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

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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.*

3.2 Description of Current Treatment Options

Non pharmacologic interventions for management of PH include exercise as tolerated, counselling against smoking, and maintaining a normal body mass index (BMI). Current FDA-approved treatment options for PH include prostacyclin derivatives, endothelin receptor antagonists (ERA), phosphodiesterase-5 (PDE-5) inhibitor, and a soluble guanylate cyclase (sGC) stimulator (Table 1).

Table 1: FDA-Approved Treatment Options for Pulmonary Hypertension

Product Trade Name (Generic)	Year of Approval	Administration	REMS (Boxed Warning)	Warnings and Precautions
Prostacyclin Derivatives				
Flolan, Veletri (epoprostenol)	1995, 2008	IV	No	Rebound PH following Abrupt Withdrawal, Hypotension, Bleeding, PVOD
Ventavis (iloprost)	2004	INH		Syncope, PVOD, Bronchospasm, Avoid Contact with Skin and Eyes, and Ingestion
Orenitram, Remodulin, Tyvaso (treprostinil)	2013, 2002, 2009	Oral, IV, SubQ, INH		Hypotension, Bleeding, Rebound PAH following Abrupt Withdrawal
Uptravi (selexipag)	2015	Oral, IV		PVOD
Endothelin Receptor Antagonists				
Letairis (ambrisentan)	2007	Oral	Yes (Embryo-Fetal Toxicity)	Fluid Retention, Hemoglobin and Hematocrit Decrease, PVOD, Decreased Sperm Counts
Tracleer (bosentan)	2001		Yes (Embryo-Fetal Toxicity and Hepatotoxicity)	Fluid Retention, Hemoglobin and Hematocrit Decrease, PVOD, Decreased Sperm Counts
Opsumit (macitentan)	2013		Yes (Embryo-Fetal Toxicity)	Hepatotoxicity, Fluid Retention, Hemoglobin and Hematocrit Decrease, PVOD, Decreased Sperm Counts
Phosphodiesterase-5 (PDE-5) Inhibitors				
Revatio (sildenafil)	2005	Oral, IV	No	Mortality with Pediatric Use, Epistaxis, Vaso-Occlusive Crisis, Hypotension, PVOD, Visual Loss, Hearing Impairment, Priapism
Adcirca (tadalafil)	2009	Oral		Hypotension, PVOD, Visual Loss, Hearing Impairment, Priapism
Soluble Guanylate Cyclase (sGC) Stimulator				
Adempas (riociguat)	2013	Oral	Yes (Embryo-Fetal Toxicity)	Hypotension, Bleeding, PVOD

No safety issues warranting a REMS have been identified for current FDA-approved prostacyclin derivatives or PDE-5 inhibitors. All ERAs and the sGC stimulator require a REMS with elements to assure safe use (ETASU) to ensure the benefits outweigh the risk of embryo-fetal toxicity. The bosentan REMS also addresses the risk of hepatotoxicity. In general, the warnings and precautions for prostacyclin derivatives are similar, as are the warnings and precautions for PDE-5 inhibitors. Pulmonary Veno-Occlusive Disease (PVOD) has been identified in all classes of currently FDA-approved treatment options for PH despite similar signs and symptoms of PVOD and progressive PH. Modest changes in mortality rates and progressive clinical manifestations of PH represent an unmet medical need.

4 Benefit Assessment

The efficacy of treprostinil inhalation powder 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 relies on the Agency's previous findings of safety and effectiveness for the referenced approved formulations and excipients. Additional efficacy data was evaluated as a secondary outcome measure in one single-sequence, open-label, multicenter phase 1b study (TIP-PH-101 [NCT03950739]). The study enrolled 51 patients (8 males and 43 females), 23 to 82 years of age (median age at baseline 57 years) with PAH on a stable regimen of treprostinil inhalation solution for at least 3 months with a baseline 6-Minute Walk Distance (6MWD) of at least 150 meters and evidence of forced expiratory volume in one second (FEV1) of at least 60% and FEV1/forced vital capacity ratio of at least 60% during the six months prior to enrollment. Patients were excluded if they were pregnant or lactating, taking any other prostacyclin derivatives, had a history of uncontrolled sleep apnea, parenchymal lung disease, or hemodynamically significant left-sided heart disease, or had experienced an acute exacerbation of disease or hospitalization for any reason within 30 days of the screening visit or between screening and baseline. The study evaluated a 32 mcg, 48 mcg, and 64 mcg dose of treprostinil inhalation powder administered four times daily for three weeks. At the end of the treatment phase, patients were offered the opportunity to continue treprostinil inhalation powder in the Optional Extension Phase (OEP) of the study with clinic visits every eight weeks. The main evaluation of efficacy included a 6-Minute Walk Test (6MWT), Preference Questionnaire for Inhaled Treprostinil Devices (PQ-ITD) and the PAH-Symptoms and Impact (PAH-SYMPACT) Questionnaire (Table 2).

Table 2: Summary of Efficacy Results From TIP-PH-101 Study

Treatment Phase Dose	32 mcg	48 mcg	64 mcg	Overall
Baseline (n)	2	27	22	51
Week Three (n)	2	24	20	46
6MWD Change from baseline (m)				p=0.0217
Mean (SD)	43.5 (47.4)	17.8 (33.8)	0.8 (28.1)	11.5 (32.9)
Median	43.5	14	-2	8
Interquartile	10, 77	-1.5, 33	-20, 14.5	-14, 33
Min, Max	10, 77	-46, 110	-46, 60	-46, 110
PQ-ITD statement "I am satisfied with the inhaler" (n)				p=0.0001
Strongly Disagree	0	1	0	1
Disagree	0	0	0	0
Neutral	0	1	0	1
Agree	0	2	3	5
Strongly Agree	2	20	17	39
PAH-SYMPACT Questionnaire Change from baseline				
Cardiopulmonary Symptoms Domain Score				p=0.2451
Mean (SD)	0.16 (0.01)	-0.06 (0.25)	-0.05 (0.31)	-0.05 (0.27)
Median	0.16	0	-0.16	0
Interquartile	0.16, 0.17	-0.25, 0.17	-0.17, 0.17	-0.17, 0.17
Min, Max	0.2, 0.2	-0.7, 0.3	-0.7, 0.05	-0.7, 0.5
Cardiovascular Symptoms Domain Score				p=0.2492
Mean (SD)	0.10 (0.71)	-0.08 (0.30)	-0.05 (0.34)	-0.06 (0.33)
Median	0.10	0	0	0
Interquartile	-0.40, 0.60	-0.20, 0	-0.20, 0.10	-0.20, 0
Min, Max	-0.4, 0.6	-0.8, 0.6	-1, 0.6	-1, 0.6
Physical Impacts Domain Score				p=0.0438
Mean (SD)	-0.01 (1.01)	-0.09 (0.40)	-0.21 (0.48)	-0.14 (0.46)
Median	-0.01	-0.14	-0.07	-0.14
Interquartile	-0.72, 0.71	-0.28, 0	-0.57, 0.07	-0.43, 0
Min, Max	-0.7, 0.7	-1.1, 1	-1, 0.7	-1.1, 1
Cognitive and Emotional Impacts Domain Score				p=0.0048
Mean (SD)	-0.38 (0.53)	-0.19 (0.41)	-0.14 (0.39)	-0.17 (0.40)
Median	-0.38	0	0	0
Interquartile	-0.75, 0	-0.25, 0	-0.38, 0	-0.25, 0
Min, Max	-0.8, 0	-1.3, 0.3	-1, 0.5	-1.3, 0.5

Source: Adapted from Applicant's original submission April 16, 2021; Table 4-3, 4-5, 4-6, and 4-7, Appendix 2.7.3

An 11.5 meter mean increase from baseline was observed in the 6MWD at week three for treprostinil inhalation powder. According to a response of agree or strongly agree to the PQ-ITD statement "I am satisfied with the inhaler," patient-reported satisfaction with the inhaled treprostinil device was improved at week three (95.7% [44/46]) compared to baseline (31.4% [16/51]). Mean changes at week three compared to baseline improved for all domain scores. According to results from the PAH-SYMPACT Questionnaire, the mean scores (-0.05 to -0.17) for all domains improved at week three compared to baseline. Improved domain scores for the physical impacts (-1.1 to 1 [p=0.0438]) and cognitive and emotional impacts (-1.3 to 0.5 [p=0.0048]) were statistically significant. The Applicant concluded the supplemental efficacy data from the TIP-PH-101 study demonstrated significant improvements in the 6MWD, PQ-ITD, and PAH-SYMPACT Questionnaire for patients with PAH.

The clinical reviewer concluded the short-term efficacy results of the TIP-PH-101 study did not show clinical worsening for patients transitioning from treprostinil inhalation solution to treprostinil inhalation powder.[e] This determination relied on the eight meter median increase from baseline in 6MWD and unchanged median results for the cardiopulmonary symptoms, cardiovascular symptoms, and cognitive and emotional impacts domain scores from the PAH-SYMPACT Questionnaire.

5 Risk Assessment & Safe-Use Conditions

The safety of treprostinil inhalation powder 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 relied on the Agency's previous findings of safety and effectiveness for the referenced approved formulations and excipients. Additional safety analysis relies on data from the treatment phase and OEP in the TIP-PH-101 study. A total of 51 patients enrolled in the study and 49 patients enrolled in the OEP after completing the treatment phase. The three most common adverse events (AE) during the treatment phase (incidence ≥ 4%) include cough, headache, and dyspnea.

There were no deaths or treprostinil related serious adverse events during the TIP-PH-101 study. During the treatment phase, two patients experienced AEs of dyspnea and globus pharyngeus leading to treprostinil discontinuation. During the OEP, two additional patients experienced AEs leading to treprostinil discontinuation due to dyspnea and chest pain with dyspnea.

The review team also evaluated the use of the FDKP excipient in treprostinil inhalation powder. The TIP-PH-101 study included 12 patients with respiratory disease (COPD [5], asthma [4], and ILD [3]). No patients with a history of COPD, asthma, or non-PAH respiratory disease withdrew from treprostinil inhalation powder therapy and there was no evidence of bronchospasm in this small cohort of patients. Additional review of the TIP-PH-101 study demonstrated little to no dose-dependent increase of AEs (respiratory, thoracic, and mediastinal disorders) for treprostinil inhalation powder and a substantial increase in AEs associated with the transition from treprostinil inhalation solution to treprostinil inhalation powder was not observed.

Overall, the most commonly reported adverse events for treprostinil inhalation powder observed in the TIP-PH-101 study were similar to the adverse events in the placebo-controlled study (TRIUMPH I [NCT00147199]) conducted for the referenced approved formulation of treprostinil inhalation solution.[7] The clinical reviewer concluded the safety profile of treprostinil is consistent with predicted risks of prostacyclin mimetic therapy and the overall benefit-risk profile appears acceptable.

6 Expected Postmarket Use

Treprostinil is likely to be prescribed in an outpatient setting by cardiologists and pulmonologists familiar with PAH therapy. The likely prescribers are expected to be familiar with predicted risks of inhaled prostacyclin therapy and closely monitor patients for disease progression and response to therapy with frequent follow-up visits for this rare disease.

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for treprostinil beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The clinical reviewer recommends approval of treprostinil citing the Agency's previous findings of safety and efficacy for the referenced approved formulations and excipients (NDA 022387, NDA 021272, NDA 203496, and BLA 022472), safety and efficacy data from the phase 1b TIP-PH-101 study, the seriousness of PH, and an adequately favorable benefit-risk profile.

A REMS for Afrezza (BLA 022472), referenced in this application for the excipient FDKP, was approved on June 27, 2014 with a REMS that comprised of a communication plan 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.[2] DRM documented, in detail, the Agency decision regarding the need for a REMS.[8] The rationale for the REMS included that additional measures were needed to disseminate information about the risk of acute bronchospasm in patients with chronic lung disease, citing concern for the estimated size of the population likely to use the drug outside a clinical study and that prescribers of insulin do not routinely need to consider lung function when prescribing insulin. In addition, no reports of serious bronchospasm were identified during the 3-year REMS assessment review.

Although acute bronchospasm in patients with asthma and patients with chronic obstructive pulmonary disease (COPD) was observed in material reviewed for BLA 022472, no patients with a history of COPD, asthma, or non-PAH respiratory disease withdrew from treprostinil inhalation powder therapy in the TIP-PH-101 study and there was no evidence of bronchospasm in these 12 patients with respiratory disease.

Previous findings for the referenced approved formulations and excipients (NDA 022387, NDA 021272, NDA 203496, and BLA 022472) and data from the phase 1b TIP-PH-101 study evaluated efficacy and safety of treprostinil inhalation powder in adults with PH. The short-term efficacy and safety results of the TIP-PH-101 study did not show clinical worsening for patients transitioning from treprostinil inhalation solution to treprostinil inhalation powder and did not produce any new safety findings for treprostinil inhalation powder compared to treprostinil inhalation solution, which is not currently approved with a REMS. In general, healthcare providers who treat PH should be familiar with predicted risks of inhaled prostacyclin therapy and closely monitor patients for disease progression and response to therapy with frequent follow-up visits for this rare disease. Relying on a smaller estimated patient population size, likely prescribers to include cardiologists and pulmonologists, and limited therapeutic options for patients with PH compared to those identified in BLA 022472, a REMS is not necessary to ensure that the benefits outweigh the risks for treprostinil inhalation powder for the intended population. Therefore, this reviewer is not recommending a REMS for the management of the risks of treprostinil inhalation powder.

9 Conclusion & Recommendations

Relying on the data available, a REMS is not necessary to ensure the benefits of treprostinil inhalation powder outweigh the risks for cough and throat irritation, headache, nausea, flushing, and syncope. The safety concerns associated with treprostinil inhalation powder use are similar to the referenced approved formulations of treprostinil and they are not currently approved with a REMS. Healthcare providers who treat PAH should be familiar with monitoring and treating predicted risks of inhaled prostacyclin therapy. The risks of cough and throat irritation, headache, nausea, flushing, and syncope will be communicated in labeling in Adverse Reactions. At the time of this review, labeling is still under negotiation and the clinical review is ongoing. Should DCN have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10 Appendices

10.1 References

[1] Lang IM, Gaine SP. Recent advances in targeting the prostacyclin pathway in pulmonary arterial hypertension. European Respiratory Review. 2015;24:630-641.

[2] Pippins, J. Afrezza REMS Elimination Memo. DARRTS Reference ID: 4249716. April 13, 2018.

[3] Bisserier M, Pradhan N, Hadri L. Current and emerging therapeutic approaches to pulmonary hypertension. Reviews in Cardiovascular Medicine. 2020;21(2):163-179.

[4] Prins KW, Thenappan T. World Health Organization Group I Pulmonary Hypertension: Epidemiology and Pathophysiology. Cardiology Clinics. 2016;34(3):363-374.

[5] George MG, Schieb LJ, Ayala C, Talwalkar A, Levant S. Pulmonary hypertension surveillance: United States, 2001 to 2010. Chest. 2014;146(2):476-495.

[6] Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. Chest. 2012;142(2):448-456.

[7] See Tyvaso at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022387s017lbl.pdf

[8] See FDA REMS Review for Afrezza (BLA 22472), dated June 24, 2014, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/022472Orig1s000RiskR.pdf

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