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APPLICATION NUMBER:

214324Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

NDA or BLA Number	214324
Link to EDR	\\Cdsesub1\evsprod\NDA214324
Submission Date	04/16/2021
Submission Type	Priority review
Brand Name	Tyvaso DPI®
Generic Name	Treprostinil Inhalation Powder (TreT)
Dosage Form and Strength	Inhalation powder: Single-dose cartridges containing 16 µg, 32 µg, 48 µg, or 64 µg of treprostinil as a dry powder formulation for oral inhalation.
Route of Administration	Inhalation
Proposed Indication	Pulmonary arterial hypertension to improve exercise ability. Pulmonary hypertension associated with interstitial lung disease to improve exercise ability.
Applicant	United Therapeutics Corporation
Associated IND	IND134582
OCP Review Team	Xiaomeng Xu, Manoj Khurana

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1. Executive Summary

The Applicant, United Therapeutics Corporation, has submitted this 505(b)(1) NDA 214324 seeking approval for TreT (Tyvaso DPI®), a treprostinil inhalation powder, intended to treat pulmonary arterial hypertension (PAH) and pulmonary hypertension associated with interstitial lung disease to improve exercise ability. It is a new dosage form for treprostinil being a dry powder for oral inhalation (Tyvaso DPI®) compared to the solution for oral inhalation (Tyvaso®; NDA 022387, US Approval 2002) currently marketed by the same sponsor.

The NDA package for Tyvaso DPI® was received by the Agency on April 16, 2021 under a priority review with the PDUFA date of October 16, 2021.

The applicant submitted three clinical studies, including a single dose-escalation Study MKC-475-001 in healthy subjects, an open-label Study TIP-PH-101 assessing safety and tolerability of TreT in subjects with PAH currently using Tyvaso, as well as a relative bioavailability and bioequivalence (BA/BE) study TIP-PH-102 between TreT and Tyvaso in healthy subjects.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) has reviewed NDA 214324 submitted on 4/16/2021 and finds it acceptable to support approval.

1.2 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

The clinical pharmacological findings of this application rely on the results from the relative BA/BE study TIP-PH-102 and supported by the open-label study TIP-PH-101. Study MKC-475-001 dose not contribute to the systemic exposure comparison of TreT and Tyvaso, however, was reviewed only for supportive information for the dose proportionality assessment.

- TIP-PH-102: a 6-period crossover study comparing systemic exposure of 3 doses (16, 48, 64 µg) of TreT and 3 doses (18, 54, 72 µg) of Tyvaso in healthy volunteers. The TreT product doses of 16, 48, and 64 µg were claimed to provide similar systemic exposure to Tyvaso 18, 54, and 72 µg, selected to accommodate the design and delivery differences between the two inhalation products.

- TIP-PH-101: an open-label study to evaluate the safety and tolerability of TreT in subjects with PAH currently using Tyvaso. TreT was administered for three consecutive weeks, where the safety, clinical effect, as well as the exposure of TreT at the end of week 3 were evaluated.

The key results from the relative BA/BE study TIP-PH-102 are as followings:

- C_{max} of TreT were consistently higher (24% to 39%) than Tyvaso (geometric mean ratios of TreT / Tyvaso and 90% CI were not within 80 - 125% bounds) across three tested does (low-, mid-, and high-dose levels of 16 µg TreT vs 18 µg Tyvaso, 48 µg TreT vs 54 µg Tyvaso, and 64 µg TreT vs 72 µg Tyvaso, respectively).

- $AUC_{0\text{-}5hr}$ of TreT and Tyvaso was comparable at mid- and high- dose levels. Whereas the $AUC_{0\text{-}5hr}$ ratio for low-dose level (i.e., 16 µg TreT versus 18 µg Tyvaso) was 15% higher.

- The safety data (though limited) from the single and multiple dose studies did not indicate any notable respiratory adverse events (AEs) difference between TreT and Tyvaso.

Given that clinical use of TreT involves titration to therapeutic goal and the observations on respiratory AEs, which were comparable between TreT and Tyvaso across all doses, the higher C_{max} level of TreT in the context of comparable overall AUC (except the modest deviation at the lowest tested dose) do not appear to be clinically relevant.

2. QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of Tyvaso DPI®, treprostinil inhalation powder (TreT)?

The Applicant, United Therapeutics Corporation, submitted this 505(b)(1) application for Tyvaso DPI®, intended for the treatment of PAH and pulmonary hypertension associated with interstitial lung disease to improve exercise ability. The proposed dose regimen: to initiate Tyvaso DPI® from 16 µg per treatment, 4 separate treatment sessions each day, and to increase by additional 16 µg per treatment session at approximately 1- to 2- week intervals, if tolerated.

The main objective of this 505(b)(1) NDA review is to provide evaluations of Study TIP-PH-102, which aimed to compare the systemic exposure of TreT and Tyvaso, as well as study TIP-PH-101, where the efficacy, safety, and tolerability of TreT were assessed. Tyvaso® was originally approved in 2002 under NDA 022387, intended for the treatment of PAH to improve exercise ability, as well as pulmonary hypertension associated interstitial lung disease to improve exercise ability. United Therapeutics Corporation is seeking approval of Tyvaso DPI® for the same indication as Tyvaso®.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What general clinical pharmacology features of treprostinil are relevant to the current submission?

Three studies containing clinical pharmacology information were submitted in the current submission, including a single dose-escalation study MKC-475-001, an open-label study TIP-PH-101, and a relative BA/BE study TIP-PH-102. Food effect study, drug-drug interaction study, as well as special population study were not conducted in the current submission. For details on the general clinical pharmacology of treprostinil, readers are referred to the original NDA 022387 review for Tyvaso®.

2.2.2 Is the systemic exposure of Tyvaso DPI ® (treprostinil inhalation powder, TreT) comparable to that of Tyvaso® (treprostinil inhalation solution, Tyvaso) according to the data from the relative BA/BE study TIP-PH-102?

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