CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214324Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214324
PDUFA Goal Date	October 16, 2021
OSE RCM #	2021-794
Reviewer Name(s)	Brian Caruth, Pharm.D., BCPS
Team Leader	Laura Zendel, Pharm.D., BCPS
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	October 4, 2021
Subject	Evaluation of Need for a REMS
Established Name	Treprostinil
Trade Name	Tyvaso DPI
Name of Applicant	United Therapeutics Corporation
Therapeutic Class	Prostacyclin Mimetic
Formulation(s)	Inhalation Powder
Dosing Regimen	16 mcg to 64 mcg inhaled orally four times daily during waking hours

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for Tyvaso DPI (treprostinil) is necessary to ensure the benefits outweigh its risks. United Therapeutics Corporation submitted a New Drug Application (NDA) 214324 for treprostinil with the proposed indication for the treatment of pulmonary arterial hypertension ([PAH]; World Health Organization [WHO] Group 1) or pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability in adult patients. Treprostinil is associated with an increased risk for cough and throat irritation, headache, nausea, flushing, and syncope. The Applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRM) has determined that a REMS is not needed to ensure the benefits of treprostinil outweigh its risks. The increased risk for cough and throat irritation, headache, nausea, flushing, and syncope are similar to the currently approved referenced formulations (NDA 022387 [treprostinil inhalation solution], NDA 021272 [treprostinil injection], NDA 203496 [treprostinil diolamine]). The excipient, fumaryl diketopiperazine (FDKP), is referenced in the approved BLA 022472 ([insulin human] inhalation powder). The most commonly reported adverse events for treprostinil inhalation powder observed in the single-sequence safety and tolerability study (TIP-PH-101 [NCT03950739]) were similar to the adverse events in the placebo-controlled study (TRIUMPH I [NCT00147199]) conducted for the referenced formulation of treprostinil inhalation solution. Treprostinil is likely to be prescribed in a specialized setting by cardiologists and pulmonologists familiar with pulmonary hypertension (PH) therapy. Prescribers are expected to closely monitor patients for disease progression and response to therapy with frequent follow-up visits. The risks of treprostinil will be communicated in the Adverse Reactions section in labeling.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for Tyvaso DPI (treprostinil) is necessary to ensure the benefits outweigh its risks. United Therapeutics Corporation submitted a New Drug Application (NDA) 214324 for treprostinil with the proposed indication for the treatment of pulmonary arterial hypertension (PAH; World Health Organization [WHO] Group 1) or pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability in adult patients. This application is under review in the Division of Cardiology and Nephrology (DCN). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 Product Information

Treprostinil is a prostacyclin mimetic proposed for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) or pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability in adult patients. Prostacyclins are potent dilators of pulmonary and systemic blood vessels and also mediate a variety of cellular processes including inhibiting inflammation, smooth muscle cell proliferation, and platelet aggregation.[1] Inhalation of prostacyclin analogs provide selectivity of the hemodynamic effects to the lung vasculature reducing pulmonary arterial pressure and stabilizing systemic arterial pressure.

Tyvaso DPI is proposed to be available as an inhalation powder in a 16 mcg, 32 mcg, 48 mcg, or 64 mcg single dose cartridge. The content of the cartridge is administered using the corresponding inhaler. Duration of treatment is expected to be long term and likely administered in an outpatient setting.[a]

Tyvaso DPI, while not a new molecular entity, utilized the 505(b)2 pathway relying on the Agency's previous findings of safety and effectiveness for the referenced approved formulations and excipients.[b] Tyvaso DPI uses the same active pharmaceutical ingredient (API) approved in Remodulin (treprostinil injection, NDA 021272) and Tyvaso (treprostinil inhalation solution, NDA 022387). It is also the same active moiety as the drug substance approved in Orenitram (treprostinil diolamine, NDA 203496).

Tyvaso DPI contains 1% treprostinil adsorbed onto carrier particles consisting of fumaryl diketopiperazine (FDKP). Afrezza (insulin human inhalation powder, BLA 022472) uses FDKP and was approved on June 27, 2014 with a Communication Plan REMS to ensure the benefits of the drug outweighed the risk of acute bronchospasm in patients with chronic lung disease. The REMS was eliminated on April 13, 2018 according to available safety data, the status of the communication plan activities, and the results of the 3-Year Assessment Review findings that the goals of the REMS were being met.[2]

2.2 Regulatory History

The following is a summary of the regulatory history for NDA 214324 relevant to this review:

- 01/29/2018: IND 134582 received for treprostinil
- 04/16/2021: NDA 214324 received for treprostinil
- 06/15/2021: FDA granted Priority Review designation citing the use of a Rare Pediatric Disease Priority Review Voucher (PRV BLA 761171)

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Pulmonary Arterial Hypertension (PAH) is a progressive and fatal lung disease of multifactorial etiology.[3] Clinical presentation typically involves exertional dyspnea and fatigue that progresses over time until severe pulmonary hypertension (PH) with right ventricular (RV) failure develops. Increased pulmonary pressures leading to RV failure is the major cause of death in this rare disease.[c] According to international registry data, the incidence and prevalence ranges from 2.5 to 7.1 cases per million and 5 to 52 per million adults, respectively.[4,d] Surveillance data in the United States suggests increased mortality associated with PH in men, women, and all race and ethnic groups.[5] The 7-year survival rate is about 49%.[6]

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

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