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Approval Package for:

APPLICATION NUMBER:

NDA 021-272/S-020

Trade Name: Remodulin Injection

Generic Name: Treprostinil

Sponsor: United Therapeutics Corporation

Approval Date: September 26, 2013

Indications: Remodulin is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%). Remodulin is also indicated for patients who require transition from Flolan®, to reduce the rate of clinical deterioration. The risks and benefits of each drug should be carefully considered prior to transition.

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021272/S-020

SUPPLEMENT APPROVAL

United Therapeutics Corporation
Attention: Rex Mauthe
Associate VP, Regulatory Affairs
55 TW Alexander Drive
P.O. Box 14186
Research Triangle Park, NC 27709

Dear Mr. Mauthe:

Please refer to your Supplemental New Drug Application (sNDA) dated and received May 23, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Remodulin (treprostinil) 20 mg, 50 mg, 100 mg, and 200 mg for Injection.

This "Prior Approval" supplemental new drug application provides for labeling revised as follows (additions are marked as underlined text and deletions are marked as ~~strikethrough text~~):

1. In **HIGHLIGHTS**, the following text was added/deleted:

Dosage and Administration (2.1)	~~1/2010~~ 09/2013
Warnings and Precautions (5.1)	~~1/2010~~ 09/2013

2. In **HIGHLIGHTS/DOSAGE AND ADMINISTRATION,** the following text was deleted from the first bullet:

   - Initial dose for patients new to prostacyclin infusion therapy: 1.25 ng/kg/min (or 0.625 ng/kg/min if not tolerated); dose increase based on clinical response (increments of 1.25 ng/kg/min per week for the first 4 weeks of treatment, later 2.5 ng/kg/min per week). ~~Limited experience with doses > 40 mg/kg/min.~~ Abrupt cessation of infusion should be avoided. (2.2, 2.3)

3. In **INDICATIONS AND USAGE/Pulmonary Arterial Hypertension**, the following text was added to the second paragraph of the first section:

   It may be administered as a continuous subcutaneous infusion or continuous intravenous (IV) infusion; however, because of the risks associated with chronic indwelling central venous catheters, including serious blood stream infections (BSIs), continuous intravenous infusion should be reserved for patients who are intolerant of the subcutaneous route, or in whom these risks are considered warranted. *[see Warnings and Precautions 5.1]*

4. Under **DOSAGE AND ADMINISTRATION/General**, the following text was added/deleted:

> Remodulin is supplied in 20 mL vials containing 20, 50, 100, or 200 mg of treprostinil (1 mg/mL, 2.5 mg/mL, 5 mg/mL or 10 mg/mL). Remodulin can be administered as supplied or diluted for intravenous infusion with Sterile Water for Injection, 0.9% Sodium Chloride Injection, Sterile Diluent <u>for Flolan, or Sterile Diluent for Epoprostenol Sodium</u> ~~for Injection~~ prior to administration.

5. Under **DOSAGE AND ADMINISTRATION/Dosage Adjustments**, the following text was deleted from the second paragraph:

> 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 mg/kg/min.~~ Abrupt cessation of infusion should be avoided *[see Warnings and Precautions (5.4)]*. 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.

6. Under **DOSAGE AND ADMINISTRATION/Intravenous Administration,** the following text was added/deleted to the first, second, and sixth paragraphs:

> **Remodulin must be diluted with either Sterile Water for Injection, 0.9% Sodium Chloride Injection, ~~or Flolan~~ Sterile Diluent <u>for Flolan, or Sterile Diluent for Epoprostenol Sodium</u> ~~for 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. 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 ±6% or better of the hourly dose, and (4) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass.
>
> <u>Infusion sets with an in-line 0.22 or 0.2 micron pore size filter should be used.</u>
>
> The calculated amount of Remodulin Injection is then added to the reservoir along with the sufficient volume of diluent (Sterile Water for Injection, 0.9% Sodium Chloride Injection, ~~or Flolan~~ Sterile Diluent for <u>Flolan, or Sterile Diluent for</u>

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