bottle. A standard certified pelleted commercial laboratory diet (PMI Certified Rodent 5002: PMI Nutrition International, Inc.) and tap water (purified by reverse osmosis and exposed to ultraviolet light) were freely available.

Treatment

Doses Administered: 0, 50, 300 and 900 ng/kg/min

Infusion Rate: 0.75 ml/kg/hr

Concentrations of Test Solutions: 0, 4, 24 and 72 µg/ml for 0, 50, 300 and 900 ng/kg/min doses, respectively

The test/control articles were administered by continuous iv infusion for 13 weeks into the vena cava via a catheter inserted at the femoral vein.

Observations and Measurements

Clinical Signs and Mortality: twice daily

Physical Examination: weekly

Body Weight: pretest, weekly throughout the treatment and recovery periods, and before scheduled necropsy (body weight measurements were taken for TK animals, but were not reported)

Food Consumption: weekly (excluding TK animals)

Ophthalmology: pre-dose (all animals) and during week 13 (excluding TK animals)

Hematology: at necropsy (all main study and recovery animals) [parameters evaluated – RBC, WBC (total and differential) platelet and reticulocyte counts, hemoglobin, hematocrit, mean platelet volume, prothrombin and activated partial thromboplastin time, blood cell morphology, MCV, MCH and MCHC]

Clinical Chemistry: at necropsy (all main study and recovery animals) [parameters evaluated – BUN, creatinine, glucose, alkaline phosphatase, alanine and aspartate aminotransferases, total protein, albumin, globulin, A/G ratio, total bilirubin, cholesterol, triglycerides, calcium, chloride, inorganic phosphorus, potassium and sodium]

Urinalysis: end of weeks 13 and 17 (main study and recovery animals) [parameters evaluated – volume, color and appearance, specific gravity, pH, blood, bilirubin, urobilinogen, protein, glucose, ketones, nitrite, and microscopy of centrifuged sediments]

Toxicokinetics: Blood samples were collected from all TK animals on Day 1, at 3 hours post start of infusion, and on Days 7, 21, 35, 49, 63, 77 and 91 (at the same time as on Day 1) . [All TK animals were discarded after collection of the last blood sample without further examination.]

Postmortem Evaluation: At the end of the treatment or recovery period, complete necropsies were performed on all surviving animals, and adrenals, brain, heart, kidneys, liver, lungs, ovaries, pituitary, prostate, spleen, testes, thymus, thyroid lobes (with parathyroids) and uterus were weighed. The tissues listed in Table 1 were fixed in neutral buffered 10% formalin (except epididymides, eyes, optic nerves and testes, which were fixed in Zenker's fluid), and slides were prepared for microscopic examination. (Tissues were similarly collected from animals that were euthanized *in extremis* or that were found dead.) All tissues from control and high dose animals and gross lesions (all groups) were examined microscopically.

TABLE 1.

adrenals	
aorta (thoracic)	sciatic nerve
bone and marrow (sternum)	seminal vesicles
brain (cerebrum, cerebellum, midbrain and medulla oblongata)	skeletal muscle
cecum	skin (inguinal)
colon	spinal cord (cervical)
duodenum	spleen
epididymides	stomach
esophagus	testes
eyes	thymus
Harderian glands	thyroid lobes (and parathyroids)
heart (including section of aorta)	tongue
ileum	trachea
infusion site(s) [with catheter tip(s)]	urinary bladder
jejunum	uterus (cervix, horns and body)
kidneys	vagina
lacrimal glands	all gross lesions
liver (sample of 2 lobes)	
lungs	
lymph nodes (mandibular and mesenteric)	
mammary gland (inguinal)	
optic nerves	
ovaries	
pancreas	
pituitary	
prostate	
rectum	
salivary gland	

Statistical Analyses: For each parameter, group variances were compared using Levene's test. When differences between group variances were not found to be significant, a one-way analysis of variance (ANOVA) was performed. If significant differences among the means were indicated by the ANOVA, then the Dunnett's "t" test was used to perform the group mean comparisons between the control and treated groups.

Whenever Levene's test indicated heterogeneous group variances, then the Kruskal-Wallis test was used for group comparisons. If the Kruskal-Wallis test was significant, then the significance of the differences between control and treated groups was assessed using Dunn's test.

Results

Mortality: One high dose female (No.4508) and one low dose female (No.2506) were euthanized on Days 56 and 57, respectively, due to unresolvable catheter non-patency issues as the animals could no longer be dosed. A mid dose male (No.3008) was found dead on Day 64. On the day prior to death, red urine, swelling of the right inguinal region and enlarged testes were noted. A mass, noted from Day 39 and observed at necropsy in the right hindlimb area, correlated with microscopic findings of hemorrhage and abscess formation at that site. The cause of death of this animal was not determined.

A low dose TK male (No.2021) was euthanized on Day 54 due to deteriorating condition. This occurred 3 days after a repair surgery to fix a blocked catheter. Clinical signs noted included decreased activity, cold to touch, weakness, red stained fur, slight to moderate swelling of the abdominal and urogenital regions, red urine and decreased fecal output.

Clinical Signs: Increased incidences of skin redness of the fore and hind paws and/or of the pinnae were noted in mid and high dose males and in high dose females. No other treatment-related clinical signs were seen.

Body Weights: Body weight gain was slightly reduced for high dose animals during the first week of treatment, but was higher than control for the remainder of the treatment period and during the recovery period. No significant differences in weight gain were noted between control and lower dose groups.

Food Consumption: Food consumption was slightly higher than control for high dose males throughout the treatment period except for the first week of dosing when consumption was reduced. For females, food consumption was generally comparable between treated and control groups, with occasional increases in consumption at the high dose. No effect on food consumption was noted for either sex during the recovery period.

Ophthalmology: There were no treatment related findings.

Hematology: Dose-related decreases in platelet counts and increases in mean platelet volume were noted in all treated males and females (statistically significant at mid and

high dose levels) at the end of the treatment. After the recovery period, the platelet counts were slightly higher than control for both sexes at the high dose level.

Clinical Chemistry: There were no treatment related effects on clinical chemistry parameters except for a dose-related reduction in serum potassium levels in mid and high dose males and females.

Urinalysis: A slight increase in urine volume, compared to control, was noted for high dose females at the end of the treatment period.

Organ Weights: Increases in absolute and relative adrenal, heart, liver and lung weights were observed in high dose males and females. Following the 4-week recovery period, although the organ weight increases were reversible, heart weights were still slightly, though not significantly, increased in high dose animals.

Gross Pathology: Macroscopic lesions were seen at the infusion sites of control and treated animals. These lesions were described as “firm”, “mass”, “swelling” or “thickening”, and were seen in all groups. Lymph node enlargement in control and treated groups and splenic enlargement in treated groups were also observed.

Histopathology: Microscopically, lesions which were mainly seen at the infusion site (vena cava) of control and treated animals included vascular and perivascular inflammation, intimal proliferation, abscess formation and thrombosis. The incidence and the severity of lesions are given in Table 2. These infusion site lesions were considered to be test article delivery system (catheter)-related, rather than due to test article itself, since the incidences and severity were generally similar for treated and control groups. After a 4-week recovery period, thrombosis was present in control and high dose males and females (in more than 60% of animals) and perivascular inflammation was present in high dose females (in 60% of animals, Table 3)

Increased incidences of lymphoid hyperplasia of lymph nodes and increased extramedullary hematopoiesis in the spleen were seen in treated animals.

Toxicokinetics: The overall mean plasma steady-state UT-15 concentration values (C_{ss}) were comparable between male and female rats at each of the three doses tested. A linear relationship was observed between C_{ss} and UT-15 dose. The steady-state plasma concentrations were 2.68, 13.97 and 29.71 ng/ml for females and 2.48, 13.89 and 37.35 ng/ml for males at 50, 300 and 900 ng/kg/min dose levels, respectively.

TABLE 2. Incidence and Severity^b of Microscopic Findings at the Intravenous Infusion Site, Rat—Main Period

Group designation ^a	Male				Female			
	1	2	3	4	1	2	3	4
Dose	vehicle	50 ng/kg/min	300 ng/kg/min	900 ng/kg/min	vehicle	50 ng/kg/min	300 ng/kg/min	900 ng/kg/min
# of animals examined	15	4 ^c	8	15	15	7	8	15
Proliferation: intimal - total	1	0	0	0	0	0	0	0
Grade 1								
Grade 2	1							
Grade 3								
Grade 4								
Grade 5								
Thrombosis – total	13	2	5	10	13	7	8	11
Grade 1	4			1	2			4
Grade 2	4		2	5	2	2	4	
Grade 3	4		2	2	3		1	1
Grade 4	1	1	1	2	5	4	2	5
Grade 5					1	1	1	1
Inflammation: vascular – total	1	2	2	2	4	1	0	0
Grade 1								
Grade 2			1	1	1			
Grade 3		2	1		1			
Grade 4	1			1	2	1		
Grade 5								

^a Group 1 = vehicle control; Group 2 = 3 µg/kg/h (50 ng/kg/min); Group 3 = 18 µg/kg/h (300 ng/kg/min); Group 4 = 54 µg/kg/h (900 ng/kg/min)

^b Grade 1 = minimal; Grade 2 = slight; Grade 3 = moderate; Grade 4 = marked; Grade 5 = severe

^c in one animal (2015), the infusion site was examined but no findings were noted to correlate with the gross findings

TABLE 2. Incidence and Severity^b of Microscopic Findings at the Intravenous Infusion Site, Rat—Main Period (continued)

Group designation ^a	Male				Female			
	1	2	3	4	1	2	3	4
Dose	vehicle	50 ng/kg/min	300 ng/kg/min	900 ng/kg/min	vehicle	50 ng/kg/min	300 ng/kg/min	900 ng/kg/min
# of animals examined	15	4 ^c	8	15	15	7	8	15
Inflammation: perivascular - total	6	3	6	9	11	7	5	10
Grade 1	4	1	3	3	6	1	1	1
Grade 2	1		1	4				3
Grade 3					1	2		2
Grade 4		2	1	2	1	2	3	1
Grade 5	1		1		3	2	1	3
Abscess - total	0	1	0	0	3	2	2	3
Grade 1								
Grade 2		1						
Grade 3						1	2	
Grade 4					3	1		2
Grade 5								1

^a Group 1 = vehicle control; Group 2 = 3 µg/kg/h (50 ng/kg/min); Group 3 = 18 µg/kg/h (300 ng/kg/min); Group 4 = 54 µg/kg/h (900 ng/kg/min)

^b Grade 1 = minimal; Grade 2 = slight; Grade 3 = moderate; Grade 4 = marked; Grade 5 = severe

^c in one animal (2015), the infusion site was examined but no findings were noted to correlate with the gross findings

TABLE 3. Incidence and Severity^b of Microscopic Findings at the Intravenous Infusion Site, Rat—Recovery Period

Group designation ^a	Male			Female		
	1		4	1		4
Dose	vehicle		900 ng/kg/min	vehicle		900 ng/kg/min
# of animals examined	5		5	5		5
Proliferation: intimal - total	0		0	0		0
Thrombosis - total	4		4	5		3
Grade 1	2		1			1
Grade 2	2		3	2		1
Grade 3				3		1
Grade 4						
Grade 5						
Inflammation: vascular - total	0		0	0		0
Inflammation: perivascular - total	1		0	0		3
Grade 1						
Grade 2	1					2
Grade 3						1
Grade 4						
Grade 5						
Abscess - total	0		0	0		0

^a Group 1 = vehicle control; Group 2 = 3 µg/kg/h (50 ng/kg/min); Group 3 = 18 µg/kg/h (300 ng/kg/min); Group 4 = 54 µg/kg/h (900 ng/kg/min)

^b Grade 1 = minimal; Grade 2 = slight; Grade 3 = moderate; Grade 4 = marked; Grade 5 = severe

13-Week Continuous Intravenous Infusion Toxicity Study of Treprostinil Sodium in the Dog with a 4-Week Recovery Period

Key Study Findings: Continuous iv administration of treprostinil sodium at 0, 50, 100 and 200 ng/kg/min for 13 weeks produced dose-related reductions in platelet counts in treated males and females. Infusion site lesions were observed in both control and treated animals of both sexes. The infusion site lesions are considered to be associated with the test article delivery system (catheter).

Project Number: 500220

Location of Data: Amendments dated May 4, 2004 & July 21, 2004

Conducting Laboratory:  (b) (4)

Date of Treatment Initiation: September 30, 2003

GLP Compliance: yes

QA Report: yes

Drug Lot # : 802324; purity - 99%

Formulation: Treprostinil sodium injection (1 mg/ml) was diluted daily to appropriate concentrations with the vehicle (containing citric acid, sodium citrate, sodium chloride and metacresol dissolved in sterile water for injection, with a final pH of 6.0 to 7.2). The dose formulations were stored at room temperature, protected from light, prior to use. Dose formulations were determined to be stable for 48 hr at 40°C.

MethodsAnimals

Species/Strain: Dogs/Beagle - obtained from  (b) (4)

No./Sex/Group: 4 for main study, 2 for reversibility (control and high dose only)

Age: 6-7 months

Weight: males – 6.0 to 8.0 kg; females – 6.2 to 7.7 kg

Animals were housed individually in stainless steel cages equipped with a bar-type floor and an automatic watering valve. Mesh-floors were provided as considered necessary. A standard certified pelleted commercial dog food (about 400 g of Certified Canine Diet 5007, PMI Nutrition International, Inc.) was provided to each animal once daily. Tap water (purified by reverse osmosis and exposed to ultraviolet light) was freely available.

Treatment

Doses Administered: 0, 50, 100 and 200 ng/kg/min

Infusion Rate: 0.75 ml/kg/hr

Concentrations of Test Solutions: 0, 4, 8 and 16 µg/ml for 0, 50, 100 and 200 ng/kg/min doses, respectively

The test/control articles were administered by continuous iv infusion for 13 weeks into the vena cava via a catheter inserted at the femoral vein.

Observations and Measurements

Clinical Signs and Mortality: twice daily

Physical Examination: weekly

Body Weight: pretest, weekly throughout the treatment and recovery periods, and before scheduled necropsy

Food Consumption: daily during the last week of pretreatment period, and throughout the treatment and recovery periods

Electrocardiography: pretest and during week 13 (6-lead EKG on all animals)

Ophthalmology: pretest and during week 13

Clinical Pathology Investigations: Blood and urine were collected pretest and during weeks 13 and 17 for hematology, clinical chemistry and urinalysis evaluations.

Hematology: parameters evaluated – RBC, WBC (total and differential), platelet and reticulocyte counts, hemoglobin, hematocrit, mean platelet volume, prothrombin and activated partial thromboplastin time, blood cell morphology and erythrocyte indices (MCV, MCH, MCHC and red cell volume distribution width)

Clinical Chemistry: parameters evaluated – BUN, creatinine, glucose, alkaline phosphatase, alanine and aspartate aminotransferases, total protein, albumin, globulin, A/G ratio, total bilirubin, cholesterol, triglycerides, calcium, chloride, inorganic phosphorus, potassium and sodium

Urinalysis: parameters evaluated – Color and appearance, volume, specific gravity, pH, blood, bilirubin, urobilinogen, protein, glucose, ketones, nitrite and microscopy of centrifuged sediments

Toxicokinetics: Blood samples were collected prior to the start of infusion, at 3 hours post start of infusion on Day 1 and on Days 7, 21, 35, 49, 63, 77 and 91 at the same time as on Day 1 for toxicokinetic evaluations.

Postmortem Evaluations: At the end of the treatment or recovery period, complete necropsies were performed on all surviving animals, and brain, heart, kidneys, liver, lungs, ovaries/testes, pituitary, spleen, thymus, thyroid lobes (with parathyroids) and uterus were weighed. Tissues listed in Table 4 were fixed in neutral buffered 10% formalin (except epididymides, eyes, optic nerves and testes, which were fixed in Zenker's fluid), and slides were prepared for microscopic examination. (Tissues were

similarly collected from animals that were euthanized unscheduled during the course of the study.)

From all euthanized animals, 3 femoral bone marrow smears were prepared, one of which was stained. (These smears were not evaluated.)

TABLE 4.

adrenals	ovaries
aorta (thoracic)	pancreas
bone and marrow (sternum)	pituitary
brain (cerebrum, cerebellum, midbrain and medulla oblongata)	prostate
cecum	rectum
colon	salivary gland (submandibular)
duodenum	sciatic nerve
epididymides	skeletal muscle
esophagus	skin (inguinal)
eyes	spinal cord (cervical)
gallbladder	spleen
heart (including section of aorta)	stomach
ileum	testes
infusion site(s) with catheter tip(s)	thymus
jejunum	thyroid lobes (and parathyroids)
kidneys	tongue
lacrimal glands	trachea
liver (sample of 2 lobes)	urinary bladder
lungs	uterus (horns, body and cervix)
lymph nodes (mandibular and mesenteric)	vagina
mammary gland (inguinal)	all gross lesions
optic nerves	

Statistical Analyses: For each parameter, group variances were compared using Levene's test. When differences between group variances were not found to be significant, a one-way analyses of variance (ANOVA) was performed. If significant differences among the means were indicated by the ANOVA, then Dunnett's "t" test was used to perform the group mean comparisons.

Whenever Levene's test indicated heterogeneous group variances, then the Kruskal-Wallis test was used for group comparisons. If the Kruskal-Wallis test was significant, then the significance of the differences between the control and treated groups was assessed using Dunn's test.

Results

Mortality: One high dose male (No.406) and a low dose male (No.201) were euthanized on Days 47 and 88, respectively, due to patency problems with the catheter. Both these animals had elevated total white blood cell count, globulin and total protein levels, with reductions in A/G ratio and glucose levels. Elevated mean platelet volume was also observed in the high dose animal.

Clinical Signs: Liquid or soft feces, occasionally with mucoid material, and redness of the skin of pinnae, muzzle or lower jaw were seen more frequently in high dose animals than in controls.

Soft or liquid feces was not observed during the recovery period; however, redness of the skin persisted in a high dose female till the last week of the recovery period.

Body Weights: While body weights for high dose males were lower than control throughout the treatment and recovery periods, high dose females had lower weights only during the first three weeks of treatment. For lower dose groups, male and female body weights were generally comparable to control.

Food Consumption: Food consumption was slightly higher in high dose males throughout the treatment period except during the first week of dosing. For high dose females, food consumption was lower than control pretreatment, throughout treatment and during the recovery period.

Ophthalmology and Electrocardiography: There were no treatment related findings.

Hematology: A dose-related decrease (not statistically significant) in platelet counts for treated males and females, with an increase in mean platelet volume (statistically significant in males at the high dose and in females at mid and high dose levels), was observed. After the recovery period, the platelet counts were higher than control for both sexes at the high dose level and the mean platelet volume values were comparable to control.

Clinical Chemistry: There were no treatment-related effects on clinical chemistry parameters.

Urinalysis: No treatment-related effects.

Organ Weights: There were no treatment-related effects on organ weights except for an increase in absolute heart weight for all treated male groups (no dose response relationship) and an increase in relative heart weight for high dose males. After the 4-week recovery period, no significant heart weight effects were noted.

Gross Pathology: There were macroscopic findings at the infusion sites of control and treated dogs. These lesions were described as “firm”, “mass” or “thickening”, and females appeared to be less affected than males. Lymph node enlargement, mottling and dark discoloration were observed in some animals with infusion site lesions.

Histopathology: Microscopic lesions, which were mainly observed at the intravenous infusion site, included intimal proliferation, thrombosis and vascular and perivascular inflammation. The incidence and severity of these lesions are given in Table 5. These infusion site lesions were considered to be test article delivery system (iv catheter)-related, rather than due to the test article itself, since incidences and severity were generally similar for treated and control groups. After a 4-week recovery period, thrombosis was present in control and treated males and females (Table 6).

Erythrocytosis/hemorrhage of lymph nodes was present in both control and treated animals.

Toxicokinetics: A dose-related increase in steady-state plasma UT-15 concentration (C_{ss}) was observed in both males and females. No gender difference in C_{ss} values was observed. Steady-state plasma concentrations were 1.66, 3.46 and 6.76 ng/ml for females and 1.45, 2.96 and 4.79 ng/ml for males at 50, 100 and 200 ng/kg/min dose levels, respectively.

TABLE 5. Incidence and Severity^b of Microscopic Findings at the Intravenous Infusion Site, Dogs—Main Period

Group designation ^a	Male				Female			
	1	2	3	4	1	2	3	4
Dose	vehicle	50 ng/kg/min	100 ng/kg/min	200 ng/kg/min	vehicle	50 ng/kg/min	100 ng/kg/min	200 ng/kg/min
# of animals examined	4	4	4	5	4	4	4	4
Proliferation: intimal - total	2	1	0	1	0	0	1	1
Grade 1		1		1			1	
Grade 2	2							
Grade 3								1
Grade 4								
Thrombosis - total	1	2	4	4	4	4	3	3
Grade 1					2			1
Grade 2			2	1		3	1	2
Grade 3	1	1	2	1	2	1	2	
Grade 4		1		2				
Inflammation: vascular - total	1	0	0	1	0	0	0	0
Grade 1								
Grade 2								
Grade 3				1				
Grade 4	1							
Inflammation: perivascular- total	1	0	0	1	0	1	0	0
Grade 1								
Grade 2								
Grade 3	1			1				
Grade 4						1		
Abscess - total	0	0	0	0	0	0	0	0

^a Group 1 = vehicle control; Group 2 = 3 µg/kg/h (50 ng/kg/min); Group 3 = 6 µg/kg/h (100 ng/kg/min); Group 4 = 12 µg/kg/h (200 ng/kg/min)

^b Grade 1 = minimal; Grade 2 = slight; Grade 3 = moderate; Grade 4 = marked

TABLE 6. Incidence and Severity^b of Microscopic Findings at the Intravenous Infusion Site, Dogs —Recovery Period

Group designation ^a	Male				Female			
	1 vehicle	50 ng/kg/min	100 ng/kg/min	4 200 ng/kg/min	1 vehicle	50 ng/kg/min	100 ng/kg/min	4 200 ng/kg/min
# of animals examined	2			1	2			2
Proliferation: intimal - total	0			0	1			0
Grade 1					1			
Grade 2								
Grade 3								
Grade 4								
Grade 5								
Thrombosis - total	1			1	1			2
Grade 1								
Grade 2								
Grade 3	1				1			1
Grade 4				1				1
Grade 5								
Inflammation: vascular - total	1			0	0			0
Grade 1								
Grade 2								
Grade 3								
Grade 4								
Grade 5	1							
Inflammation: perivascular - total	0			0	0			0
Abscess - total	0			0	0			0

^a Group 1 = vehicle control; Group 2 = 3 µg/kg/h (50 ng/kg/min); Group 3 = 6 µg/kg/h (100 ng/kg/min); Group 4 = 12 µg/kg/h (200 ng/kg/min)

^b Grade 1 = minimal; Grade 2 = slight; Grade 3 = moderate; Grade 4 = marked; Grade 5 = severe

SUMMARY AND EVALUATION

Treprostinil sodium (Remodulin), a tricyclic benzindene analogue of prostacyclin (PGI₂, epoprostenol) with potent systemic and pulmonary vasodilatory and platelet antiaggregatory effects, is being proposed for chronic administration as a continuous **intravenous** (iv) infusion for the treatment of patients with pulmonary arterial hypertension (PAH). Unlike PGI₂, Remodulin is chemically stable at room temperature.

Remodulin was approved earlier by the U.S. FDA for continuous **subcutaneous** (sc) administration in treating patients with PAH. Infusion site pain and infusion site reaction were reported to be the most common adverse events among patients treated subcutaneously with Remodulin. The purpose of this supplemental NDA submission is to request approval of a proposed labeling extension to allow the use of Remodulin as a continuous iv infusion via an indwelling central venous catheter, (b) (4)

It is proposed that continuous infusion be started at a rate of 1.25 ng/kg/min with (b) (4) adjustments based on PAH symptoms and treatment-related adverse effects. It is recommended that the increments not exceed 1.25 ng/kg/min per week for the first four weeks and then no more than 2.5 ng/kg/min per week for the remaining duration of infusion, depending on clinical response. It is also recommended that for iv infusion, Remodulin be diluted with Sterile Water for Injection or 0.9% Sodium Chloride Injection prior to administration. For sc infusion, it is administered without any dilution.

This NDA supplemental application for approval of the new iv route of administration is supported by 13-week continuous central venous iv infusion toxicity studies in rats and dogs.

Treprostinil sodium was administered to rats at 0, 50, 300 and 900 ng/kg/min, and was administered to dogs at 0, 50, 100 and 200 ng/kg/min. The notable findings, observed in both species, included dose-related decreases in platelet counts with increases in mean platelet volume in treated males and females, and microscopic lesions at the infusion site. The infusion site lesions, which included intimal proliferation, thrombosis, abscess formation, and vascular and perivascular inflammation, were seen in both control and treated animals.

After the 4-week drug-free recovery period, the platelet counts were higher than control at the high dose in both species, and thrombosis was present at the infusion site in control and high dose rats and dogs (lower dose animals not examined).

Infusion site lesions were also observed in control and treated animals in 14-day continuous iv infusion studies in rats and dogs.

The infusion site lesions are considered to be test article delivery system (catheter)-related, rather than due to the test article itself, since the incidences and severity of lesions were generally similar for treated and control animals. Catheter-related

thrombosis and infection are reported to be two of the most common and clinically important complications associated with central line catheters [Hubbard and Jenkins, 1990. Chemotherapy administration: Practical guidelines. *In* Cancer Chemotherapy: Principles and Practice. Chabner, B.A. and Collins, J.M. (eds). J.B. Lippincott Co. Philadelphia, pp 449-464.]

With Flolan [epoprostenol sodium, a drug approved for the long-term iv treatment of primary pulmonary hypertension (PPH) via an indwelling central venous catheter] therapy, adverse events attributable to the drug delivery system observed in a 12-week controlled clinical trial included local infection (up to 21% of patients) and pain at the injection site (up to 13% of patients). In a long-term follow-up to the PPH trial, sepsis was reported at least once in 14% of patients and occurred at a rate of 0.32 infections/patient per year in patients treated with Flolan. This rate was higher than reported in patients receiving parenteral nutrition via chronic indwelling central venous catheters, but lower than reported in oncology patients using these catheters.

In vitro studies with human and canine blood have shown neither hemolysis nor precipitation of plasma proteins at a concentration of 200 ng treprostinil sodium/ml. Studies in rats showed that 14-day continuous iv infusion at doses up to 1500 ng/kg/min (at a concentration of 120 µg treprostinil sodium/ml) or 13-week continuous iv infusion at doses up to 900 ng/kg/min (at a concentration of 72 µg/ml) did not produce any adverse effects on erythrocyte parameters (RBC count, hemoglobin, hematocrit or erythrocyte indices). Remodulin labeling indicates that there is little experience with clinical doses > 40 ng/kg/min, and that for a 75 kg individual, at a dose of 30 ng/kg/min, the concentration of diluted iv Remodulin solution for infusion is calculated to be 67.5 µg/ml. Since concentrations above this level were used in toxicity studies without any adverse effects on erythrocyte parameters, this concentration is considered to be safe. (The average sc dose achieved in clinical trials is determined to be 9.3 ng/kg/min.)

Studies in adult volunteers showed that Remodulin (10 ng/kg/min) administered by the iv route is bioequivalent at steady-state to the drug given by the sc route.

Both rat and dog studies appear to have been adequately performed.

In summary, no significant drug-specific adverse effects were noted in the 13-week continuous iv infusion toxicity studies in rats and dogs. Reductions in platelet counts observed in these iv studies were not seen in 6-month continuous sc infusion studies. Platelet count reductions, of up to 51% relative to baseline, have been reported in patients following iv Remodulin administration, with no clinically adverse consequences. Infusion site lesions, observed in both control and treated animals, appear to be related to the test article delivery system rather than to the drug itself. Similar lesions are reported to be commonly observed as clinical complications associated with central line catheters.

RECOMMENDATION

The NDA supplement is approvable, and the revised labeling acceptable, from the perspective of pharmacology/toxicology.

Xavier Joseph, D.V.M.

Accepted by _____ on _____

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Xavier Joseph
9/1/04 10:47:07 AM
PHARMACOLOGIST

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-272/S-002

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-272	Submission Date(s): 1/30/04, 3/05/04
Brand Name	Remodulin
Generic Name	Treprostinil sodium, UT-15
Reviewer	B. Nhi Beasley, Pharm.D.
Team Leader	Patrick Marroum, Ph.D.
OCPB Division	One
ORM division	Cardio-Renal
Sponsor	United Therapeutics Corp
Submission Type; Code	SE 002
Formulation; Strength(s)	Injection, 1.0, 2.5, 5.0, 10.0 mg/mL
Indication	Pulmonary arterial hypertension with NYHA Class II-IV

1 EXECUTIVE SUMMARY

Treprostinil sodium is a direct vasodilator of pulmonary and systemic arterial vascular beds that is approved for pulmonary arterial hypertension in patients with NYHA Class II-IV symptoms to diminish symptoms associated with exercise. The approved route of administration is subcutaneous (SC). The sponsor is proposing that the drug also be given by the intravenous (IV) route via a central venous catheter.

To obtain approval for this new route of administration, the sponsor showed that treprostinil sodium administered through a peripheral IV line was bioequivalent at steady state to treprostinil sodium administered subcutaneously (study REM 1:14). The primary analysis consisted of 51 healthy subjects who completed at least 24 hours of dosing in each period (72 hours of continuous treprostinil sodium 10 ng/kg/min). Table 1 shows the mean and ratios with 90 % confidence intervals for AUC_{ss} and $C_{max_{ss}}$. The routes of administration are bioequivalent.

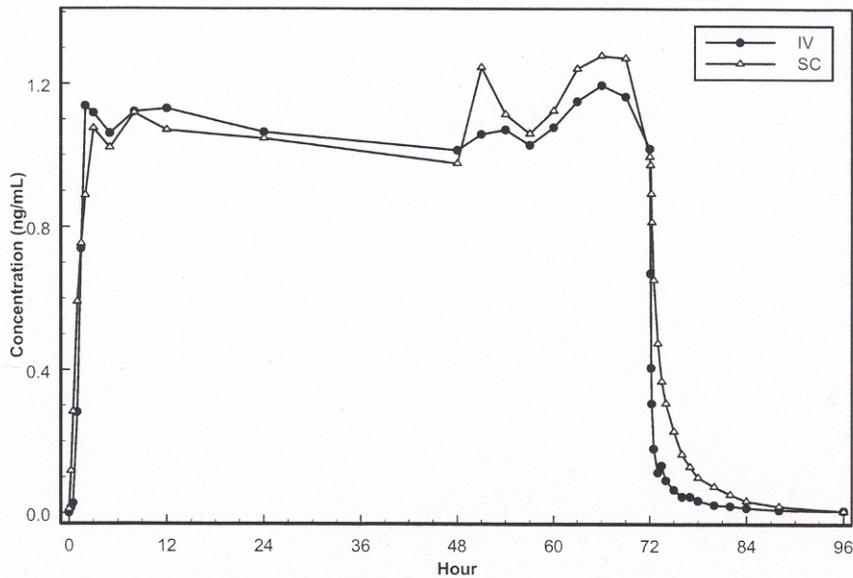
Table 1. PK parameters in all 51 subjects – primary analysis

Parameter	Geometric LS Mean (CV %)		Comparison ¹
	IV	SC	
AUC_{ss} (ng • hr/mL)	25.7 (22.0)	27.6 (16.2)	92.9 (89.8, 96.1)
$C_{max_{ss}}$ (ng/mL)	1.5 (37.5)	1.4 (16.1)	106.0 (99.4, 113.0)

1. Comparisons are based on a general linear model for a two period crossover design fit using PROC GLM or MIXED, SAS ver 8.0. Number is ratio of geometric LS means with 90 % CI

Figure 1 shows that the concentrations of treprostinil administered by both routes are very similar.

Figure 1. Mean plasma concentration of Remodulin IV and SC Infusion (linear plot)



1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the submission and recommends that the intravenous route of administration is bioequivalent to the subcutaneous route of administration provided that no major deficiencies have been identified at the study site.

The labeling comments should be addressed.

1.2 Phase IV Commitments

Not applicable.

The optional intra-division briefing was held on April 12, 2004. Drs. Patrick Marroum and Mehul Mehta were present.

B. Nhi Beasley, Pharm.D.
Division of Pharmaceutical Evaluation I

FT Initialed by Patrick Marroum, Ph.D. _____
CC list: HFD-110: NDA 21-272; HFD-860: (Mehta, Sahajwalla); CDER Central Document Room

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3 SUMMARY OF CPB FINDINGS

The sponsor showed that treprostinil sodium administered through a peripheral IV line was bioequivalent at steady state to treprostinil sodium administered subcutaneously (study REM 1:14). The primary analysis consisted of 51 healthy subjects who completed at least 24 hours of dosing in each period (72 hours of continuous treprostinil sodium 10 ng/kg/min). Table 1 (page

1 of Executive Summary) shows the mean and ratios with 90 % confidence intervals for AUC_{ss} and C_{max,ss}. The routes of administration are bioequivalent. Figure 1, (page 2 of Executive Summary) shows that the concentrations of treprostinil sodium administered by both routes are very similar.

4 QBR

4.1 General Attributes

N/A

4.2 General Clinical Pharmacology

N/A

4.3 Intrinsic Factors

N/A

4.4 Extrinsic Factors

N/A

4.5 General Biopharmaceutics

4.5.1 Was treprostinil sodium administered by the IV route bioequivalent to treprostinil sodium administered by the SC route?

Yes, after 72 hours of continuous infusion, the two formulations were bioequivalent. Figure 1, on page 2 of the Executive Summary illustrates that the concentration time profiles are very similar. Table 1 on page 1 of the Executive Summary shows that the 90 % confidence interval of the ratios for AUC and C_{max} were within the accepted 80 – 125 % confidence limits; mean (90 % confidence interval) for AUC_{ss} was 93 % (90 – 96 %) and for C_{max,ss} was 106 % (99 – 113 %).

4.6 Analytical

4.6.1 Was the analytical method acceptable?

The sponsor used a validated LC-MS/MS assay with a sensitivity (lower limit of quantification - LLOQ) of 10 pg/mL (or 0.01 ng/mL) for a 300 uL aliquot of plasma. Inter-assay precision was as high as 53 % (34% over the accepted limit of 20 % for lower concentrations). Thus, there was less reliability in the day-to-day precision of the assay at lower concentrations (0.03 ng/mL). However, there were only four time points when mean concentrations were ≤ 0.03 ng/mL. In contrast, the inter-assay precision of the medium (1.920 ng/mL) and high (3.840 ng/mL) quality control was acceptable. Inter-assay accuracy, intra-assay precision and accuracy and linearity were acceptable.

Mean concentrations ranged from 0.006 to 1.280 ng/mL.

5 LABELING

The sponsor proposes the following changes in the Clinical Pharmacology section:

(b) (4)



6.2 Individual Study Review

6.2.1 Pharmacokinetics – healthy volunteers

6.2.1.1 Bioequivalence study of intravenous versus subcutaneous UT-15

Study: REM 01:14

Volumes: 8-12

Title: An open-label, randomized, two-period, crossover comparative pharmacokinetics and steady state bioequivalence study of Remodulin administered intravenously and subcutaneously to normal volunteers

Principal investigator: Thomas Hunt

Clinical laboratory: PPD Development, Austin, TX USA

Study initiation date: August 20, 2003

Study completion date: October 4, 2003

Objectives: To compare the pharmacokinetic profiles and assess the steady state bioequivalence of Remodulin® administered intravenously and subcutaneously to healthy volunteers.

Study design: randomized, open-label, single center, two-period, crossover study

Population: Fifty-five adult subjects (see Table 2) were dosed, however only 51 (32 males, 19 females) subjects completed at least 24 hours of dosing in each period. The primary analysis consisted of these 51 subjects.

Table 2. Demographics of subjects

Patients Enrolled	22 F / 33 M
Race (w/b/h/a/ai)	28 / 9 / 16 / 1 / 1
Age (yrs)	36 ± 13 (19 – 63)
Height (cm)	171 ± 8 (156 – 187)
Weight (kg)	74 ± 9 (58 – 91)

Data as mean ± SD (range)

Race = White, Black, Hispanic, Asian, American Indian

Procedure: Each volunteer received a 72 hour infusion of Remodulin via the subcutaneous or intravenous route. After a four day washout, each subject crossed over to the other route of administration. Plasma concentrations were collected before, during, and for 24 hours after the infusion ended.

Although the protocol specified that concomitant medications (with the exception of oral contraceptives and multivitamins) were not allowed for seven days (non-prescription) or 14 days (prescription) prior to and during the Treatment Phase, two subjects (14015 and 14025) received

oral ibuprofen to treat infusion site pain, and one subject (14026) received Tequin (gatifloxacin) 400 mg daily for the treatment of hidradenitis suppurative during the study.

Treatment: 10 ng/kg/min for 72 hours

IV - Remodulin was diluted for intravenous administration in normal saline and infused at a rate of 1 mL/hour using a Baxter Syringe Pump (Model AS-50) via a dedicated peripheral IV line in the arm.

SC - Remodulin was administered subcutaneously without dilution using a MiniMed (Model 407C) pump with a catheter inserted at an abdominal site.

Formulation: Remodulin 1 mg/mL was supplied in a sterile solution in 20 mL multi-dose vials, lot number 802324

Assay: Remodulin concentrations were assayed by [REDACTED] ^{(b) (4)}. A validated LC-MS/MS assay with a sensitivity (lower limit of quantification - LLOQ) of 10 pg/mL (or 0.01 ng/mL) for a 300 uL aliquot of plasma was used for analysis of plasma samples.

Both the inter-assay precision for the LLOQ and the low quality control were higher than the recommended 20 %. Inter-assay precision (% CV) was less than or equal to 26 % for the LLOQ, 10 pg/mL. For the low quality control, 30 pg/mL, the inter-assay % CV was 53.6 %. For the LLOQ, four samples did not meet the sponsor's acceptance criteria ($\geq 2/3$ of the quality controls at each concentration level must be within 20 % of their nominal concentration). When one sample (19.4 pg/mL) was not considered in the precision calculation, the %CV dropped to 17.2 %. For the low quality control, two samples (104 and 41.4 pg/mL) were considered outliers ($\geq 2/3$ of the quality controls within 15% of the nominal value). When these two samples were not included in the precision calculation, the %CV was better, 5.1 %. The inter-assay precision of the medium (1920 pg/mL or 1.92 ng/mL) and high (3840 pg/mL or 3.84 ng/mL) quality control was acceptable, 6.1 % and 3.4 %, respectively.

Inter-assay accuracy was within 10 % for the LLOQ, medium and high quality controls. Inter-assay accuracy for the low quality control was within 11.4 %, however when the two outliers were dropped, the accuracy was better (within 4.9 %).

Intra assay precision and accuracy were acceptable. Precision was ≤ 17.5 %CV and accuracy was within 5 %.

Linearity was good (≥ 0.9990).

Pharmacokinetics: A total of 36 plasma samples were collected in each dosing period per patient: predose, 15, 30 minutes and at 1, 1.5, 2, 3, 5, 8, 12, 24, 48, 51, 54, 57, 60, 63, 66, 69 and 72 hours after study drug administration and at 5, 10, 15, 30 minutes and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after termination of the infusion. Every effort was made to obtain the post-infusion PK samples in subjects who discontinued the infusion early, but who received at least 24 hours of infusion.

Analysis: AUC_{ss} and $C_{max_{ss}}$ were used for the bioequivalence determinations. These parameters were analyzed by ANOVA of logarithmically transformed data. The ratio of the geometric mean values and their 90 % confidence intervals were calculated.

An analysis of variance was performed on AUC_{ss} and $C_{max_{ss}}$ using the general linear models (GLM) and or mixed effect models (MIXED) in SAS version 8.0. The statistical model included effects for Sequence, Subjects (nested within Sequence), Period, and Treatment.

The primary analysis was per protocol, any subject who received Remodulin for greater than 24 hours in each period (n=51). The confirmatory analysis population A consisted of all 51 subjects in the primary analysis, however, five outlier plasma concentrations were removed; one sample from patient 14008, 14017, 14019, 14040, and 14054. The outlier concentrations were up to 6.76 fold greater than the plasma concentration three hours before or after the outlier sample. The confirmatory analysis population B were those subjects in Population A that received Remodulin without interruption during steady state (n= 42). Nine subjects (14001, 14025, 14031, 14033, 14037, 14038, 14041, 14047, and 14048) who had infusion delays during steady state were excluded. The safety population (n=55) includes any subject who received Remodulin for any duration.

Results:

Plasma concentration – time profile

The figures below show the mean plasma concentration time profile for the 51 subjects included in the primary analysis (≥ 24 hours of drug in each period). The mean curves are virtually superimposable – especially early in the infusion, however during elimination, mean concentrations are eliminated slower after SC administration compared to IV administration (at least during the first 24 hours after the infusion is stopped).

Figure 2. Mean plasma concentration of Remodulin IV and SC Infusion (linear plot)

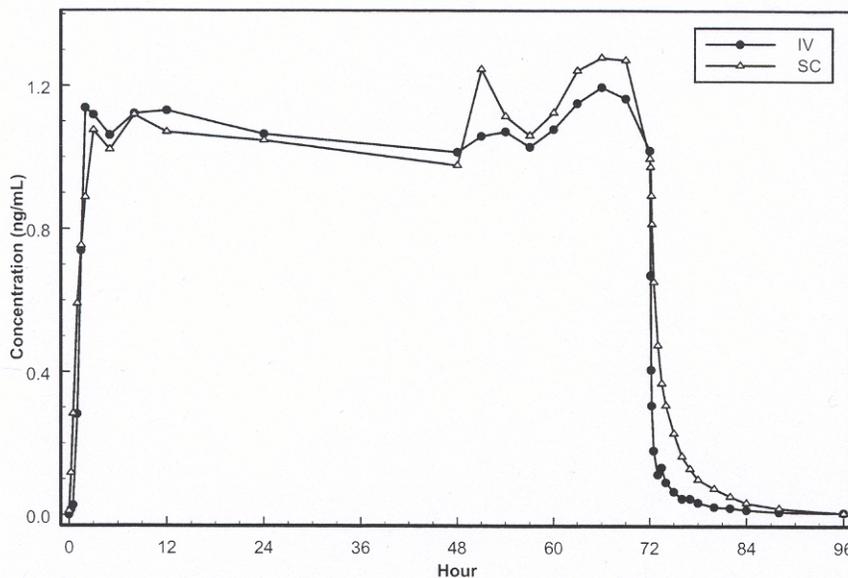


Figure 3. Mean plasma concentration of Remodulin IV and SC Infusion (log-linear plot)

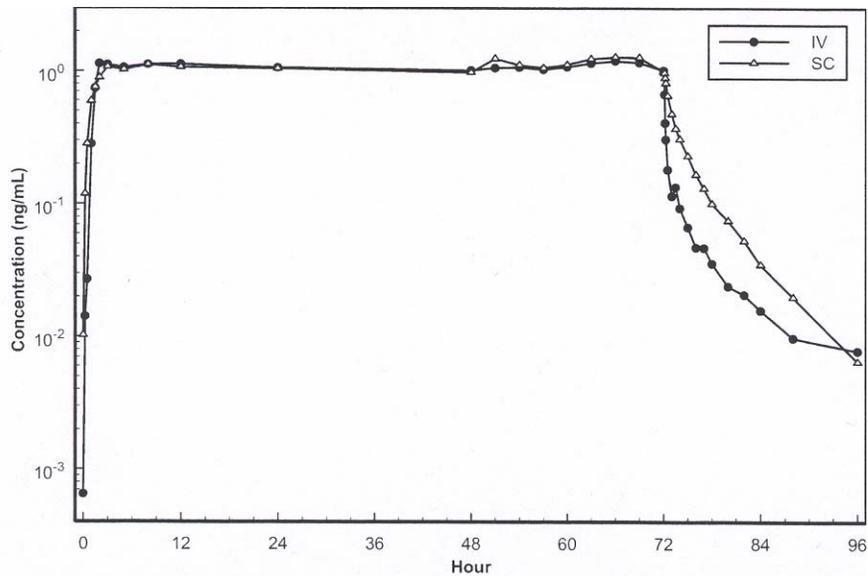
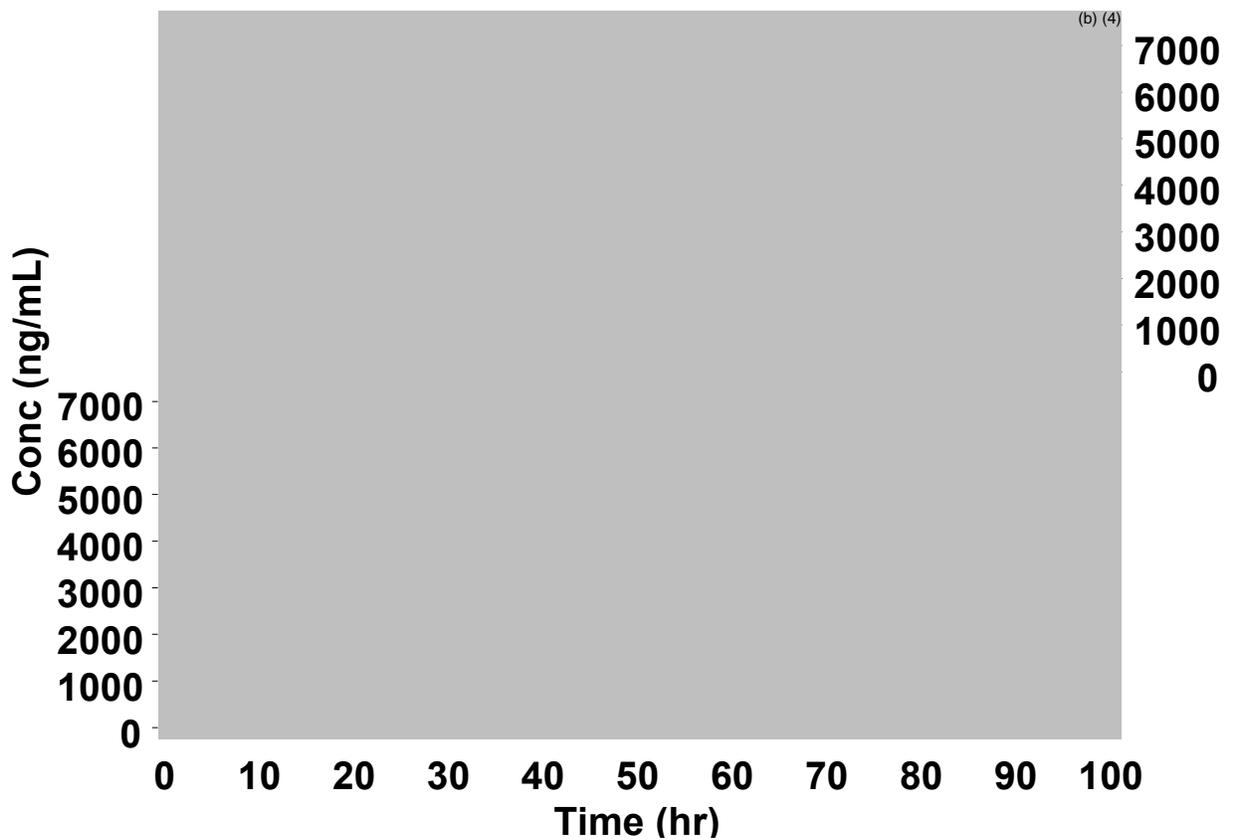


Figure 4 shows all the concentration data by both routes of administration in all patients. Concentrations by the IV route tended to have more outliers.

Figure 4. All concentration data by SC and IV route



Pharmacokinetic parameters

Geometric mean Remodulin AUC_{ss} and Cmax_{ss} are shown in Table 3 for all 51 subjects. The mean ratio indicates that overall exposure is 7 % less with the IV route and maximum concentrations are 6 % higher with the IV route, however the two routes of administration are bioequivalent since the 90 % confidence intervals are well within 80-125%.

Table 3. PK parameters in all 51 subjects – primary analysis

Parameter	Geometric LS Mean (CV %)		Comparison ¹
	IV	SC	
AUC _{ss} (ng • hr/mL)	25.7 (22.0)	27.6 (16.2)	92.9 (89.8, 96.1)
Cmax _{ss} (ng/mL)	1.5 (37.5)	1.4 (16.1)	106.0 (99.4, 113.0)

1. Comparisons are based on a general linear model for a two period crossover design fit using PROC GLM or MIXED, SAS ver 8.0. Number is ratio of geometric LS means with 90 % CI

The individual ratios of AUC_{ss} ranged from 0.68 to 1.40 and Cmax_{ss} ranged from 0.65 to 2.38.

Other PK parameters are included in Table 4. It is noted that the geometric mean Tmax is more than the geometric mean T_{1/2}.

Table 4. Other PK parameters from SC and IV Remodulin

Parameter	Geometric LS Mean (CV %)	
	IV	SC
AUC _{inf} (ng • hr/mL)	76.4 (16.3)	78.4(15.1)
AUC ₀₋₉₆ (ng • hr/mL)	76.3 (16.3)	78.4 (15.1)
Cmax (ng/mL)	1.7 (52.6)	1.4 (15.7)
Cavg _{ss} (ng/mL)	1.1 (21.2)	1.1 (16.3)
Cmin _{ss} (ng/mL)	0.7 (27.1)	0.9 (20.9)
Tmax (hr)	21.3 (75.0)	36.4 (46.6)
T _{1/2} (hr)	3.5 (90.2)	4.1 (59.0)
CL (mL/min/kg)	9.4 (16.6)	9.2 (15.0)

Confirmatory Analysis

These two analyses were done to ensure the robustness of the data since there were five outlier concentrations, fourteen subjects had IV infusion interruptions, and seven subjects had SC infusion interruptions.

Infusion interruptions

Six out of 54 subjects receiving subcutaneous Remodulin had one infusion interruption, and one subject had two infusion interruptions. Three of these seven patients had interruptions that occurred during steady state. Eleven out of 53 subjects receiving intravenous Remodulin had one infusion interruption, while three subjects had two interruptions. Ten of these fourteen subjects had interruptions or discontinuations during steady state.

Table 5 identifies the subjects that did not receive the full 72 hours of dosing in both arms.

Table 5. Subjects that did not receive the full 72 hours of treatment

DOSING TIME	SC	IV
< 72 hours	14003	14027
	14007	15050
	14047	
< 24 hours	14003	14050
No dose	14027	14003
		14007

Confirmatory analysis A

Table 6 shows the analysis after excluding the five outlier samples. The results are similar to the primary analysis. In fact the discrepancy between mean Cmax is even smaller.

Table 6. PK parameters in 51 subjects – excluding outlier samples – confirmatory analysis A

Parameter	Geometric LS Mean (CV %)		Comparison ¹
	IV	SC	
AUC _{ss} (ng • hr/mL)	25.3 (21.4)	27.6 (16.2)	91.7 (88.7, 94.9)
Cmax _{ss} (ng/mL)	1.4 (29.9)	1.4 (16.1)	101.3 (96.0, 106.9)

1. Comparisons are based on a general linear model for a two period crossover design fit using PROC GLM or MIXED, SAS ver 8.0. Number is ratio of geometric LS means with 90 % CI

Confirmatory analysis B

Table 7 shows the analysis that includes only those subjects that received the full 72 hours of infusion without interruptions. The two routes are still bioequivalent, however total exposure is approximately 10 % less when given IV versus SC, compared to 7 % for the primary analysis.

Table 7. PK parameters in 42 subjects –full 72 hours without interruptions – confirmatory analysis B

Parameter	Geometric LS Mean (CV %)		Comparison ¹
	IV	SC	
AUC _{ss} (ng • hr/mL)	25.1 (20.6)	27.9 (16.7)	89.9 (87.1, 92.7)
Cmax _{ss} (ng/mL)	1.4 (23.4)	1.4 (16.0)	98.4 (93.4, 103.6)

1. Comparisons are based on a general linear model for a two period crossover design fit using PROC GLM or MIXED, SAS ver 8.0. Number is ratio of geometric LS means with 90 % CI

Period and sequence effects

Period and sequence effects were tested for all three analyses. There were no significant sequence effects. Only a significant period effect for the primary and confirmatory A analysis of Cmax was found (p=0.005, and p=0.042, respectively). Period effect from the primary analysis of AUC was close to significant, p=0.063. The period effect indicates that irrespective of treatment administration, Cmax in period 1 was higher compared to period 2. It is possible that the period

effect was due to the outliers and dosing interruptions because the effect was not significant in the confirmatory analysis B ($p=0.098$).

Adverse events

Adverse events (AE) were reported in 51 out of 54 subjects administered Remodulin SC. The most common AE involved the infusion site; erythema (67%), infusion site pain (59%), infusion site reaction (30%), and infusion site tenderness (20 %).

Adverse events (AE) were reported in 50 out of 53 subjects administered Remodulin IV. The most common AE involved the infusion site; erythema (55%), infusion site pain (57%), infusion site tenderness (13 %), and infusion site edema (43 %).

Sponsor's Conclusions:

- Remodulin administered by the intravenous route is bioequivalent to that administered by the subcutaneous route.
- The apparent elimination half-life is 4.4 hours and 4.6 hours after IV and SC Remodulin, respectively.
- Remodulin was well tolerated, and the adverse events were similar in both routes of administration.

Reviewer's Comments:

- The reviewer agrees that the two routes of administration produced bioequivalent plasma concentrations.
- Inter-assay precision was as high as 34% over the acceptable limit of 20 % for the lower concentrations. Thus, there is less reliability in the day-to-day precision of the assay at lower concentrations (0.03 ng/mL). However, there were only four time points when mean concentrations were ≤ 0.03 ng/mL.
- In contrast, the inter-assay precision of the medium (1.920 ng/mL) and high (3.840 ng/mL) quality control was acceptable. Inter-assay accuracy, intra assay precision and accuracy and linearity were acceptable. Mean concentrations ranged from 0.006 to 1.280 ng/mL.
- It is noted that the sponsor's analysis was done in SAS version 8.0.

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/s/

Nhi Nguyen
4/12/04 01:39:07 PM
BIOPHARMACEUTICS

Patrick Marroum
4/12/04 01:55:44 PM
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-272/S-002

OTHER REVIEW(S)

RHPM Overview of NDA 21-272/S-002
Remodulin (treprostinil sodium) Injection
November 24, 2004

Sponsor: United Therapeutics Corporation
Type: SE3 / S
Receipt Date: January 30, 2004
User Fee Goal Date: November 30, 2004
AP Letter Issued: November 24, 2004
Final Draft Labeling: November 24, 2004 (Enclosed in the AP letter)

Background

Remodulin (treprostinil sodium) Injection (NDA 21-272) was issued an approval letter under Subpart H-Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses (21 CFR 314.510) on May 21, 2002 for the treatment of pulmonary arterial hypertension (PAH). The drug is currently given by subcutaneous infusion. The sponsor was granted Orphan Drug designation on November 2, 1999 for the indication pulmonary arterial hypertension.

This supplemental new drug application (sNDA) provides bioequivalence data to support a new route of administration and labeling revisions for the infusion of Remodulin via an indwelling central venous catheter in concordance with a pre-submission teleconference with the Division on December 15, 2003. The primary study was conducted to demonstrate steady-state bioequivalence of intravenous and subcutaneous Remodulin in a randomized, two-period, cross-over study of subcutaneous and intravenous administrations in normal volunteers and support the proposed labeling changes in this supplement.

United Therapeutics Corporation, to date, has not fulfilled their post-marketing commitments for the original NDA approved under Subpart H; therefore, the regulatory action for this sNDA will proceed under 21 CFR 314.510.

Division Director's Memorandum

In his Division Director's memo dated 11/24/04, Dr. Stockbridge noted the clinical review identified numerous apparently line-related adverse events (infection or pain), but no novel safety findings. Dr. Karkowsky's review stops short of a recommendation on approval, but he does recommend that the IV route be reserved for use in patients not able to tolerate pain associated with the SC route, although no study demonstrated that the IV route is superior in this regard. The safety concern for the IV administration of Remodulin is amply supported by a post-marketing safety review of (again) presumed line-related events with Flolan. And certainly, there are inadequate data to support exchange of Remodulin for Flolan. The original approval of Remodulin was under Subpart H, and the sponsor has not met its post-marketing commitments. Approval of Remodulin by this new route will continue to be subject to the original commitments.

Medical Review

In his review dated July 6, 2004, Dr. Karkowsky states that he does not recommend approval of the intravenous route for administration of Remodulin (treprostinil sodium). Aside from an abstract and an adverse event, we do not have data when Remodulin is administered by a central route of administration. Once the data and safety of those treated by this route has been submitted for review, the issue of safety by this route can be reconsidered. In addition, flocculation and hemolysis studies using adequate concentrations should be performed.

Dr. Karkowsky's review (October 25, 2004) of the sponsor's response to our deficiency and request for information letters dated June 22 and September 15, 2004, respectively, states "Should the application be approved, the intravenous route of Remodulin infusion should be limited to those not tolerating subcutaneous infusion. The additional risk attendant to the use of an indwelling intravenous line would make the intravenous route of administration inherently more risky. I would discourage switching from

intravenous Flolan to intravenous Remodulin. There is inadequate information that efficacy of Remodulin is equivalent between the effect of Flolan.”

Labeling recommendations were attached to the medical review dated October 25, 2004.

There are no additional mandatory phase 4 studies for this sNDA.

Financial Disclosure is not applicable as noted on page 15 of the medical review dated July 6, 2004.

Pharmacology Review

In his review, Dr. Joseph states that the supplemental NDA is recommended for approval and the revised labeling is acceptable, from the perspective of pharmacology/toxicology. No significant drug-specific adverse effects were noted in the 13-week continuous intravenous (IV) infusion toxicity studies in rats and dogs. Reductions in platelet counts observed in these IV studies were not seen in 6-month continuous subcutaneous infusion studies. Platelet count reductions, of up to 51% relative to baseline, have been reported in patients following IV Remodulin administration, with no clinically adverse consequences. Infusion site lesions, observed in both control and treated animals, appear to be related to the test article delivery system rather than to the drug itself. Similar lesions are reported to be commonly observed as clinical complications associated with central line catheters.

Biopharmaceutical Review

In her review, Dr. Beasley states the Office of Clinical Pharmacology and Biopharmaceutics recommends that the intravenous route of administration is bioequivalent to the subcutaneous route of administration provided that no major deficiencies have been identified at the study site.

There are no additional Phase IV Commitments.

Labeling recommendations are noted in the biopharmaceutical review on pages 5-7.

Chemistry Review

In his review, Dr. Advani states that the chemistry and microbiology data are acceptable and he recommends that the sNDA be approved from the Chemistry, Manufacturing and Controls perspective. The sponsor’s claim for categorical exclusion from the Environmental Assessment is satisfactory.

The proposed draft labeling and revised vial and carton labeling are acceptable with the addition of a statement that “(b) (4).” This recommendation is based on results of stability studies of Remodulin diluted in common IV diluents. The agreed upon labeling (discussions between the sponsor and the Division) states that the intravenous infusion of Remodulin **must be diluted with either Sterile Water for Injection or 0.9% Sodium Chloride Injection.**

Statistical Review

There was no statistical review completed for this supplemental NDA.

DSI

In his memorandum, Dr. Tampal states that DSI conducted an audit of the clinical and analytical portions of the bioequivalence study titled “An Open Label, Randomized, Two-Period Crossover Comparative Pharmacokinetics and Steady-State Bioequivalence Study of Remodulin Administered Intravenously and Subcutaneously to Normal Volunteers.” The Division of Scientific Investigations recommends that:

1. Plasma concentrations for subject 11 be excluded from the bioequivalence determination
2. The Office of Clinical Pharmacology and Biopharmaceutics reviewer should consider correcting for the pre-dose plasma concentrations for subjects 10, 18 and 43 in period one and determine if this finding had any significant impact on the study outcome.

Pediatric Rule

Remodulin was designated as an Orphan Drug product for the treatment of pulmonary hypertension and the sponsor received an exemption for conducting studies in the pediatric population.

Labeling:

The sponsor submitted the most recent draft labeling and revised carton and container labels as email attachments on November 8 & 11, 2004, respectively.

This sNDA will be approved on draft labeling.

Advisory Committee Meeting

This application did not go before the Advisory Committee.

Project Manager’s Summary

To my knowledge, there are no issues that might prevent taking regulatory action on this sNDA.

Daryl Allis, R.N., M.S., F.N.P.
Regulatory Health Project Manager

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this page is the manifestation of the electronic signature.**

/s/

Daryl L. Allis
11/29/04 03:11:01 PM
CSO

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: 9/14/04

DESIRED COMPLETION DATE: 10/15/04

ODS CONSULT#: 04-0218

TO: Norman Stockbridge, MD
Acting Director, Division of Cardio-Renal Drug Products
HFD-110

THROUGH: Daryl Allis, Division of Cardio-Renal Drug Products
Project Manager
HFD-110

PRODUCT NAME:

Remodulin®
(Trepstinil Sodium) Injection
1 mg/mL, 2.5 mg/mL, 5 mg/mL and 10 mg/mL

NDA: 21-272/S-002

NDA SPONSOR:

United Therapeutics Corp.

SAFETY EVALUATOR: Felicia Duffy, RN

DMETS RECOMMENDATIONS:

DMETS recommends implementation of the package insert labeling revisions outlined in the Section III of this review in order to minimize potential user error.

Carol Holquist, RPh
Director, Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PACKAGE INSERT LABELING REVIEW

DATE OF REVIEW: September 22, 2004

NDA # 21-272/S-002

NAME OF DRUG: Remodulin®
(Treprostinil Sodium) Injection
1 mg/mL, 2.5 mg/mL, 5 mg/mL and 10 mg/mL

NDA HOLDER: United Therapeutics Corp.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Cardio-Renal Drug Products (HFD-110) to review the package insert labeling of Remodulin which was submitted on January 30, 2004. Remodulin was approved for subcutaneous administration on May 21, 2002. Currently, Remodulin is administered by continuous subcutaneous infusion, via a self-inserted subcutaneous catheter, using an infusion pump designed for subcutaneous drug delivery. The sponsor submitted this NDA supplement to reflect a new continuous intravenous route of administration of Remodulin.

PRODUCT INFORMATION

Remodulin contains the active ingredient treprostinil sodium. Treprostinil is a tricyclic benzidine analogue of prostacyclin (PGI₂) with potent pulmonary and systemic vasodilatory activity. It is also a potent inhibitor of platelet aggregation. The vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. Remodulin is indicated for the long-term subcutaneous or intravenous treatment of Pulmonary Arterial Hypertension in New York Heart Association (NYHA) Class II, III, and IV patients. Remodulin will be administered by continuous subcutaneous and intravenous infusion through an indwelling central venous catheter, via an infusion pump. The dosage is initiated at 1.25 ng/kg/min. If this initial dose cannot be tolerated, the dosage should be reduced to 0.625 ng/kg/min. The infusion rate is adjusted based on Pulmonary Arterial Hypertension (PAH) signs and symptoms and drug side effects. The product will be supplied in 20 mL vials with the following concentrations: 1 mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL.

II. ADVERSE EVENT REPORTING SYSTEM (AERS)

Since Remodulin has been marketed since 2002, DMETS searched the FDA Adverse Events Reporting System (AERS) database to identify any post-marketing safety reports of medication errors associated with Remodulin. The MedDRA Preferred Terms (PT), “Medication Error”, “Accidental Overdose”, and “Pharmaceutical Product Complaint” were used to perform the searches along with the tradename “Remodulin”, verbatim entry “Remodu%”, and the active ingredient “Treprostiniil”. The search strategy retrieved one case. This involved a 68 year old patient on Remodulin therapy who suffered a grand mal seizure and hypotension that resulted in hospitalization. The patient had a history of secondary pulmonary hypertension, primary biliary cirrhosis, hepatic encephalopathy, portal hypertension and systemic hypertension. The patient had no history of seizures. A home health nurse assisted the patient’s husband in changing the Remodulin pump and infusion set. The patient’s blood pressure was stable prior to changing the pump and infusion set. The pump and infusion set were changed without incident. Approximately 4-5 minutes after the insertion of the infusion set at the new infusion site, the patient appeared to have a grand mal seizure that lasted about 2 minutes. The reporter noted that the rate of the newly placed pump was actually 0.01 mL/hr (1.5 ng/kg/min) instead of 0.008 ml/hr (1.25 ng/kg/min). The patient was taken to the emergency room where the patient’s blood pressure was 60/palp mm Hg. Remodulin therapy was discontinued, and the patient was treated for hypotension. The patient was discharged in stable condition 3 days after admission. It was also noted that the patient was not dosed according to recommendations for patients with hepatic insufficiency. To date, this is the only medication error reported related to Remodulin.

III. LABELING AND SAFETY RELATED ISSUES

In the review of the “Remodulin” package insert labeling, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which may minimize potential user error.

A. GENERAL COMMENTS

1. DMETS questions the necessity of having a (b) (4) We recognize that Remodulin is currently part of a specialized distribution process. However, with the approval of the intravenous route of administration, will hospitals be able to purchase and prepare this drug? If so, the increased accessibility of Remodulin in the hospital setting will increase the potential for selection errors between the (b) (4) vial due to similar strengths which may result in a 10-fold medication error.
2. DMETS is concerned about the potential for selection errors and calculation errors with Remodulin. We question if the sponsor has received any medication errors with Remodulin (e.g. selection or calculation errors) for the existing distribution system.
3. DMETS notes that trailing zeros are utilized throughout the labeling when specifying the dose or product concentration. DMETS recommends deleting the trailing zeros to prevent 10-fold dosing errors. For example, “1.0 mg/mL” can easily be mistaken for “10 mg/mL”. Please revise accordingly.
4. The use of the abbreviation “µg” appears in the “Pharmacokinetics” section of the package insert. Please revise the abbreviation for micrograms from “µg” to “mcg” to avoid the misinterpretation of “µg” as “mg” (for example, 8 µg should read 8 mcg).

5. We note the proposed expression of strength is expressed in terms of mg amount per mL. However, the drug product is dosed in nanograms. Nanograms are not commonly utilized when expressing strength or dose. Therefore, to minimize calculation errors when trying to convert “mg” to “ng” we recommend including the “ng equivalent amount/mL” on the container and carton as follows:

1 mg/mL (1,000,000 ng/mL)	2.5 mg/mL (2,500,000 ng/mL)	5 mg/mL (5,000,000 ng/mL)
10 mg/mL (10,000,000 ng/mL)		

In addition, wherever the strength is expressed in terms of “milligrams” within the text of the insert the “nanogram equivalent amount” should immediately follow in parenthesis

B. PRECAUTIONS (General)

To emphasize the importance of avoiding abrupt withdrawal of Remodulin, please bold the statement: “Abrupt withdrawal or sudden large reductions in dosage may result in worsening of PAH symptoms and should be avoided.”

C. DOSAGE AND ADMINISTRATION

1. General Comment

We recommend reorganizing the “Dosage and Administration” section to simplify the flow of information for the reader. Specifically, a reader who is interested in the intravenous route of administration should not have to read through the subcutaneous subsection to obtain pertinent information (the initial dose and dosage adjustments). Currently, this information is presented once in the Dosage and Administration section. All information pertaining to the subcutaneous infusion route of administration should be presented together (e.g., initial dose, preparation, dosage adjustments) and all information pertaining to the intravenous infusion route of administration should be presented together. DMETS recognizes that in some instances this will duplicate information (e.g., initial dose), however, it will help the reader obtain the information needed without having to refer back to different sections of the insert labeling.

2. Introduction

In the introduction section, please clarify the second sentence referencing the administration of Remodulin. DMETS recommends the following: “Remodulin can be administered as supplied for subcutaneous infusion. For intravenous infusion, Remodulin **MUST BE DILUTED** with Sterile Water for injection or 0.9% Sodium Chloride prior to administration.”

3. Initial Dose Subsection

- a. To provide understanding about the administration about Remodulin, please revise the first sentence to read, “Remodulin is administered by continuous subcutaneous and intravenous infusion.”
- b. The “Initial Dose” subsection states the “*infusion rate initiated at 1.25 ng/kg/min*”. In the latter half of the insert that contains the infusion formulas, the “Infusion Rate” is defined as “mL/hr” and “Dose” as “ng/kg/min”. If the dose is calculated as “ng/kg/min”, the insert should be revised to state “dose” rather than “infusion rate”.
- c. The “Special Populations” section of the insert recommends patients with hepatic insufficiency begin Remodulin therapy at a significantly lower initial dose (0.625 ng/kg/min as opposed to 1.25 ng/kg/min). DMETS recommends including a statement about hepatic dosing in this section. This may prevent hepatic patients from being overdosed with their initial dose of Remodulin.

4. Dosage Adjustments Subsection

Relocate this section to follow the calculation examples. This helps the reader to follow the step by step procedure for medication preparation then read through dosage adjustments if needed.

5. Administration Subsection

a. Subcutaneous Infusion

- i. To ensure Remodulin for subcutaneous infusion is not diluted, we recommend revising this section to read: “**SUBCUTANEOUS INFUSION- NO DILUTION REQUIRED**”.
- ii. Please highlight the statement about the length of time a single reservoir of Remodulin can be administered: “...**undiluted Remodulin can be administered up to 72 hours at 37°C.**”
- iii. We recommend isolating the subcutaneous infusion formula from the subcutaneous infusion calculations shown by boxing the formula and labeling it: “Subcutaneous Infusion Formula” (see below).

Subcutaneous Infusion Formula

$$\text{Subcutaneous Infusion Rate (mL/hr)} = \frac{\text{Dose (ng/kg/min)} \times \text{Weight (kg)} \times 0.00006^*}{\text{Remodulin Vial Strength (mg/mL)}}$$

*Conversion factor of 0.00006 = 60 min/hour x 0.000001 mg/ng

- iv. In Example 1 of the calculations, the final subcutaneous infusion rate is listed as 0.005 mL/hr. The actual subcutaneous infusion rate calculation is 0.0045 mL/hr, but it was rounded up to 0.005 mL/hr. DMETS assumes that the rate was rounded up because the

drug is only recommended to be used with pumps that are adjustable to approximately 0.002 mL/hr. Although, the information about the pump is provided in the introduction of subcutaneous infusion section, the reader may not link the rounding up of the dose to pump limitations. We recommend that this be noted in the example. Please clarify.

b. Intravenous Infusion

- i. To ensure Remodulin for intravenous infusion is diluted prior to administration, please revise this section to read: **“INTRAVENOUS INFUSION-REMODULIN MUST BE DILUTED WITH STERILE WATER FOR INJECTION OR 0.9% SODIUM CHLORIDE INJECTION”**
- ii. Please highlight the statement about the length of time a single reservoir of Remodulin can be administered: **“Diluted Remodulin has been shown to be stable at 37°C for up to 48 hours at....”**
- iii. Since the intravenous infusion section contains multiple steps, please simply each step by numbering them. Additionally, we recommend isolating the intravenous infusion formulas from the intravenous infusion examples shown by boxing the formulas and labeling them: “Intravenous Infusion Formulas” (see below).
- iv. Add the explanation of the conversion factor (0.00006) to Step 1 of the formula as noted in the subcutaneous infusion formula (see below).

Intravenous Infusion Formulas

Step 1: Calculate the diluted intravenous Remodulin concentration:

$$\frac{\text{Diluted Intravenous Remodulin Concentration (mg/mL)}}{\text{Intravenous Infusion Rate (mL/hr)}} = \frac{\text{Dose (ng/kg/min)} \times \text{Weight (kg)} \times 0.00006}{\text{Intravenous Infusion Rate (mL/hr)}}$$

*Conversion factor of 0.00006 = 60 min/hour x 0.00001 mg/ng

Step 2: Calculate the Amount of Remodulin Injection needed to make the required Diluted Intravenous Remodulin Concentration for the given reservoir size by using the following formula:

$$\text{Amount of Remodulin Injection (mL)} = \frac{\text{Diluted Intravenous Remodulin Concentration (mg/mL)}}{\text{Remodulin Vial Strength (mg/mL)}} \times \text{Total Volume of Diluted Remodulin Solution in Reservoir (mL)}$$

- v. Add a third step explaining the volume of diluted Remodulin to add to the reservoir. For example:

Step 3: Calculate the amount of diluent to add (i.e., QS) to the Amount of Remodulin Injection to fill the reservoir volume.

$$\text{Reservoir Volume (mL)} - \text{Amount of Remodulin Injection (mL)} = \text{Amount of Diluent to achieve Reservoir Volume}$$

III. DMETS RECOMMENDATIONS:

DMETS recommends implementation of the labeling revisions outlined in Section III of this review.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Felicia Duffy, RN
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Felicia Duffy
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DRUG SAFETY OFFICE REVIEWER

Denise Toyer
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DRUG SAFETY OFFICE REVIEWER

Carol Holquist
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DRUG SAFETY OFFICE REVIEWER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-272 **Supplement # SE3 - 002**

Trade Name: Remodulin
Generic Name: treprostinil sodium injection
Strengths: 1, 2.5, 5, and 10 mg/ml

Applicant: United Therapeutics Corporation

Date of Application: January 30, 2004
Date of Receipt: January 30, 2004
Date clock started after UN: N/A
Date of Filing Meeting: March 9, 2004
Filing Date: March 30, 2004
74 Day Letter Date: April 13, 2004
User Fee Goal Date: November 30, 2004

Indication requested: Treatment of pulmonary arterial hypertension

Type of Application: (b)(1) Supplement NDA 21-272/S-002
Therapeutic Classification: Standard

User Fee Status: Exempt: No clinical data; Orphan Drug Product

Form 3397 (User Fee Cover Sheet) submitted: YES

Clinical data? NO

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application? YES
If yes, explain: Received 7 year Orphan Drug Exclusivity to expire 21 May 09.

Does another drug have orphan drug exclusivity for the same indication? YES

Is the application affected by the Application Integrity Policy (AIP)? NO

- Does the submission contain an accurate comprehensive index? YES
- Was form 356h included with an authorized signature? YES
- Submission complete as required under 21 CFR 314.50? YES
- If an electronic NDA, does it follow the Guidance? N/A
- If in Common Technical Document format, does it follow the guidance? N/A
- Is it an electronic CTD? NO
- Patent information submitted on form FDA 3542a? YES

- Exclusivity requested? NO
- Correctly worded Debarment Certification included with authorized signature?
The Debarment Certification statement is included in the cover letter. YES
- Financial Disclosure forms included with authorized signature? YES
- Field Copy Certification (that it is a true copy of the CMC technical section)? N/A

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES
- Drug name/Applicant name correct in COMIS? YES
- List referenced IND numbers: IND 36,704 and 67,561
- End-of-Phase 2 Meeting(s)? NO
- Pre-sNDA Teleconference? Date: December 15, 2003 YES

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? N/A
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment?
If no, did applicant submit a complete environmental assessment?
If EA submitted, consulted to Nancy Sager (HFD-357)? YES
- Establishment Evaluation Request (EER) submitted to DMPQ? N/A
- If a parenteral product, consulted to Microbiology Team (HFD-805)? N/A

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 9, 2004

BACKGROUND:

Remodulin (treprostinil sodium) Injection was issued an approval letter under subpart H on May 21, 2002 for the treatment of pulmonary arterial hypertension (PAH). The drug is currently given by subcutaneous infusion. On November 2, 1999, the sponsor was granted Orphan designation for the indication pulmonary arterial hypertension.

This supplemental new drug application provides data to support a new route of administration and labeling revisions for the infusion of Remodulin via an indwelling central venous catheter in concordance with a pre-submission teleconference with the Division on December 15, 2003. The primary study was conducted to demonstrate steady-state bioequivalence of intravenous and subcutaneous Remodulin in a randomized, two-period, cross-over study of subcutaneous and intravenous administrations in normal volunteers and support the proposed labeling changes in this supplement.

ATTENDEES:

Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Deputy Director, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical Officer, HFD-110
Thomas Marciniak, M.D.	Team Leader, Medical Officer, HFD-110
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, HFD-810
Jahver Advani, Ph.D.	Chemist, HFD-810
B. Nhi Beasley, Pharm.D.	Biopharmaceutist/Clinical Pharmacologist, HFD-860
Albert DeFelice, Ph.D.	Team Leader, Pharmacology, HFD-110
Xavier Joseph, D.V.M.	Pharmacologist, HFD-110
John Lawrence, Ph.D.	Statistician, HFD-710
Michael Skelly, Ph.D.	DSI, HFD-45
Zelda McDonald	Chief, Project Management Staff, HFD-110
Daryl Allis, M.S., F.N.P.	Regulatory Health Project Manager, HFD-110
Dianne C. Paroan	Regulatory Health Project Manager, HFD-110

ASSIGNED REVIEWERS:

Discipline	Reviewer	Completion Date
Medical:	Abraham Karkowsky, M.D.	1 August 2004
Statistical:	John Lawrence, Ph.D.	1 August 2004
Pharmacology:	Xavier Joseph, Ph.D.	1 August 2004
Statistical Pharmacology:	N/A	
Chemistry:	Jahver Advani, Ph.D.	1 August 2004
Environmental Assessment (if needed):	N/A	
Microbiology, sterility:	N/A	
Biopharmaceutical:	B.Nhi Beasley, Pharm.D.	1 August 2004
DSI:	Michael Skelly, Ph.D.	1 August 2004
Regulatory Project Management:	Daryl Allis	
Other Consults: DDMAC	Andy Haffer	

Per reviewers, are all parts in English or English translation? YES

DISCUSSION:

Clinical

Dr. Karkowsky recommended additional clinical data to support safety for administering Remodulin via a central venous catheter. There are no data to show there is no injury at the point of tissue exposure at the central site, e.g. thrombosis, pseudo-aneurysm. The BE study was done using a peripheral IV site (limiting the risks of a central line placement for healthy volunteers) and there were adverse events for pain at the site. He believes this could be a signal for local tissue injury. Dr. Throckmorton stated that we did not request additional clinical data, and he believes this would be a review issue.

Biopharmaceutics

Dr. Beasley would like clarification from the sponsor regarding the proposed labeling. The proposed label does not indicate that the drug should be administered centrally but only to those who are intolerable to subcutaneous administration as discussed in the pre-sNDA teleconference. Dr. Throckmorton stated that if we have acceptable bioequivalence data for the 2-routes of administration, it seems likely that we would label the drug to be administered subcutaneously or intravenously.

Pharmacology

Dr. Joseph stated that the supplement includes 14 day animal data; they have 3 month rat and dog toxicology studies in progress and the data should be submitted soon. Dr. Joseph will contact the sponsor and request them to provide a written plan for submitting these data.

Chemistry

Drs. Srinivasachar and Advani would like clarification for the proposed changes in the How Supplied section of the label. They propose that the vial should not be used for more than 30 days rather than 14 days after the initial introduction into the vial as indicated in the currently approved label. Data to support the 30 days was not submitted in the supplemental application. Dr. Throckmorton asked the chemists to review the original NDA to see if there are data to support the 14 days referenced in the approved label.

CLINICAL		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• Clinical site inspection needed:		NO
	• Advisory Committee Meeting needed?		NO
	• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?		N/A
CLINICAL MICROBIOLOGY	N/A <input checked="" type="checkbox"/>	FILE <input type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
STATISTICS		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
BIOPHARMACEUTICS		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• Biopharm. inspection needed:	Dr. Skelly to proceed with scheduling.	YES
PHARMACOLOGY		FILE <input checked="" type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
	• GLP inspection needed:		NO

CHEMISTRY

FILE

REFUSE TO FILE

- Establishment(s) ready for inspection? N/A
- Microbiology N/A

ELECTRONIC SUBMISSION: Labeling in the EDR. YES

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

Filing issues to be communicated by Day 74.

ACTION ITEMS:

- The Division will document the filing issues to the applicant in the 74 day letter by April 13, 2004.

(See electronic signature page)

Daryl Allis, M.S., F.N.P.
Regulatory Health Project Manager, HFD-110

Draft: 3/10/04 Final: 03/19/04

RD

Throckmorton: 03/17/04

Stockbridge: 03/17/04

McDonald: 03/17/04

Karkowsky: 03/17/04

Marciniak: 03/16/04

Lawrence: 03/15/04

Beasley: 03/15/04

DeFelice: 03/12/04

Joseph: 03-12-04

Srinivasachar: 03-12-04

Advani: 03/11/04

Skelly: 03/10/04

Allis: 03/10/04

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Daryl L. Allis
3/19/04 11:01:29 AM
CSO

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-272/S-002

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY FOR NDA # 21-272 SUPPL # 002

Trade Name Remodulin Injection Generic Name treprostinil sodium
HFD-110

Applicant Name United Therapeutics Corporation

Approval Date If Known November 24, 2004

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES / X / NO / ___ /

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1) SE3

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / ___ / NO / X /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The data submitted with this application was from a bioequivalence study entitled "An open-label, randomized, two-period, crossover comparative pharmacokinetics and steady state bioequivalence study of Remodulin administered intravenously and subcutaneously to normal volunteers.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

 N/A

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /X/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

 N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate) N/A

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations"

to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /X/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # _____ YES /___/ ! NO /___/ Explain: _____
! !
Investigation #2 !
IND # _____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
YES /___/ Explain _____ ! NO /___/ Explain _____
! !

! !

! !
Investigation #2 !
YES /___/ Explain _____ ! NO /___/ Explain _____
! !

! !

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

Signature: Daryl Allis Date 11/24/04
Title: Regulatory Project Manager

Signature: Norman Stockbridge, M.D., Ph.D. Date 11/24/04
Title: Acting, Division Director

Form OGD-011347 Revised 05/10/2004

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this page is the manifestation of the electronic signature.**

/s/

Norman Stockbridge
11/24/04 12:34:11 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-272 Supplement Type (e.g. SE5): SE3 Supplement Number: 002

Stamp Date: January 30, 2004 Action Date: November 30, 2004

HFD-110 Trade and generic names/dosage form: Remodulin (treprostinil sodium) Injection

Applicant: United Therapeutics Corporation Therapeutic Class: Standard

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: 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.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: Orphan Drug designation for the indication pulmonary arterial hypertension on November 2, 1999.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Daryl Allis, RN, MSN, FNP
Regulatory Project Manager

cc: NDA 21-272
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Daryl L. Allis
5/28/04 10:05:34 AM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-272	Efficacy Supplement Type SE-3	Supplement Number 002
Drug: Remodulin (treprostinil sodium) Injection		Applicant: United Therapeutics Corporation
RPM: Mr. Daryl Allis		HFD-110 Phone # 301-594-5332
<p>Application Type: (<input checked="" type="checkbox"/>) 505(b)(1) () 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p>(<input checked="" type="checkbox"/>) N/A</p>	<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): N/A</p>	
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority 	(<input checked="" type="checkbox"/>) Standard () Priority	
<ul style="list-style-type: none"> • Chem class (NDAs only) 	N/A	
<ul style="list-style-type: none"> • Other (e.g., orphan, OTC) 	Orphan Drug (11/2/99)	
❖ User Fee Goal Dates		
November 30, 2004		
❖ Special programs (indicate all that apply)		
() None Subpart H (<input checked="" type="checkbox"/>) 21 CFR 314.510 (accelerated approval) () 21 CFR 314.520 (restricted distribution) () Fast Track () Rolling Review () CMA Pilot 1 () CMA Pilot 2		
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee 	() Paid UF ID number N/A	
<ul style="list-style-type: none"> • User Fee waiver 	() Small business N/A () Public health () Barrier-to-Innovation () Other (specify) _____	
<ul style="list-style-type: none"> • User Fee exception 	(<input checked="" type="checkbox"/>) Orphan designation () No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) () Other (specify) _____	
❖ Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP 	() Yes (<input checked="" type="checkbox"/>) No	

<ul style="list-style-type: none"> This application is on the AIP 	() Yes (X) No
<ul style="list-style-type: none"> Exception for review (Center Director's memo) 	N/A
<ul style="list-style-type: none"> OC clearance for approval 	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
<ul style="list-style-type: none"> Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	(X) Verified
❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	Exclusivity Form completed New Chemical Exclusivity 5/21/07
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	(X) Yes, 5/21/09 Application # <u>21-272</u> () No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	PM overview 11/24/04
General Information	
❖ Actions	
<ul style="list-style-type: none"> Proposed action 	(X) AP () TA () AE () NA
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 	Original NDA approved under Subpart H
<ul style="list-style-type: none"> Status of advertising (approvals only) 	(X) Materials requested in AP letter (X) Reviewed for Subpart H
❖ Public communications	
<ul style="list-style-type: none"> Press Office notified of action (approval only) 	() Yes (X) Not applicable
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	Attached to AP letter
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	Yes; 11/08/04
<ul style="list-style-type: none"> Original applicant-proposed labeling 	Yes
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings) 	DMETS 10/15/04; T-con w/ sponsor 11/8/04
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	Remodulin; Flolan
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	N/A
<ul style="list-style-type: none"> Applicant proposed 	Yes; 11/11/04
<ul style="list-style-type: none"> Reviews 	CMC, Labeling T-con 11/8/04
❖ Post-marketing commitments	
<ul style="list-style-type: none"> Agency request for post-marketing commitments 	Subpart H Phase 4 commitments for original NDA noted in letter

<ul style="list-style-type: none"> Documentation of discussions and/or agreements relating to post-marketing commitments, 	T-con w/ Sponsor 8/4/04
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Yes
❖ Memoranda and Telecons	Yes
❖ Minutes of Meetings	
<ul style="list-style-type: none"> EOP2 meeting (indicate date) 	None
<ul style="list-style-type: none"> Pre-sNDA meeting (indicate date); T-con to discuss requirements for IV administration 	12/15/03
<ul style="list-style-type: none"> Pre-Approval Safety Conference (indicate date; approvals only) 	N/A
<ul style="list-style-type: none"> Other 	8/24/04; Post-marketing commitments for original NDA
❖ Advisory Committee Meeting	
<ul style="list-style-type: none"> Date of Meeting 	N/A
<ul style="list-style-type: none"> 48-hour alert 	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	11/24/04; Division Director's Memo
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	7/6/04; 10/25/04
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	Included in clinical review
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Yes; In DFS
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	N/A
❖ Biopharmaceutical review(s) (indicate date for each review)	4/12/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
<ul style="list-style-type: none"> Clinical studies 	N/A
<ul style="list-style-type: none"> Bioequivalence studies 	8/9/04
CMC Information	
❖ CMC review(s) (indicate date for each review)	8/2/04
❖ Environmental Assessment	
<ul style="list-style-type: none"> Categorical Exclusion (indicate review date) 	Yes; 8/2/04
<ul style="list-style-type: none"> Review & FONSI (indicate date of review) 	N/A
<ul style="list-style-type: none"> Review & Environmental Impact Statement (indicate date of each review) 	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: N/A () Acceptable () Withhold recommendation

❖ Methods validation	(X) Completed; Original NDA () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	9/2/04
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	N/A
❖ CAC/ECAC report	Exemption letter: 4/11/00

APPEARS THIS WAY ON ORIGINAL

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/s/

Daryl L. Allis
11/29/04 03:06:19 PM



NDA 21-272\S-002

INFORMATION REQUEST LETTER

United Therapeutics Corporation
Attention: Mr. Dean Bunce
One Park Drive
Research Triangle Park, NC 27709

Dear Mr. Bunce:

Please refer to your supplemental new drug application dated January 30, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Remodulin® (treprostinil sodium) 1, 2.5, 5 & 10 mg/mL Injection.

We also refer to your submission dated August 26, 2004.

We are reviewing the Clinical section of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

Please provide a copy of all the case report forms (CRFs) for the investigator-initiated clinical study titled "An Open-Label, Uncontrolled Study of the Safety and Efficacy of Chronic Intravenous Remodulin® in Patients with Pulmonary Arterial Hypertension." Include the CRFs for both the 12-week treatment period and the open-label extension with a 12-month follow-up visit.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm

9/15/04 11:34:44 AM



FILING COMMUNICATION

NDA 21-272/S-002

United Therapeutic Corporation
Attention: Mr. Dean Bunce
One Park Drive
Research Triangle Park, NC 27709

Dear Mr. Bunce:

Please refer to your supplemental new drug application, dated January 30, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Remodulin (treprostinil sodium) 1, 2.5, 5, & 10 mg/ml Subcutaneous and Intravenous Injection.

We also refer to your submissions dated March 5, 15 and April 5, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on March 30, 2004, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. The final study reports for the 13 week toxicology studies in rats and dogs were not submitted in the supplemental new drug application. We understand that these studies were in progress at the time of submission, and the data will be available for review by April 30, 2004.
2. There are no data that define the safety of Remodulin when the drug is administered by way of a central intravenous line, the proposed route of administration.
3. The labeling for Remodulin that reflects the safety for the new route of administration refers to the safety of a competing product, Flolan. The relevance of the safety of Remodulin to Flolan has not been established.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We request that you submit the following information:

1. The final study reports for the 13 week toxicology studies in rats and dogs, as previously agreed, by April 30, 2004, and
2. Information that defines the safety for Remodulin when it is administered by way of a central intravenous line.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5309

Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Doug Throckmorton
4/9/04 12:05:31 PM



NDA 21-272/S-002

United Therapeutics Corporation
Attention: Mr. Dean Bunce
One Park Drive
Research Triangle Park, NC 27709

Dear Mr. Bunce

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Remodulin (treprostinil sodium) 1, 2.5, 5, and 10 mg/mL Injection

NDA Number: 21-272

Supplement number: 002

Review Priority Classification: Standard (S)

Date of supplement: January 30, 2004

Date of receipt: January 30, 2004

This supplemental application proposes to add the infusion of Remodulin via an indwelling central venous catheter to the labeling.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 30, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 30, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred or it is for an indication for which orphan drug designation has been granted. We note that the indication for this application has been granted orphan drug designation. Therefore, pediatric studies are not required for this application.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5309

Sincerely,

{See appended electronic signature page}

Zelda McDonald
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Zelda McDonald
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