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APPLICATION NUMBER:

22-387

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 22-387	Submission Dates: 06/27/08 and 08/25/08
Relevant IND	70,362
Submission Type; Code	Original NDA; N-000
PDUFA Goal Date	April 24, 2009
Brand Name	TYVASO™
Generic Name	Treprostinil sodium
Formulation; Strength	Solution for inhalation; 0.6 mg/mL
Indication	Pulmonary Arterial Hypertension
Applicant	United Therapeutics Corporation
Reviewer	Robert O. Kumi, Ph.D.
Secondary Reviewer	Angelica Dorantes, Ph.D.
OCP Division	DCP1
OND Division	Cardiovascular and Renal Products
Briefing Date	March 23, 2009

Briefing Attendees: A. Dorantes, M. Mehta, D. Brum, R. Uppoor, K. Reynolds, S. Schrieber, J. Cho, I. Younis, D. Menon-Andersen, S. Brar, M. Pacanowski, T. Ong, J. Park, A. Karkowsky, S. Berkman, R. Kumi

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1 Executive Summary

Introduction

In NDA 22-387, TYVASO™ (treprostinil sodium) inhalation solution is proposed for the indication of Pulmonary Arterial Hypertension (WHO Group 1) in patients with New York Heart Association Class III — ymptoms. Treprostinil is currently approved for the same indication as Remodulin injection for subcutaneous and intravenous administration (NDA 21-272). The applicant, United Therapeutics, was granted orphan designation for the stated indication in 1999. b(4)

Treprostinil is a stable, synthetic analog of prostacyclin. The major pharmacological effects of treprostinil are vasodilatation, inhibition of platelet aggregation and inhibition of smooth muscle cell proliferation. Tyvaso will be supplied in 2.9 mL ampoules containing 0.6 mg treprostinil per milliliter and is intended for oral inhalation use with a nebulizer (Optineb). The proposed product will be dosed in four separate inhalation sessions per day, during the waking hours. Each breath is expected to deliver a dose of 6 µg. Initial therapy should begin with three breaths (18 µg treprostinil) and the maximal target dose per session is 54 µg (9 breaths).

The clinical development program for NDA 22-387 includes approximately 20 studies involving the assessment of pharmacokinetics (PK) of inhaled treprostinil, drug interactions with oral treprostinil, and in vitro metabolism. The PK studies were conducted to characterize the bioavailability of the new formulation, whereas the latter sets of studies were conducted to supplement existing information on approved or investigational treprostinil products. Nine of the 20 studies were reviewed as they are most relevant to the current application. The remaining studies submitted in NDA 22-387, including investigator sponsored studies were not reviewed as they did not provide pertinent information.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed the information submitted to NDA 22-387. The clinical pharmacology and biopharmaceutics information provided in NDA 22-387 is acceptable, pending confirmation from the CDRH consultant that the inhalation device accurately delivered the dose reported in the pharmacokinetic (PK) studies. Without this confirmation, the reliability PK information is unclear and renders the PK information related to inhalation unacceptable. OCP has the following comments:

General Comments

1. If CDRH does not confirm the precision/accuracy of the delivery system, the applicant will need to conduct a bioavailability (PK) assessment of inhaled treprostinil using the to-be-marketed formulation and device.

2. In multiple studies, some subjects (one or more) had undetectable or low treprostinil exposure compared to other subjects. The reason for these low exposures is unclear but may be related to the failure of the inhalation device (nebulizer) or factors intrinsic (e.g. CYP2C8 polymorphism) to the patients. In this reviewer's opinion, the low drug exposure is more likely due to issues related to the drug delivery device, and should be addressed by the Applicant.

Labeling Comments

Overall, the labeling proposed by the Applicant is acceptable; the majority of information is obtained from the labeling for NDA 21-272 (Remodulin). There should be minor modifications to the pharmacokinetics section: 1) statements regarding the linear range following inhaled treprostinil administration and 2) general editorial changes to the pharmacokinetic section to make the information clearer.

1.2 Phase IV Commitments

None

1.3 Key Clinical Pharmacology and Biopharmaceutics Findings

General Treprostinil Pharmacokinetics Following Inhalation

The following estimates for PK measures (healthy volunteers) were obtained for inhaled treprostinil (single dose) for doses ranging from 18 to 90 µg:

- Tmax range = 0.12 – 0.25 hr (three studies)
- T1/2 range = 0.46 – 0.62 hr (three studies)
- Vz/F range = 45 - 64 L (two studies); 0.78 – 1.00 L/kg (one study)
- CL/F range = 60 - 77 L/hr (two studies); 1.01 – 1.45 L/hr/kg (one study)

Absolute Bioavailability

The absolute bioavailability (F) estimations for inhaled treprostinil are summarized in the following table; F appeared to depend on dose.

Table 1: Statistical Analysis in treprostinil absolute bioavailability* study (n = 18, per group)

	Three Breaths = 18 µg	Six Breaths = 36 µg
	Bioavailability (F %)	
Mean (CV %)	61.52 (29.68)	74.05 (21.23)
Median (Range)	60.84 (13.08 – 90.69)	70.27 (52.36 – 115.99)

* IV dose = single 15 ng/kg/min infusion for 60 minutes

PK Linearity (Dose Proportionality)

Based on pooled plasma exposure data from three studies, treprostinil exposure was dose proportional over the 18 to 90 µg range following single dose administration.

Intersubject variability

The intersubject variability in pharmacokinetic measures ranged form approximately 20 to 67 %. In some instances, subjects had low or undetectable concentrations; the source of the variability is not clear, but is likely associated with the lack of reproducibility of the inhalation device (uncertainty of the administered dose).

In Vitro Metabolism

The metabolism of treprostinil was evaluated in two *in vitro* studies. The results showed that;

- CYP Substrate Status: Treprostinil is metabolized primarily by CYP2C8 followed by CYP2C9 to a minor extent; other CYP enzymes do not play a role in treprostinil metabolism.

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