**CENTER FOR DRUG EVALUATION AND RESEARCH**

**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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***APPLICATION NUMBER:***

# NDA 021-272/S-020

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# NDA 021-272/S-020

# 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>

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

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

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/s/

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MARY R SOUTHWORTH
09/26/2013

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# NDA 021-272/S-020

# LABELING

## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use Remodulin safely and effectively. See full prescribing information for Remodulin.**

**REMODULIN® (treprostinil) Injection**
**Initial U.S. Approval: May 2002**

**----------RECENT MAJOR CHANGES----------**

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

**----------INDICATIONS AND USAGE----------**

Remodulin is a prostacyclin vasodilator indicated for:

- 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%) (1.1)
- 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. (1.2)

**----------DOSAGE AND ADMINISTRATION----------**

PAH in patients with NYHA Class II-IV symptoms:

- 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). Abrupt cessation of infusion should be avoided. (2.2, 2.3)
- Mild to moderate hepatic insufficiency: Initial dose should be decreased to 0.625 ng/kg/min ideal body weight; cautious dosage increase. Severe hepatic insufficiency: No studies performed. (2.4)

Transition from Flolan:
Increase the Remodulin dose gradually as the Flolan dose is decreased, based on constant observation of response. (2.7)
Administration:
Continuous subcutaneous infusion (undiluted) is the preferred mode. Use intravenous (IV) infusion (dilution required) if subcutaneous infusion is not tolerated. (2.1, 2.6)
See Full Prescribing Information.

**----------DOSAGE FORMS AND STRENGTHS----------**

- 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). (3)

**----------CONTRAINDICATIONS----------**

None

**----------WARNINGS AND PRECAUTIONS----------**

- 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. Remodulin should be used only by clinicians experienced in the diagnosis and treatment of PAH. (5.2)
- Adjust dosage based on clinical response, including infusion site symptoms. (5.3)
- Do not abruptly lower the dose or withdraw dosing. (5.4)

**----------ADVERSE REACTIONS----------**

Most common adverse reactions (incidence >3%) reported in clinical studies with Remodulin: subcutaneous infusion site pain and reaction, headache, diarrhea, nausea, jaw pain, vasodilatation, dizziness, edema, pruritus and hypotension. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact United Therapeutics Corp. at 1-866-458-6479 or via e-mail at drugsafety@unither.com, or contact FDA at 1-800-FDA-1088 or** www.fda.gov/medwatch**.**

**----------DRUG INTERACTIONS----------**

- Blood pressure lowering drugs (e.g., diuretics, antihypertensive agents, or vasodilators): Risk of increased reduction in blood pressure (7.1)
- Remodulin inhibits platelet aggregation. Potential for increased risk of bleeding, particularly among patients on anticoagulants. (7.2)
- Remodulin dosage adjustment may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn. (7.6)

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised:** 09/2013

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**FULL PRESCRIBING INFORMATION: CONTENTS***



*Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

## REMODULIN® (treprostinil) Injection

### 1. INDICATIONS AND USAGE

#### 1.1 Pulmonary Arterial Hypertension

Remodulin is 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%) *[see Clinical Studies (14.1)]*.

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]*

#### 1.2 Pulmonary Arterial Hypertension in Patients Requiring Transition from Flolan®

In patients with pulmonary arterial hypertension requiring transition from Flolan (epoprostenol sodium), Remodulin is indicated to diminish the rate of clinical deterioration. The risks and benefits of each drug should be carefully considered prior to transition.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 General

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 for Flolan, or Sterile Diluent for Epoprostenol Sodium prior to administration.

#### 2.2 Initial Dose for Patients New to Prostacyclin Infusion Therapy

Remodulin is indicated for subcutaneous (SC) or intravenous (IV) use only as a 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.

#### 2.3 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. 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.

### 2.4 Patients with Hepatic Insufficiency

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 *[see Warnings and Precautions (5.5), Use In Specific Populations (8.6)* and *Clinical Pharmacology (12.3)]*.

### 2.5 Patients with Renal Insufficiency

No studies have been performed in patients with renal insufficiency. No specific advice about dosing in patients with renal impairment can be given.
*[see Clinical Pharmacology (12.3)].*

### 2.6 Administration

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.

**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 patients 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:

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

**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:

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

**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:

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

**Intravenous Infusion**

**Remodulin must be diluted with either Sterile Water for Injection, 0.9% Sodium Chloride Injection, Sterile Diluent for Flolan, or Sterile Diluent for Epoprostenol Sodium** 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.

Infusion sets with an in-line 0.22 or 0.2 micron pore size filter should be used.

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:

**Step 1**

$$\textbf{Diluted Intravenous Remodulin} = \frac{\textbf{Dose} \text{ (ng/kg/min)} \times \textbf{Weight} \text{ (kg)} \times \textbf{0.00006}}{}$$

$$\textbf{Concentration (mg/mL)} = \frac{\textbf{Intravenous Infusion Rate (mL/hr)}}{}$$

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**

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

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, Sterile Diluent for Flolan, or Sterile Diluent for Epoprostenol Sodium) 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**

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

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**

$$\textbf{Amount of Remodulin Injection (mL)} = \frac{\textbf{0.018} \text{ mg/mL}}{\textbf{1} \text{ mg/mL}} \times \textbf{50} \text{ mL} = \textbf{0.9} \text{ mL}$$

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**

$$\textbf{Diluted Intravenous Remodulin Concentration (mg/mL)} = \frac{\textbf{30} \text{ ng/kg/min} \times \textbf{75} \text{ kg} \times \textbf{0.00006}}{\textbf{2} \text{ mL/hr}} = \textbf{0.0675} \text{ mg/mL } (67{,}500 \text{ ng/mL})$$

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**

$$\textbf{Amount of Remodulin Injection (mL)} = \frac{\textbf{0.0675} \text{ mg/mL}}{\textbf{2.5} \text{ mg/mL}} \times \textbf{100} \text{ mL} = \textbf{2.7} \text{ mL}$$

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.

### 2.7 Patients Requiring Transition from Flolan

Transition from Flolan to Remodulin is accomplished by initiating the infusion of Remodulin and increasing it, while simultaneously reducing the dose of intravenous Flolan. The transition to Remodulin should take place in a hospital with constant observation of response (e.g., walk distance and signs and symptoms of disease progression). During the transition, Remodulin is initiated at a recommended dose of 10% of the current Flolan dose, and then escalated as the Flolan dose is decreased (see Table 1 for recommended dose titrations).

Patients are individually titrated to a dose that allows transition from Flolan therapy to Remodulin while balancing prostacyclin-limiting adverse events. Increases in the patient's symptoms of PAH should be first treated with increases in the dose of Remodulin. Side effects normally associated with prostacyclin and prostacyclin analogs are to be first treated by decreasing the dose of Flolan.

**Table 1: Recommended Transition Dose Changes**

| Step | Flolan Dose | Remodulin Dose |
|---|---|---|
| 1 | Unchanged | 10% Starting Flolan Dose |
| 2 | 80% Starting Flolan Dose | 30% Starting Flolan Dose |
| 3 | 60% Starting Flolan Dose | 50% Starting Flolan Dose |
| 4 | 40% Starting Flolan Dose | 70% Starting Flolan Dose |
| 5 | 20% Starting Flolan Dose | 90% Starting Flolan Dose |
| 6 | 5% Starting Flolan Dose | 110% Starting Flolan Dose |

| | | |
|---|---|---|
| 7 | 0 | 110% Starting Flolan Dose + additional 5-10% increments as needed |

## 3 DOSAGE FORMS AND STRENGTHS

20-mL vial containing 20 mg treprostinil (1 mg per mL).
20-mL vial containing 50 mg treprostinil (2.5 mg per mL).
20-mL vial containing 100 mg treprostinil (5 mg per mL).
20-mL vial containing 200 mg treprostinil (10 mg per mL).

## 4 CONTRAINDICATIONS

None

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Risks Attributable to the 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. Therefore, continuous subcutaneous infusion (undiluted) is the preferred mode of administration.

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 when compared to neutral diluents (sterile water, 0.9% sodium chloride) when used along with catheter care guidelines.

### 5.2 General Conditions of Use

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.

### 5.3 Dose Modification

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 (2)]*.

### 5.4 Abrupt Withdrawal or Sudden Large Dose Reduction

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

### 5.5 Patients with Hepatic or Renal Insufficiency

Titrate slowly in patients with hepatic or renal insufficiency, because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic or renal

function *[see Dosage and Administration (2.4, 2.5), Use In Specific Populations (8.6, 8.7), and Clinical Pharmacology (12.3)]*.

### 5.6 Effect of Other Drugs on Treprostinil

Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both $C_{max}$ and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness *[see Drug Interactions (7.5)* and *Clinical Pharmacology (12.3)]*.

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in labeling: Infections associated with intravenous administration *[see Warnings and Precautions (5.1)]*.

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

**Adverse Events with Subcutaneously Administered Remodulin**

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 12-Week 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.

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% of patients): anorexia, vomiting, infusion site infection, asthenia, and abdominal pain

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. 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 and Precautions (5.1)]*.

### 6.2 Post-Marketing Experience

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.

## 7 DRUG INTERACTIONS

Pharmacokinetic/pharmacodynamic interaction studies have been conducted with treprostinil administered subcutaneously (Remodulin) and orally (treprostinil diethanolamine).

***Pharmacodynamics***

### 7.1 Antihypertensive Agents or Other Vasodilators

Concomitant administration of Remodulin with diuretics, antihypertensive agents or other vasodilators may increase the risk of symptomatic hypotension.

### 7.2 Anticoagulants

Since treprostinil inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulants.

***Pharmacokinetics***

### 7.3 Bosentan

In a human pharmacokinetic study conducted with bosentan (250 mg/day) and an oral formulation of treprostinil (treprostinil diethanolamine), no pharmacokinetic interactions between treprostinil and bosentan were observed.

### 7.4 Sildenafil

In a human pharmacokinetic study conducted with sildenafil (60 mg/day) and an oral formulation of treprostinil (treprostinil diethanolamine), no pharmacokinetic interactions between treprostinil and sildenafil were observed.

### 7.5 Effect of Treprostinil on Cytochrome P450 Enzymes

*In vitro* studies of human hepatic microsomes showed that treprostinil does not inhibit cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A. Additionally, treprostinil does not induce cytochrome P450 isoenzymes CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A. Thus Remodulin is not expected to alter the pharmacokinetics of compounds metabolized by CYP enzymes.

### 7.6 Effect of Cytochrome P450 Inhibitors and Inducers on Treprostinil

Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil diethanolamine) indicated that co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor gemfibrozil increases exposure (both $C_{max}$ and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inducer rifampin decreases exposure to treprostinil. It has not been determined if the safety and efficacy of treprostinil by the parenteral (subcutaneously or intravenously) route are altered by inhibitors or inducers of CYP2C8 *[see Warnings and Precautions (5.6)]*.

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

### 7.7 Effect of Other Drugs on Treprostinil

Drug interaction studies have been carried out with treprostinil (oral or subcutaneous) co-administered with acetaminophen (4 g/day), warfarin (25 mg/day), and fluconazole (200 mg/day), respectively in healthy volunteers. These studies did not show a clinically significant effect on the

pharmacokinetics of treprostinil. Treprostinil 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 infusion of treprostinil at an infusion rate of 10 ng/kg/min.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category B - In pregnant rats, continuous subcutaneous infusions of treprostinil 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/m$^2$ 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/m$^2$ 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.

### 8.2 Labor and Delivery

No treprostinil 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.

### 8.3 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.

### 8.4 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.

### 8.5 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.

### 8.6 Patients with Hepatic Insufficiency

Remodulin clearance is reduced in patients with hepatic insufficiency. In patients with mild or moderate hepatic insufficiency, decrease the initial dose of Remodulin to 0.625 ng/kg/min ideal body weight, and monitor closely. Remodulin has not been studied in patients with severe hepatic insufficiency *[see Dosage and Administration (2.4), Warnings and Precautions (5.5) and Clinical Pharmacology (12.3)]*.

### 8.7 Patients with Renal Insufficiency

No studies have been performed in patients with renal insufficiency. No specific advice about dosing in patients with renal impairment can be given. *[see Clinical Pharmacology (12.3)]*.

## 10 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).

One pediatric patient was accidentally administered 7.5 mg of Remodulin via a central venous catheter. Symptoms included flushing, headache, nausea, vomiting, hypotension and seizure-like activity with loss of consciousness lasting several minutes. The patient subsequently recovered.

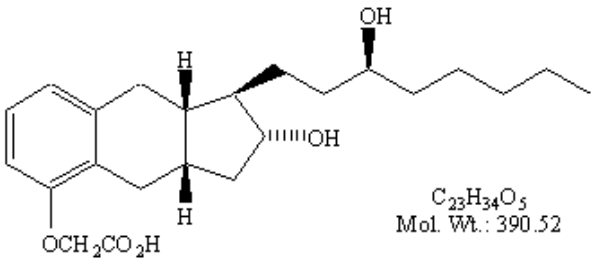
## 11 DESCRIPTION

Remodulin (treprostinil) Injection is a sterile solution of treprostinil formulated for subcutaneous or intravenous administration. Remodulin is supplied in 20 mL multidose vials in four strengths, containing 20 mg, 50 mg, 100 mg, or 200 mg (1 mg/mL, 2.5 mg/mL, 5 mg/mL or 10 mg/mL) of treprostinil. Each mL also contains 5.3 mg sodium chloride (except for the 10 mg/mL strength which contains 4.0 mg sodium chloride), 3 mg metacresol, 6.3 mg sodium citrate, and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2.

Treprostinil is chemically stable at room temperature and neutral pH.

Treprostinil 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. Treprostinil has a molecular weight of 390.52 and a molecular formula of $C_{23}H_{34}O_5$.

The structural formula of treprostinil is:



## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds, and inhibition of platelet aggregation.

### 12.2 Pharmacodynamics

In animals, the vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. Other studies have shown that treprostinil causes a dose-related negative inotropic and lusitropic effect. No major effects on cardiac conduction have been observed.

Treprostinil produces vasodilation and tachycardia. Single doses of treprostinil up to 84 mcg by inhalation produce modest and short-lasting effects on QTc, but this is apt to be an artifact of the rapidly changing heart rate. Treprostinil administered by the subcutaneous or intravenous routes has the potential to generate concentrations many-fold greater than those generated via the inhaled route; the effect on the QTc interval when treprostinil is administered parenterally has not been established.

### 12.3 Pharmacokinetics

The pharmacokinetics of continuous subcutaneous Remodulin are linear over the dose range of 1.25 to 125 ng/kg/min (corresponding to plasma concentrations of about 15 pg/mL to 18,250 pg/mL) and can be described by a two-compartment model. Dose proportionality at infusion rates greater than 125 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 2,000 pg/mL.

#### 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 and Excretion

Treprostinil is substantially metabolized by the liver, primarily by CYP2C8. In a study conducted in healthy volunteers using [$^{14}$C] treprostinil, 78.6% and 13.4% of the subcutaneous dose was recovered in the urine and feces, respectively, over 10 days. Only 4% was excreted as unchanged treprostinil in the urine. Five metabolites were detected in the urine, ranging from 10.2% to 15.5% and representing 64.4% of the dose administered. Four of the metabolites are products of oxidation of the 3-hydroxyloctyl side chain and one is a glucuroconjugated derivative (treprostinil glucuronide). The identified metabolites do not appear to have activity.

The elimination of treprostinil (following subcutaneous administration) is biphasic, with a terminal elimination half-life of approximately 4 hours using a two compartment model. Systemic clearance is approximately 30 L/hr for a 70 kg person.

Based on in vitro studies treprostinil does not inhibit or induce major CYP enzymes *[see Drug Interactions (7.5)]*.

**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.

***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.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 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 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/$m^2$ 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.

## 14 CLINICAL STUDIES

### 14.1 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 (11%), III (81%), or IV (7%) pulmonary arterial hypertension (PAH). PAH was idiopathic/heritable in 58% of patients, associated with connective tissue diseases in 19%, and the result of congenital systemic-to-pulmonary 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 Section 2, 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 4, chronic therapy with Remodulin resulted in small hemodynamic changes consistent with pulmonary and systemic vasodilation.

**Table 4: Hemodynamics during Chronic Administration of Remodulin in Patients with PAH in 12-Week Studies**

| 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 12-week 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 from a baseline of approximately 345 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.

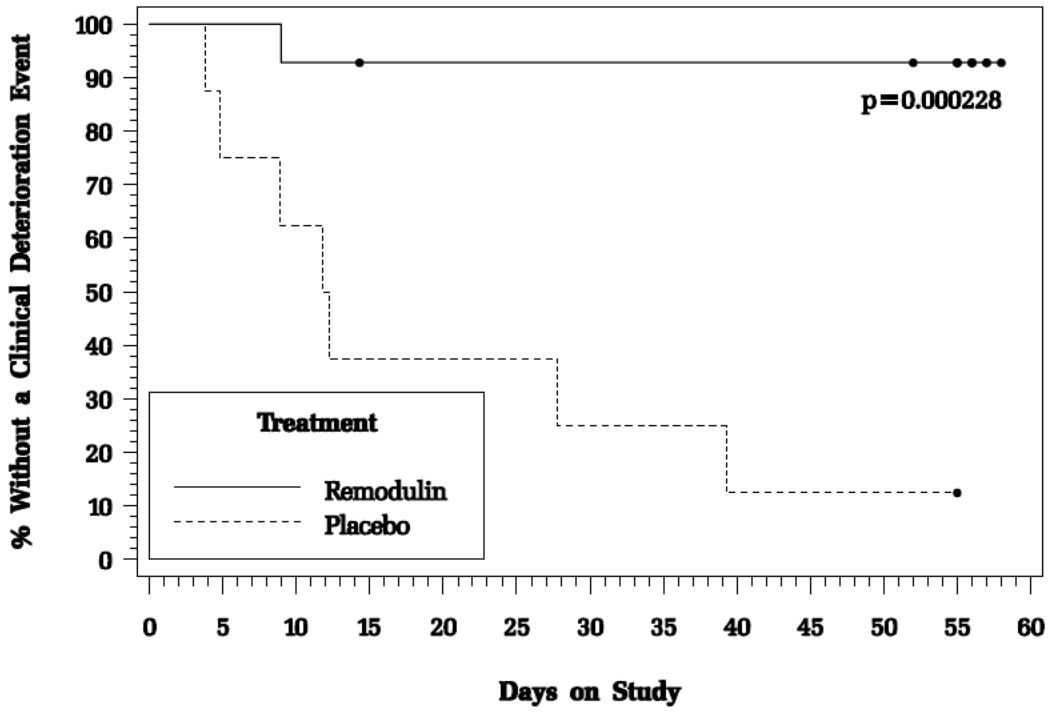
**14.2 Flolan-To-Remodulin Transition Study**

In an 8-week, multicenter, randomized, double-blind, placebo-controlled study, patients on stable doses of Flolan were randomly withdrawn from Flolan to placebo or Remodulin. Fourteen Remodulin and 8 placebo patients completed the study. The primary endpoint of the study was the time to clinical deterioration, defined as either an increase in Flolan dose, hospitalization due to PAH, or death. No patients died during the study.

During the study period, Remodulin effectively prevented clinical deterioration in patients transitioning from Flolan therapy compared to placebo (Figure 1). Thirteen of 14 patients in the

Remodulin arm were able to transition from Flolan successfully, compared to only 1 of 8 patients in the placebo arm (p=0.0002).

**Figure 1: Time to Clinical Deterioration for PAH Patients Transitioned from Flolan to Remodulin or Placebo in an 8-Week Study**




## 16 HOW SUPPLIED / STORAGE AND HANDLING

Remodulin is supplied in 20 mL multidose vials containing 20, 50, 100, or 200 mg of treprostinil at concentrations of 1 mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL treprostinil, respectively, as sterile solutions in water for injection, individually packaged in cartons. 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, 0.9% Sodium Chloride Injection, Sterile Diluent for Flolan or Sterile Diluent for Epoprostenol Sodium . 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:

20-mL vial containing 20 mg treprostinil (1 mg treprostinil per mL), carton of 1 (NDC 66302-101-01).

20-mL vial containing 50 mg treprostinil (2.5 mg treprostinil per mL), carton of 1 (NDC 66302-102-01).

20-mL vial containing 100 mg treprostinil (5 mg treprostinil per mL), carton of 1 (NDC 66302-105-01).

20-mL vial containing 200 mg treprostinil (10 mg treprostinil per mL), carton of 1 (NDC 66302-110-01).

**17 PATIENT COUNSELING INFORMATION**

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).



REMODULIN manufactured for:

United Therapeutics Corp.
Research Triangle Park, NC 27709

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# NDA 021-272/S-020

# LABELING REVIEW

## DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

***Safety Labeling Review***

| | |
|---|---|
| **NDA**: | 021272/S-020 |
| **Date of submission:** | **May 23, 2013** |
| **Review date**: | August 2, 2013 |
| **Applicant**: | United Therapeutics Corporation |
| **Product:** | **Remodulin (treprostinil) Injection** |
| **Reviewers**: | Lori Anne Wachter, RN, BSN, R.A.C.<br>Regulatory Project Manager for Safety<br><br>Mary Ross Southworth, Pharm. D.<br>Deputy Director for Safety |

**Background:**

Remodulin is a prostacyclin vasodilator approved for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I). Remodulin was initially approved in 2002 and is supplied as 1 mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL for Injection.

The currently approved label for Remodulin allows for dilution of the product with sterile water for injection, 0.9% sodium chloride injection or Flolan Sterile Diluent prior to administration. Flolan Sterile diluent has basic properties (b) (4)

(b) (4)

[redacted] (b) (4)

The present submission proposes several changes to the **INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS**, **ADVERSE REACTIONS, HOW SUPPLIED/STORAGE AND HANDLING**, and **PATIENT COUNSELING INFORMATION** sections of the package insert.

- Adding "Sterile Diluent for Epoprostenol Sodium" as a potential diluent
- Addition of a statement that administering Remodulin with a high pH diluent reduces blood stream infections
- Recommending the use of a 0.22 or 0.2 micron pore size filter
- Addition of exposure and adverse event data from a long term open label study
- Removing a statement about limited experience with doses >40ng/kg/min

Parts of this submission (report for P01:06, a long-term, open label study) were the subject of a review by Avi Karkowsky (NDA 21-272, 02/08/13). Pertinent comments are included below.

Labeling negotiations were conducted with the sponsor via e-mail and an agreement was reached on September 20, 2013.

**Review:**
The sponsor made the following changes (additions are shown as underlined text and deletions are shown 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 |

**Evaluation and Conclusion:** This revision is acceptable and should be approved.

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 ng/kg/min.~~ Abrupt cessation of infusion should be avoided. (2.2, 2.3)

**Evaluation and Conclusion:** The open label study results submitted included patients exposed to >40 ng/kg/min (although the number of patients not any adverse events associated with higher doses is not described). This revision is acceptable and should be approved.

3. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS,** the following text was added to the first bullet:

    - 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. (b) (4) [redacted]

**Evaluation and Conclusion**: A consult was sent to ONDQA to review the sponsors proposed language regarding the use of a high glycine diluent and the reduction of blood stream infections (BSIs). Dr. Langille, Senior Microbiology Reviewer reached the following conclusion (see review in DARRTS dated 8/1/2013):

> *The applicant provided two literature references to support this claim. The first article titled "The effect of diluent pH on bloodstream infection rates in patients receiving IV treprostinil for pulmonary arterial hypertension" by Rich et. al. (Chest 141:36-42) provided evidence that blood stream infections for gram negative organisms were reduced in the patients treated with treprostinil diluted in high pH buffers. The second article titled "Stability and antimicrobial effectiveness of treprostinil sodium in sterile diluent for Flolan" by Zaccardelli et. al. (J. Clin. Prac. 64:885-891) showed that treprostinil suspended in pH 10.5 Flolan diluent passed USP <51> preservative effectiveness testing. Based upon a review of the referenced literature, the proposed labeling change is satisfactory from a product quality microbiology perspective.*

To accurately represent the findings, the statement should be revised to read:

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.

This statement should appear in section 5.1 only, not in Highlights.

4. 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. (b) (4) [redacted]

(b) (4)

**Evaluation and Conclusion**: This statement should be deleted here since it is included in 5.1. Add a cross reference to 5.1 in this section.

5. 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.

**Evaluation and Conclusion**: This revision is acceptable and should be approved.

6. 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.

**Evaluation and Conclusion**: This revision is acceptable and should be approved.

7. 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.

Infusion sets with an in-line 0.22 or 0.2 micron pore size filter should be used.

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 Flolan, or Sterile Diluent for Epoprostenol Sodium ~~Injection~~) to achieve the desired total volume in the reservoir.

**Evaluation and Conclusion**: This revision is acceptable and should be approved.

8. 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.

**Evaluation and Conclusion**: See wording described above.

9. 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.

**Evaluation and Conclusion**: This revision is acceptable and should be approved.

10. 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:

**Evaluation and Conclusion**: This revision is acceptable and should be approved.

11. 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. (b) (4) 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)~~

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**Evaluation and Conclusion**: This statement is not appropriate for patient counseling. .

12. The revision date was updated.

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

**Recommendation:**

An approval letter should be issued for these supplements as set forth under 21 CFR 314.70 (b) (3) [Any change in labeling].

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/s/

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Lori A WACHTER
11/15/2013

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# NDA 021-272/S-020

# OTHER REVIEW(S)

**M E M O R A N D U M**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**DATE:** 25 July 2013

**TO:** Lori Wachter
Regulatory Project Manager
OMPT/CDER/OND/ODEI/DCRP

**FROM:** Stephen E. Langille, Ph.D.
Senior Microbiology Reviewer
CDER/OPS/NDMS

**THROUGH:** John Metcalfe, Ph.D.
Senior Microbiology Reviewer
CDER/OPS/NDMS

**SUBJECT:** NDA 21-272/S-020

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On 23 May 2013, United Therapeutics Corp. submitted a labeling supplement for NDA 21-272 – Remodulin (treprostinil sodium). The treatment of pulmonary arterial hypertension (PAH) with treprostinil often takes place over long period of time through the use of indwelling intravenous catheters. Complications due to the use of indwelling catheters include blood stream infections which may cause significant morbidity and mortality in debilitated PAH patients.

A review request was submitted on 17 July 2013 for the NDMS to evaluate the following statement in the proposed label:

**"** *Administration of IV Remodulin with a high pH glycine diluent such as Sterile Diluent for Flolan or Sterile Diluent for Epoprostenol Sodium has been shown to reduce BSIs when used along with catheter care guidelines. (5.1)*

The applicant provided two literature references to support this claim. The first article titled *The effect of diluent pH on bloodstream infection rates in patients receiving IV treprostinil for pulmonary arterial hypertension* by Rich et. al. (*Chest* 141:36-42) provided evidence that blood stream infections for gram negative organisms were reduced in the patients treated with treprostinil diluted in high pH buffers. The second article titled *Stability and antimicrobial effectiveness of treprostinil sodium in sterile diluent for Flolan* by Zaccardelli et. al. (J. Clin. Prac. 64:885-891) showed that treprostinil suspended in pH 10.5 Flolan diluent passed USP

**M E M O R A N D U M**

<51> preservative effectiveness testing. Based upon a review of the referenced literature, the proposed labeling change is satisfactory from a product quality microbiology perspective.

**END**

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/s/

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STEPHEN E LANGILLE
08/01/2013

JOHN W METCALFE
08/01/2013
I concur.