DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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Remodulin dosage adjustment may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn.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

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