CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-387

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-387
DATE RECEIVED BY CENTER:	6/30/2008
PRODUCT:	Tyvaso™ (treprostinil sodium) Inhalation Solution (0.6 mg/ml)
INTENDED CLINICAL POPULATION:	Pulmonary arterial hypertension (PAH) patients with NYHA Class III — symptoms
SPONSOR:	United Therapeutics Corporation, Research Triangle Park, NC 27709
REVIEW DIVISION:	Division of Cardiovascular and Renal Products
PHARM/TOX REVIEWER:	Xavier Joseph
PHARM/TOX SUPERVISOR:	Charles A. Resnick
DIVISION DIRECTOR:	Norman Stockbridge
PROJECT MANAGER:	Dan Brum

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REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Xavier Joseph, D.V.M.
March 23, 2009

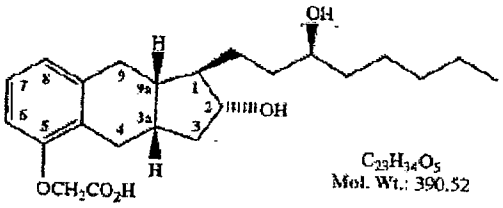
ORIGINAL NDA DATED: June 26, 2008
CENTER RECEIPT DATE: June 30, 2008
REVIEWER RECEIPT DATE: July 7, 2008

SPONSOR: United Therapeutics Corporation
One Park Drive
Research Triangle Park, NC 27709

DRUG PRODUCT: Trade name - Tyvaso™ Inhalation Solution

DRUG SUBSTANCE: Generic name – treprostinil sodium
Code names – UT-15, LRX-15 and 15AU81

Chemical Structure



FORMULATION: Tyvaso™ Inhalation Solution contains 0.6 mg treprostinil/ml, sodium chloride, sodium citrate (dihydrate), 1N hydrochloric acid, sodium hydroxide and water for injection. (1N sodium hydroxide is used for adjusting the pH of the product.) The sodium salt of treprostinil, the active ingredient, is formed during the drug product manufacturing procedure. Treprostinil inhalation solution (2.9 ml) is packaged into ampoules. [Remodulin® (treprostinil sodium) Injection, the marketed product, has the same formulation as Tyvaso except for the

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MODE OF ADMINISTRATION: Tyvaso is administered by oral inhalation using an Optineb-ir ultrasonic, pulsed delivery nebulizer; each pulse of Tyvaso contains 6 µg of treprostinil.

PHARMACOLOGICAL CLASS: Prostacyclin (PGI_2) analogue (vasodilator)

PROPOSED INDICATIONS: For the treatment of pulmonary arterial hypertension (PAH) in patients with NYHA Class III — symptoms. b(4)

PROPOSED DOSAGE REGIMEN: Treatment should be started with 3 breaths (18 µg of treprostinil) per treatment session given 4 times daily. If 3 breaths are not tolerated, the dose may be reduced to 1 or 2 breaths and later increased to 3 breaths as tolerated. The dosage should be increased to 6 breaths and subsequently to the target maintenance dose of 9 breaths (54 µg of treprostinil) per inhalation session given 4 times daily, as tolerated. The maximum dose studied in clinical trials was 12 breaths (72 µg of treprostinil) per inhalation session.

IND UNDER WHICH CLINICAL TRIALS WERE CONDUCTED: IND 70,362 (for inhalation therapy of PAH patients)

RELATED NDAs: United Therapeutics' NDA 21-272 – Remodulin for the sc treatment of PAH patients, and United Therapeutics' NDA 21-272 SE3 – Remodulin for the iv treatment of PAH patients.

EXECUTIVE SUMMARY

Tyvaso™ (treprostinil sodium for inhalation), a chemically stable tricyclic benzindene analogue of prostacyclin (PGI_2), with potent systemic and pulmonary vasodilatory as well as platelet antiaggregatory effects, is being developed for inhalation treatment of pulmonary arterial hypertension (PAH) patients. An injectable formulation of treprostinil sodium has been approved for marketing (Remodulin®) for the treatment of PAH patients either by continuous subcutaneous (sc) or intravenous (iv) routes. Infusion site pain and reactions, and catheter-related infection or sepsis were reported to be the most common adverse events among patients treated sc or iv with treprostinil. With inhalation therapy, by directly applying the drug at the primary site of manifestation of the condition, the adverse effects associated with sc or iv infusion can be avoided.

I. Recommendations

A. Recommendation on Approvability

Tyvaso™ is approvable from a nonclinical perspective.

B. Recommendations for Additional Nonclinical Studies

None

C. Recommendations for Labeling

1. Sponsor's proposed text under section **8. USE IN SPECIFIC POPULATION, 8.1 Pregnancy** presently read as follows:

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[redacted]

We recommend that the above text be revised to read as follows:

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[redacted]

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