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>

Epoprostenol Sodium ~~Injection~~) to achieve the desired total volume in the reservoir.

7. Under **WARNINGS AND PRECAUTIONS/Risks Attributable to the Drug Delivery System**, the following text was added to the first paragraph:

   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. Administration of IV Remodulin with a high pH glycine diluent such as Sterile Diluent for Flolan or Sterile Diluent for Epoprostenol Sodium has been associated with a lower incidence of BSIs compared to neutral diluents (sterile water, 0.9% sodium chloride) when used along with catheter care guidelines.

8. Under **ADVERSE REACTIONS/Adverse Events during Chronic Dosing**, the following text was added:

   The safety of Remodulin was also studied in a long-term, open-label extension study in which 860 patients were dosed for a mean duration of 1.6 years, with a maximum exposure of 4.6 years. Twenty-nine (29%) percent achieved a dose of at least 40 ng/kg/min (max: 290 ng/kg/min). The safety profile during this chronic dosing study was similar to that observed in the 12-week placebo controlled study except for the following suspected adverse drug reactions (occurring in at least 3%): anorexia, vomiting, infusion site infection, asthenia, and abdominal pain.

9. Under **HOW SUPPLIED/STORAGE AND HANDLING**, the following text was added/deleted from the second paragraph:

   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, 0.9% Sodium Chloride Injection, ~~or Flolan~~ Sterile Diluent for Flolan or Sterile Diluent for Epoprostenol Sodium ~~Injection~~. A single vial of Remodulin should be used for no more than 30 days after the initial introduction into the vial.

   Remodulin Injection is supplied as:

10. Under **PATIENT COUNSELING INFORMATION**, the following text was added/deleted:

    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. Patients should use an

infusion set with an in-line filter. 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).

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

11. The revision date was updated.

There are no other changes from the last approved package insert.

We have completed our review of this supplemental application, and it is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.
Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

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:

Lori Anne Wachter, RN, BSN
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

DOCKET ALARM

Explore Litigation Insights

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Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
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