DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203496/S-002

SUPPLEMENT APPROVAL

United Therapeutics Corporation
Attention: United Therapeutics Corporation
Attention: Rex Mauthe, MBA
Assoc. 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 March 31, 2015, received March 31, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Orenitram (treprostinil) Extended Release Tablets, 0.125 mg, 0.25 mg, 1 mg, and 2.5 mg.

This "Prior Approval" supplemental new drug application provides for revisions as follows (additions noted in underline, deletions noted in strikethrough):

In the **DOSAGE AND ADMINISTRATION** section, new subsection **2.2 Transitioning from Subcutaneous or Intravenous Routes of Administration of Treprostinil** was added to the package insert

2.2 Transitioning from Subcutaneous or Intravenous Routes of Administration of Treprostinil

Decrease the dose of Remodulin while simultaneously increasing the dose of Orenitram. The dose of Remodulin can be reduced up to 30 ng/kg/min per day and the dose of Orenitram simultaneously increased up to 6 mg per day (2 mg TID) if tolerated. The following equation can be used to estimate a comparable total daily dose of Orenitram in mg using a patient's dose of IV/SC treprostinil (in ng/kg/min) and weight (in kg).

Orenitram total daily dose (mg) = 0.0072 X Remodulin dose (ng/kg/min) X weight (kg)

In the **DOSAGE AND ADMINISTRATION** section, subsection **2.4 Interruptions and Discontinuation** was changed to subsection 2.5, with the following change:

If a dose of medication is missed, the patient should take the missed dose as soon as possible, with food. If a patient misses two or more doses, restart at a lower dose and re-titrate.
In the event of a planned short-term treatment interruption for patients unable to take oral medications, consider a temporary infusion of subcutaneous or intravenous treprostinil. To

calculate the total daily dose (mg) of treprostinil for the parenteral route ~~divide the oral total daily dose by 5~~ use the following equation

$$\text{Remodulin (ng/kg/min)} = \frac{139 \times \text{Orenitram total daily dose (mg)}}{\text{weight (kg)}}$$

When discontinuing Orenitram, reduce the dose in steps of 0.5 to 1 mg per day *[see Warnings and Precautions (5.1)]*.

In the **WARNINGS AND PRECAUTIONS** section, subsection **5.3 Increased Exposure with Alcohol** was deleted**.**

In the **ADVERSE REACTIONS** section, subsection **6.1 Clinical Trials Experience**, the following paragraph was added to the end of the subsection:

The safety of Orenitram was also evaluated in an open-label study transitioning patients from Remodulin. The safety profile during this study was similar to that observed in the three pivotal studies.

In the **DESCRIPTION** section, the last sentence of the second paragraph was edited to read:

Orenitram tablets are formulated in four strengths, which contain 0.125 mg of treprostinil (equivalent to 0.159 mg treprostinil diolamine), 0.25 mg of treprostinil (equivalent to 0.317 mg treprostinil diolamine), 1 mg of treprostinil (equivalent to 1.27 mg treprostinil diolamine), or 2.5 mg of treprostinil (equivalent to 3.17 mg treprostinil diolamine). The formulations also contain xylitol, maltodextrin, sodium lauryl sulfate, magnesium stearate, cellulose acetate, triethyl citrate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc. In addition tablets may contain colorants FD&C Blue #2, iron oxide yellow, and iron oxide red. The imprinting ink contains shellac glaze, ethanol, isopropyl alcohol USP, iron oxide black, n-butyl alcohol, and propylene glycol~~, and ammonium hydroxide~~.

In the **CLINICAL PHARMACOLOGY** section, subsection **12.3 Pharmacokinetics**, subheading **Absorption**, the following sentence was added to the end of the first paragraph:

Absorption
The absolute oral bioavailability of Orenitram is approximately 17%. Maximum treprostinil concentrations occur between approximately 4 and 6 hours following Orenitram administration. Time to reach steady-state concentrations for both BID and TID regimens is approximately 1 to 2 days.

In the **NONCLINICAL TOXICOLOGY** section, subsection **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**, the following changes were made:

Treprostinil diolamine did not demonstrate any carcinogenic effects in mouse or rat carcinogenicity studies. Oral administration of treprostinil diolamine to Tg.rasH2 mice at 0, 5, 10 and 20 mg/kg/day in males and 0, 3, 7.5 and 15 mg/kg/day in females daily for 26 weeks did not

significantly increase the incidence of tumors. The exposures obtained at the highest dose levels used in males and females are about 8- and 17-fold, respectively, the human exposure at the mean dose of 3.4 mg BID. Oral administration of treprostinil diolamine to Sprague Dawley rats at 0, 1, 3 and 10 mg/kg/day daily for 104 weeks did not significantly increase the incidence of tumors. The exposures obtained at the highest dose levels used in males and females are about 21- and 29-fold, respectively, the human exposure.

In vitro genotoxicity studies with high doses of treprostinil did not demonstrate any mutagenic or clastogenic effects. Treprostinil diolamine was tested in vivo in a rat micronucleus assay and did not induce an increased incidence of micronucleated polychromatic erythrocytes.

No adverse effect doses for fertility, fetal viability / growth, fetal development (teratogenicity), and postnatal development were determined in rats. In pregnant rabbits, external fetal and soft tissue malformations and fetal skeletal malformation occurred with the no observed adverse effect level for these adverse effects of 0.5 mg/kg/day (5 times the human exposure) [*see Use in Specific Populations (8.1)*].

In the **CLINICAL STUDIES** section, subsection **14.1 Clinical Trials in Pulmonary Arterial Hypertension (PAH)**, subheader "Remodulin to Orenitram Transition Study" was added, to read as follows:

Remodulin to Orenitram Transition Study

A 24-week, multicenter, open-label study enrolled 33 WHO Group 1 patients on stable doses of Remodulin. All patients received background therapy with a PDE-5 inhibitor and/or ERA. Patients were WHO Functional Class I or II and hemodynamically stable at baseline with a cardiac index >2.2 L/m2, RAP<11 mmHg, and PVR<10 Woods units. The primary endpoint of the study was the safety and tolerability of the transition. Successful transition was defined as transition from Remodulin to Orenitram at Week 4 (no longer receiving Remodulin) and clinically maintained on Orenitram through Week 24 (as measured by 6MWD and hemodynamics).

All patients transitioned from Remodulin to Orenitram (median time to transition of 3 days;) with thirty-one patients (94%) completing transition in 5 days (range 2 to 29 days).Two subjects discontinued Orenitram. The mean Orenitram total daily dose at the end of transition was 27 mg ± 12 mg compared to a mean Remodulin dose prior to transition of 59 ng/kg/min (25 to 111 ng/kg/min). The mean Orenitram total daily dose at Week 24 was 36 mg ± 16 mg.After 24 weeks of treatment with Orenitram, 6MWD and hemodynamics remained stable. Without a control group, these data must be interpreted cautiously.

In the **PATIENT COUNSELING INFORMATION** section, the last bullet was deleted as follows:

Tell patients:

- Abrupt discontinuation of therapy could result in worsening of PAH symptoms.

- Take Orenitram with food.
- Swallow Orenitram tablets whole. Do not split, chew, crush, or break. Do not take a tablet that is damaged or broken.
- The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the feces as an insoluble shell.
- ~~Do not take Orenitram with alcohol.~~

APPROVAL & LABELING

We have completed our review of this supplemental 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, 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, text for the patient 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 that includes labeling changes 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).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

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:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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