



NDA 21-272/S-009

United Therapeutics Corporation
Attention: Kerry McKenzie
P.O. Box 14186
One Park Drive
Research Triangle Park, NC 27709

SUPPLEMENT APPROVAL

Dear Mr. McKenzie:

Please refer to your supplemental new drug application (NDA) dated January 24, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Remodulin (treprostinil sodium) Injection 1, 2.5, 5, and 10 mg/mL.

We also refer to our supplement request letter dated February 27, 2007 and related meeting minutes dated January 22, 2008.

This supplemental new drug application provides for the following revisions to the package insert:

1. To make the following changes in the **INDICATIONS AND USAGE** section

FROM

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.

TO

Remodulin is indicated 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. It may be administered as a continuous subcutaneous infusion or continuous intravenous infusion; however, because of the risks associated with chronic indwelling central venous catheters, including serious blood stream infections, continuous intravenous infusion should be reserved for patients who are intolerant of the subcutaneous route, or in whom these risks are considered warranted.

2. To make the following changes in the **WARNINGS** section

FROM

Remodulin is indicated for subcutaneous or intravenous use only.

TO (note: in last sentence of second paragraph, “one BSI” has been changed to “1 BSI”)

Adverse Events Attributable to the Intravenous Drug Delivery System

Chronic intravenous infusions of Remodulin are delivered using an indwelling central venous catheter. This route is associated with the risk of blood stream infections (BSIs) and sepsis, which may be fatal.

In an open-label study of IV treprostinil (n=47), there were seven catheter-related line infections during approximately 35 patient years, or about 1 BSI event per 5 years of use. A CDC survey of seven sites that used IV treprostinil for the treatment of PAH found approximately 1 BSI (defined as any positive blood culture) event per 3 years of use.

3. In the **ADVERSE REACTIONS** section, to delete the statement “In addition, generalized rashes, sometimes macular or papular in nature, and cellulitis have been infrequently reported in postmarketing experience” as well as to change the following text

FROM

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, or 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.

TO (*italics show differences from last approved labeling dated March 2006*)

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, or straightening a crimped infusion line. Adverse events resulting from problems with the delivery system did not lead to clinical instability or rapid deterioration. *In addition to these adverse events due to the drug delivery system during subcutaneous administration, the following adverse events may be attributable to the IV mode of infusion including arm swelling, paresthesias, hematoma and pain (see WARNINGS).*

Adverse Events Observed During Clinical Practice

In addition to adverse reactions reported from clinical trials, the following events have been identified during post-approval use of Remodulin. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The following events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, and potential connection to Remodulin. These events are thrombophlebitis associated with peripheral intravenous infusion, thrombocytopenia and bone pain. In addition, generalized rashes, sometimes macular or papular in nature, and cellulitis have been infrequently reported.

4. To make the following changes in the **DOSAGE AND ADMINISTRATION** section

FROM

Initial Dose for Patients New to Prostacyclin Infusion Therapy

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

TO (italics show differences from last approved labeling dated March 2006)

Initial Dose for Patients New to Prostacyclin Infusion Therapy

Remodulin is indicated for subcutaneous (SC) or intravenous (IV) use only. 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 1.25 ng/kg/min per week for the first four weeks of treatment and then 2.5 ng/kg/min per week for the remaining duration of infusion, depending on clinical response. Dosage adjustments may be undertaken more often if tolerated. There is little experience with doses >40 ng/kg/min. Abrupt cessation of infusion should be avoided (see **PRECAUTIONS**). *Restarting a Remodulin infusion within a few hours after an interruption can be done using the same dose rate. Interruptions for longer periods may require the dose of Remodulin to be re-titrated.*

5. To make the following changes in the **DOSAGE AND ADMINISTRATION** section

FROM

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.

TO (italics show differences from last approved labeling dated March 2006)

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

intravenous drug delivery. *If clinically necessary, a temporary peripheral intravenous cannula, preferably placed in a large vein, may be used for short term administration of Remodulin. Use of a peripheral intravenous infusion for more than a few hours may be associated with an increased risk of thrombophlebitis.* 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.

We have completed our review of this application, and it is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon electronic labeling text. We will transmit the SPL version of the labeling with minor edits submitted on January 24, 2008 to the National Library of Medicine for public dissemination.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

Marketing the product with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Dan Brum, Pharm.D., Regulatory Project Manager, at (301)796-0578.

Sincerely,

{See appended electronic signature page}

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

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