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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	214324
Supporting document:	2
Applicant's letter date:	4/16/2021
CDER stamp date:	4/16/2021
Product:	Tyvaso DPI™ (treprostinil) Inhalation Powder
Indication:	Pulmonary arterial hypertension (PAH) and pulmonary hypertension associated with interstitial lung disease (PH-ILD)
Applicant:	United Therapeutics Corporation (UTC)
Clinical Review Division:	Division of Cardiology and Nephrology (DCN)
Pharm/Tox Division:	Division of Pharm/Tox for Cardiology, Hematology, Endocrinology, and Nephrology (DPT-CHEN)
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1 Executive Summary

1.1 Introduction (and Clinical Rationale)

Treprostinil is a prostacyclin analogue. The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. Inhaled treprostinil therapy provides selectivity of the hemodynamic effects to the lung vasculature, thus reducing systemic side effects compared to other routes of administration. Following inhalation of prostacyclin analogs, pulmonary artery pressure decreases, and systemic arterial pressure is stable.

The active pharmaceutical ingredient (API) in Tyvaso DPI™ is identical to the treprostinil drug substance approved in Remodulin (NDA 021272) and Tyvaso (NDA 022387). It is also the same active moiety as the treprostinil diolamine drug substance approved in Orenitram (treprostinil) Extended-Release Tablets (NDA 203496). The safety and efficacy of treprostinil are supported by a comprehensive set of pharmacology, pharmacokinetic (PK), toxicology, and clinical studies conducted for Tyvaso (treprostinil) Inhalation Solution (NDA 022387), Remodulin (treprostinil) Injection (NDA 021272), and Orenitram (treprostinil) Extended-Release Tablets (NDA 203496).

The safety of the excipient fumaryl diketopiperazine (FDKP) is supported by a comprehensive battery of safety pharmacology and toxicology studies conducted for Afrezza (BLA 022472).

1.2 Brief Discussion of Nonclinical Findings

In a rat PK study following intermittently delivery of treprostinil into the tracheal tube, treprostinil Tmax was ≤5 minutes. Treprostinil Inhalation Powder (TrIP) provided much higher treprostinil exposure than the nebulized reference solution. There was no evidence that the excipient FDKP, present in Tyvaso DPI, interfered with the absorption of treprostinil in the lung.

In studies to assess the potential effects of a Tyvaso DPI impurity [redacted] in vitro, the stimulating activity of [redacted] at prostanoid receptors IP1, EP2, DP1, and EP1 in tested cell lines were approximately 23-, 10-, 14-, and 25-fold [redacted] respectively, than treprostinil. [redacted] in human liver microsomes and hepatocytes, with $T_{1/2}$ < [redacted] min. In [redacted], little to no [redacted] was present at 0 minutes, suggesting that [redacted] at time zero was also observed ([redacted]%).

The potential bacterial mutagenicity of 7 impurities identified in Tyvaso DPI was evaluated by (quantitative) structure-activity relationship ((Q)SAR) using Derek Nexus

and Leadscope Model Applier. All 7 impurities ([redacted] and [redacted] were identified as inactive (non-mutagenic) in DEREK Nexus and negative (non-mutagenic) in the Leadscope Model Applier. None of the structures had any structural features which were identified as unclassified/misclassified or out of domain, respectively, in Derek Nexus or Leadscope. As such, all 7 impurities are considered Class 5 impurities and may be treated as non-mutagenic.

[redacted] is identified as an impurity in Tyvaso DPI at a concentration above the qualification threshold of 1% for drug products with a maximum daily dose of drug substance that is <10 mg. [redacted] was qualified at a concentration of up to [redacted]% in the final drug product. [redacted] was shown to have reduced pharmacodynamic effects compared to treprostinil, and it is expected to be [redacted] It is unlikely that the presence of [redacted] in Tyvaso DPI would be a safety concern for patients, if present at up to [redacted]%.

Based on the results of the nonclinical pharmacology, PK, and toxicology studies conducted to support Tyvaso (NDA 022387), Remodulin (NDA 021272), and Orenitram (NDA 203496), and the assessment of impurities present in Tyvaso DPI, it is considered that Tyvaso DPI has an acceptable safety profile and that there are no findings that preclude long-term inhalation administration in humans.

1.3 Recommendations

1.3.1 Approvability

Approvable

1.3.2 Additional Non-Clinical Recommendations

None

1.3.3 Labeling

We suggest following changes (**bold** for insert and cross out for delete):

(1) Under INDICATIONS AND USAGE on page 1

Tyvaso DPI is a ~~prostacyclin mimetic~~ [redacted] indicated for the treatment of

(2) To second paragraph under section 13.1 [redacted]

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. [redacted]

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