DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022387/S-014

SUPPLEMENT APPROVAL

United Therapeutics Corporation
Attention: Rex Mauthe, MBA
Associate Vice President, Regulatory Affairs
55 TW Alexander Drive
PO Box 14186
Research Triangle Park, NC 27709

Dear Mr. Mauthe:

Please refer to your Supplemental New Drug Application (sNDA) dated and received December 4, 2015, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tyvaso (treprostinil) 0.6 mg/mL Inhalation Solution.

This 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/WARNINGS AND PRECAUTIONS**, the following text was added/deleted from the first and third bullet:

    - ~~Safety and e~~Efficacy has~~ve~~ not been established in patients with significant underlying lung disease (such as asthma or chronic obstructive pulmonary disease). (5.1)

    - Tyvaso ~~may~~ inhibits platelet aggregation and increases the risk of bleeding, particularly in patients receiving anticoagulants. (5.4, 7.2)

2. Under **WARNINGS AND PRECAUTIONS,** the following sections were updated:

    5.1 Patients with Pulmonary Disease or Pulmonary Infections

    The ~~safety and~~ efficacy of Tyvaso ~~have~~ has not been established in patients with significant underlying lung disease (e.g., asthma or chronic obstructive pulmonary disease). Patients with acute pulmonary infections should be carefully monitored to detect any worsening of lung disease and loss of drug effect.

    5.4 Risk of Bleeding

    Tyvaso inhibits platelet aggregation and increases the risk of bleeding.~~Since Tyvaso inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulant therapy.~~

3. Under **ADVERSE REACTIONS/Adverse reactions Identified in Clinical Trials**, the following fourth paragraph was added:

> In a prospective, observational study comparing patients taking Tyvaso (958 patient-years of exposure) and a control group (treatment with other approved therapies for PAH; 1094 patient-years), Tyvaso was associated with a higher rate of cough (16.2 per 100 patient-years vs. 10.9 per 100 pt-years), throat irritation (4.5 per 100 pt-years vs. 1.2 per 100 pt-years), nasal discomfort (2.6 per 100 pt-years vs. 1.3 per 100 pt-years), and haemoptysis (2.5 per 100 pt-years vs. 1.3 per 100 pt-years) compared to the control group.

4. Under **USE IN SPECIFIC POPULATIONS/Pregnancy**, the following text was added to the first paragraph:

> Pregnancy Category B
>
> There are no adequate and well controlled studies with Tyvaso in pregnant women. Animal reproduction studies have not been conducted with treprostinil administered by the inhalation route. However, studies in pregnant rabbits using continuous subcutaneous (sc) infusions of treprostinil sodium at infusion rates higher than the recommended human sc infusion rate resulted in an increased incidence of fetal skeletal variations associated with maternal toxicity. Also, a study in pregnant rabbits administered oral treprostinil diolamine at exposures higher than those in humans resulted in external fetal and soft tissue malformations and fetal skeletal malformations *[see Nonclinical Toxicology (13.3)]*. Animal reproduction studies are not always predictive of human response.

5. Under **NONCLINCAL TOXICOLOGY/ Carcinogenesis, Mutagenesis, Impairment of Fertility**, the following was added as paragraphs 2, 3, and 4:

> 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, when based on AUC, obtained at the highest dose levels used in males and females are about 208- and 460-fold, respectively, the human exposure following a single at the target maintenance dose of 54 mcg daily.
>
> Treprostinil diolamine was tested in vivo in a rat micronucleus assay and did not induce an increased incidence of micronucleated polychromatic erythrocytes.

6. Under **NONCLINCAL TOXICOLOGY/Developmental Toxicity,** the following text was added as the second paragraph:

> In studies with treprostinil diolamine, no adverse effect doses for fetal viability/growth, fetal development (teratogenicity), and postnatal development were determined in rats. In pregnant rats, no evidence of harm to the fetus was observed following oral administration of treprostinil diolamine at the highest dose tested (20 mg/kg/day), which represents about 154 and 1479 times the human exposure, when based on C_{max} and AUC

following a single dose of 54 mcg, respectively. In pregnant rabbits, external fetal and soft tissue malformations and fetal skeletal malformation occurred. The dose at which no adverse effects were seen (0.5 mg/kg/day) represents about 9 and 145 times the human exposure, when based on C_{max} and AUC following a single dose of 54 mcg, respectively.

7. 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

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

/s/

Lori A WACHTER
06/03/2016

MARY R SOUTHWORTH
06/06/2016