



NDA 21-272/S-011

**SUPPLEMENT APPROVAL**

United Therapeutics Corporation  
Attention: Mr. Kerry McKenzie  
Regulatory Affairs Manager  
55 TW Alexander Drive  
Research Triangle Park, NC 27709

Dear Mr. McKenzie:

Please refer to your supplemental new drug application dated April 27, 2009, received April 27, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Remodulin (treprostinil) 1, 2.5, 5, and 10 mg/mL Injection.

We also acknowledge receipt of your submissions dated October 19 and December 18, 2009.

This "Changes Being Effected" supplemental new drug application provides for revisions to the carton labeling, immediate container labels, and prescribing information as follows:

**General**

The vial and carton labeling for Remodulin has been revised.

The established name for Remodulin has been revised:

FROM

treprostinil sodium

TO

treprostinil

The molecular formula and molecular weight have been updated in the labeling to reflect this change.

## “Highlights of Prescribing Information”

In **DOSAGE AND ADMINISTRATION**/Transition from Flolan, revised:

FROM

Recommended initial Remodulin dose is 10% of the current Flolan dose. Individualized dosage increase as Flolan dose is decreased, based on constant observation of response.

TO

Increase the Remodulin dose gradually as the Flolan dose is decreased, based on constant observation of response.

In **DOSAGE AND ADMINISTRATION**/Administration, revised:

FROM

Continuous subcutaneous infusion (undiluted). Intravenous infusion (dilution required) if subcutaneous infusion is not tolerated.

Complete dosing, dilution and administration instructions: See Full Prescribing Information.

TO

Continuous subcutaneous infusion (undiluted) is the preferred mode. Use intravenous infusion (dilution required) if subcutaneous infusion is not tolerated. See Full Prescribing Information.

In **DOSAGE FORMS AND STRENGTHS**, revised:

FROM

Remodulin is supplied in 20 mL vials in concentrations of 1 mg/mL, 2.5 mg/mL, 5 mg/mL and 10 mg/mL.

TO

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).

In **DRUG INTERACTIONS**, added:

Remodulin dosage adjustment may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn.

## “Full Prescribing Information”

In **DOSAGE AND ADMINISTRATION/General**, revised:

FROM

Remodulin is supplied in 20 mL vials in concentrations of 1 mg/mL, 2.5 mg/mL, 5 mg/mL and 10 mg/mL.

TO

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).

In **DOSAGE FORMS AND STRENGTHS**, revised:

FROM

20-mL vial containing treprostinil sodium equivalent to 1 mg treprostinil per mL.  
20-mL vial containing treprostinil sodium equivalent to 2.5 mg treprostinil per mL.  
20-mL vial containing treprostinil sodium equivalent to 5 mg treprostinil per mL.  
20-mL vial containing treprostinil sodium equivalent to 10 mg treprostinil per mL.

TO

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).

In **WARNINGS AND PRECAUTIONS/Risks Attributable to the Drug Delivery System**, added:

Therefore, continuous subcutaneous infusion (undiluted) is the preferred mode of administration.

In **WARNINGS AND PRECAUTIONS/Patients with Hepatic or Renal Insufficiency**, revised:

FROM

Caution should be used in patients with hepatic or renal insufficiency.

TO

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.

In **WARNINGS AND PRECAUTIONS/Effect of Other Drugs on Treprostinil**, added:

Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both C<sub>max</sub> 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.

In **ADVERSE REACTIONS**, added:

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

In **DRUG INTERACTIONS**, revised:

FROM

Reduction in blood pressure caused by Remodulin may be exacerbated by drugs that by themselves alter blood pressure, such as diuretics, antihypertensive agents, or vasodilators. Since Remodulin inhibits platelet aggregation, there is also a potential for increased risk of bleeding, particularly among patients maintained on anticoagulants. During clinical trials, Remodulin was used concurrently with anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, antipyretics, nonsteroidal anti-inflammatories, opioids, corticosteroids, and other medications.

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

**Effect of Other Drugs on treprostinil**

In vivo studies: Acetaminophen - Analgesic doses of acetaminophen, 1000 mg every 6 hours for seven doses, did not affect the pharmacokinetics of Remodulin, at a subcutaneous infusion rate of 15 ng/kg/min.

**Effect of treprostinil on Other Drugs**

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

TO

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 Cytochrome P450 Inhibitors and Inducers**

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.

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<sub>max</sub> 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).

### **7.6 Effect of Other Drugs on Remodulin**

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.

In **USE IN SPECIFIC POPULATIONS/Patients with Hepatic Insufficiency**, revised:

FROM

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.

TO

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.

In **DESCRIPTION**, revised:

FROM

Remodulin (treprostinil sodium) Injection is a sterile sodium salt formulated for subcutaneous or intravenous administration. Remodulin is supplied in 20 mL multi-use vials in four strengths, containing 1 mg/mL, 2.5 mg/mL, 5 mg/mL or 10 mg/mL of treprostinil.

Treprostinil sodium has a molecular weight of 412.49 and a molecular formula of  $C_{23}H_{33}NaO_5$ . The structural formula of treprostinil sodium is:

TO

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<sub>23</sub>H<sub>34</sub>O<sub>5</sub>.

The structural formula of treprostinil is:

**In CLINICAL PHARMACOLOGY/Pharmacodynamics, added:**

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.

**In CLINICAL PHARMACOLOGY/Pharmacokinetics/Metabolism and Excretion, revised:**

**FROM**

Remodulin is substantially metabolized by the liver, but the precise enzymes responsible are unknown. Five metabolites have been described (HU1 through HU5). The biological activity and metabolic fate of these metabolites are unknown. The chemical structure of HU1 is unknown. HU5 is the glucuronide conjugate of treprostinil. The other metabolites are formed by oxidation of the 3-hydroxyoctyl side chain (HU2) and subsequent additional oxidation (HU3) or dehydration (HU4). Based on the results of in vitro human hepatic cytochrome P450 studies, Remodulin does not inhibit CYP-1A2, 2C9, 2C19, 2D6, 2E1, or 3A. Whether Remodulin induces these enzymes has not been studied.

The elimination of Remodulin is biphasic, with a terminal half-life of approximately 4 hours. Approximately 79% of an administered dose is excreted in the urine as unchanged drug (4%) and as the identified metabolites (64%). Approximately 13% of a dose is excreted in the feces. Systemic clearance is approximately 30 liters/hr for a 70 kg ideal body weight person.

**TO**

Treprostinil is substantially metabolized by the liver, primarily by CYP2C8. In a study conducted in healthy volunteers using [14C] 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-hydroxyoctyl 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)].

In **HOW SUPPLIED / STORAGE AND HANDLING**, revised:

FROM

Remodulin is supplied in 20 mL multi-use vials at concentrations of 1 mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL treprostinil, as sterile solutions in water for injection, individually packaged in a carton. Each mL contains treprostinil sodium equivalent to 1 mg/mL, 2.5 mg/mL, 5 mg/mL, or 10 mg/mL treprostinil.

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

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

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

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

TO

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.

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).

We have completed our review of this application, as amended. 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, please submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling. For administrative purposes, please designate this submission, “**SPL for approved NDA 21-272/S-011**”.

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are the same as the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “Final Printed Carton and Container Labels for approved NDA 21-272/S-011.” Approval of this submission by FDA is not required before the labeling is used.

### **LETTERS TO HEALTH CARE PROFESSIONALS**

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

MedWatch  
Food and Drug Administration  
5600 Fishers Lane, Room 12B05  
Rockville, MD 20857

### **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 Dan Brum, Pharm.D., RAC, Regulatory Project Manager, at (301)796-0578.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure: Agreed-upon labeling including carton and container labeling

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-21272

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SUPPL-11

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UNITED  
THERAPEUTICS  
CORP

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REMODULIN(TREPROSTINIL  
SODIUM)1/2.5/10

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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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NORMAN L STOCKBRIDGE

01/08/2010