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APPLICATION NUMBER:

214324Orig1s000

CLINICAL REVIEW(S)

Clinical/Decisional Memo

Application Type	NDA
Application Number(s)	214324
Priority or Standard	Class 1 resubmission
Submit Date(s)	12/23/22
Received Date(s)	12/23/22
PDUFA Goal Date	5/23/22
Division/Office	Division of Cardiology and Nephrology
Author Name(s)	Mary Ross Southworth through Norman Stockbridge
Review Completion Date	5/23/22
Established/Proper Name	Treprostinil powder
(Proposed) Trade Name	Tyvaso DPI
Applicant	United Therapeutics
Dosage Form(s)	Single-use cartridges containing 16, 32, 48, or 64 mcg
Applicant Proposed Dosing Regimen(s)	Oral inhalation in 4 separate, equally spaced treatment sessions per day
Applicant Proposed Indication(s)/Population(s)	Pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies with Tyvaso establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). Pulmonary hypertension associated with interstitial lung disease (PH ILD; WHO Group 3) to improve exercise ability. The study with Tyvaso establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%)
Recommended Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Same as proposed.

The original application for Tyvaso DPI received a complete response on 10/15/2021 because of deficiencies at a facility involved in producing the drug product. In that review cycle, the clinical review by Mitch Psotka (finalized 9/23/2021) recommended approval based on the submitted data. The sponsor has now resubmitted the application with updated facility information and OPQ advises that the facility deficiencies have been addressed and recommends approval.

No new clinical data were included in the resubmission; however, during the original review cycle DCN became aware of a Citizens Petition (regulations.gov; FDA-2021-P-0714) submitted to the FDA that raised concerns about the pulmonary safety of fumaryl diketopiperazine (FDKP), an excipient included in Tyvaso DPI. An assessment of the Tyvaso DPI drug product in the original clinical review, did not indicate a safety concern.

The excipient FDKP is also found in Afrezza, an FDA-approved form of inhaled insulin powder. The labeling for Afrezza includes warnings[1,2] about the risk of acute bronchospasm in patients with chronic lung disease, a contraindication in patients with asthma or COPD, and instructions to screen patients for these conditions prior to initiation. The Petitioner argued there was a need for additional clinical data and specific statements in product labeling for Tyvaso DPI based on the assertion that FDKP is responsible for the acute bronchospasm observed in Afrezza's clinical trials. In responding to the Citizens Petition, the Division assessed the need for further study and changes to the proposed labeling for the Tyvaso DPI product.

Regarding the concern related to the excipient, the association between FDKP and Afrezza's bronchospasm risk is speculative, and a causal role has not been established. In the view of

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WARNING: RISK OF ACUTE BRONCHOSPASM IN PATIENTS WITH CHRONIC LUNG DISEASE

See full prescribing information for complete boxed warning.

- **Acute bronchospasm has been observed in patients with asthma and COPD using AFREZZA. (5.1)**
- **AFREZZA is contraindicated in patients with chronic lung disease such as asthma or COPD. (4)**
- **Before initiating AFREZZA, perform a detailed medical history, physical examination, and spirometry (FEV_1) to identify potential lung disease in all patients. (2.5), (5.1)**

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5.1 Acute Bronchospasm in Patients with Chronic Lung Disease

Because of the risk of acute bronchospasm, AFREZZA is contraindicated in patients with chronic lung disease such as asthma or COPD *[see Contraindications (4)]*.

Before initiating therapy with AFREZZA, evaluate all patients with a medical history, physical examination and spirometry (FEV_1) to identify potential underlying lung disease.

Acute bronchospasm has been observed following AFREZZA dosing in patients with asthma and patients with COPD. In a study of patients with asthma, bronchoconstriction and wheezing following AFREZZA dosing was reported in 29% (5 out of 17) and 0% (0 out of 13) of patients with and without a diagnosis of asthma, respectively. In this study, a mean decline in FEV_1 of 400 mL was observed 15 minutes after a single dose in patients with asthma. In a study of patients with COPD (n=8), a mean decline in FEV_1 of 200 mL was observed 18 minutes after a single dose of AFREZZA. The long-term safety and efficacy of AFREZZA in patients with chronic lung disease have not been established.

DCN, there is no need for further study or assessment of the risk given the lack of a clinical safety signal and the labeling for Tyvaso DPI, both described below.

The small clinical trial (BREEZE)[3] of Tyvaso DPI in patients with PAH which included patients with underlying respiratory co-morbidities reported no cases of bronchospasm. These data allow for adequate characterization of the safety profile and supports a positive benefit risk profile consistent with approval. This determination is unchanged from the previous clinical review.

To understand more fully the pulmonary safety of Tyvaso DPI and implications for labeling, FDA's Adverse Event Reporting system (FAERS) was searched for cases of acute bronchospasm associated with marketed Tyvaso inhalation solution (IS-treprostinil solution), which contains the same drug substance as Tyvaso DPI. Several cases of acute bronchospasm shortly after Tyvaso IS use were identified (see postmarketing review of 5/3/2022). Another prostaglandin (Ventavis, NDA 21779) is associated with bronchospasm. Despite the absence of bronchospasm cases with Tyvaso DPI at this time, bronchospasm has been identified as a potential risk for the class of inhaled prostaglandins. Tyvaso DPI will include the following in the Warnings and Precautions section of labeling:

> *5.4* (b) (4) *Bronchospasm*
> *Like other inhaled prostaglandins, Tyvaso DPI may cause acute bronchospasm. Patients with asthma or COPD, or other bronchial hyperreactivity are at increased risk for bronchospasm. Ensure that such patients are treated optimally for reactive airway disease prior to and during treatment with Tyvaso DPI.*

Including this warning in section 5 of labeling adequately informs prescribers about the risk and its mitigation. The indicated population for Tyvaso DPI would be expected to have undergone pulmonary diagnostics. The prescribers of Tyvaso DPI have expertise in managing pulmonary health and are expected to be knowledgeable about co-morbidities.

Completed Reviews

- Integrated Quality Review (1/31/2022)-recommendation approval.
- Proprietary Name Review (2/17/2022)- support approval

[3] BREEZE included 51 patients with PAH (WHO Group 1) who were switched from Tyvaso inhalation solution to Tyvaso DPI and continued use of Tyvaso DPI for 3 weeks. In the study, no cases of bronchospasm were observed. Fourteen patients who participated in BREEZE had a baseline history of chronic lung disease, including asthma, ILD, and COPD. None of these patients, however, experienced bronchospasm or other SAEs. Further, 12 of these 14 patients remained in the open-label extension of BREEZE.

- DMEPA labeling memos (2/18/2022)- support approval

Appears this way in original

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