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APPLICATION NUMBER:

214324Orig1s000

OTHER REVIEW(S)

DIVISION OF CARDIOLOGY AND NEPHROLOGY

Regulatory Project Manager Review

NDA:	214324
Drug:	Tyvaso DPI (treprostinil) inhalation powder
Class:	prostacyclin (b) (4)
Applicant:	United Therapeutics Corp.
Proposed Indications:	Treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability Treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability
Resubmission Stamp Date:	December 23, 2021
Action Date:	May 23, 2022

❖ BACKGROUND

NDA 214324 provides for a new dosage form of treprostinil, a dry powder for oral inhalation, for the treatment of 1) pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability and 2) pulmonary hypertension associated with interstitial lung disease (PHILD; WHO Group 3) to improve exercise ability.

On July 8, 2021, a Citizens Petition (CP) was submitted concerning the safety of excipient fumaryl diketopiperazine (FDKP). The review team addressed the impact of FDKP in its reviews as did the Division Director in his Memo dated October 14, 2021.

On September 16, 2021, the Office of Pharmaceutical Quality notified the Division that the Applicant's drug substance analytical testing site, (b) (4) ((b) (4) was classified as Official Action Indicated (OAI) in 2020 and cGMP issues remain unresolved. The Division issued a Discipline Review Letter on September 24, 2021, notifying the Applicant of this facility issue and conveyed that "…per 21 CFR 314.125, all manufacturing and testing processes must be adequate to preserve the identity, strength, quality, purity, and stability of the material produced and the proposed facilities must comply with the current good manufacturing practice regulations. This problem could impede approval."

A Complete Response Letter was issued on October 15, 2021, due to the aforementioned facility issue. A Type A Meeting was held with the Applicant on November 17, 2021 (minutes dated December 2, 2021). The application was resubmitted on December 23, 2021 and was filed as a Class I resubmission on January 14, 2022. This resubmitted NDA indicated the withdrawal of the (b) (4) facility and its replacement with two alternate drug substance testing facilities, (b) (4) and United Therapeutics Corporation (Silver Spring, MD).

Although the original reviews did not indicate a safety concern of FDKP, the Division issued an information request (IR) to the Applicant on February 15, 2022, requesting clarification how data obtained from Study No. TIP-PH-101 (BREEZE) supported the pulmonary safety of Tyvaso DPI for the proposed indications. The Applicant provided their response on February 18, 2022, which constituted a major amendment to this application. A Review Extension – Major Amendment letter was issued on February 23, 2022, extending the user fee goal date to May 23, 2022.

This review only provides a summary of information contained in the resubmission. See previous RPM review dated October 15, 2021, for details pertaining to the review of the original submission.

❖ REGULATORY TIMELINE and APPLICATION DETAILS

- Original NDA Stamp Date: April 16, 2021
- Complete Response Date: October 15, 2021
- Type A Meeting (post action): November 17, 2021
- Resubmission Stamp Date: December 23, 2021
- Major Amendment: February 18, 2022
- Original PDUFA Goal Date: February 23, 2022
- Extended PDUFA Goal Date: May 23, 2022
- Action Date: May 23, 2022

User Fee

This submission is a Class 1 resubmission to a previously filed application, therefore no User Fee is required.

Facilities

This resubmitted NDA indicated withdrawal of the [redacted] (b) (4) facility and its replacement with two alternate drug substance analytical testing facilities, [redacted] (b) (4) and United Therapeutics Corporation (Silver Spring, MD). The Office of Pharmaceutical Manufacturing Assessment (OPMA/OPQ) recommended approval for these new listed facilities. At the time of approval, all listed facilities were in good standing. For more information, refer to Integrated Quality Review dated January 31, 2022.

Proprietary Name

A request for Proprietary Name review of Tyvaso DPI was submitted to the original NDA on April 22, 2021, and was deemed "conditionally acceptable" (Aidoo, June 17, 2021). The Applicant resubmitted their request on December 23, 2021, and DMEPA concluded that the Applicant's proposed proprietary name was again "conditionally acceptable" (Straka/Mehta/Tu, February 17, 2022). A letter granting the name was issued on February 22, 2022.

❖ LABELING REVIEW

Package Insert

The Division initiated labeling negotiations with the Applicant on September 24, 2021 (first review cycle) and concluded on April 14, 2022 (second review cycle). Upon review of the package insert during the second review cycle, the Division included a Bronchospasm warning statement under Warnings and Precautions. Both the Applicant and FDA agreed to this addition.

Instructions for Use (IFU)

Labeling negotiations pertaining to the IFU were completed during the first review cycle (refer to submission dated September 29, 2021).

Carton and Container Labeling

During the first review cycle, the Applicant submitted revisions to carton and container labels on August 13, 2021, and additional revisions to carton labels on October 1, 2021. There were no further comments from FDA after the Applicant's October 1, 2021 response. Upon further review during the second review cycle, DMEPA provided additional formatting and layout comments to the October 1, 2021, submission, which were issued to the Applicant via email on February 11, 2022. The Applicant incorporated the requested revisions on February 17, 2022; however, due to a global supply chain issue, they requested to launch Tyvaso DPI with carton labeling printed from the previous review cycle on October 1, 2021. FDA agreed to this request and required the Applicant submit a formal notification to the NDA when carton labeling has been received and implemented. For additional information, please refer to DMEPA Memo (Mehta, 5/23/22).

For purposes of the action letter, the agreed upon carton and container labeling from submissions dated April 16, 2021 (blister labels), August 13, 2021 (titration kit and maintenance tray labels), and February 17, 2022 (institutional kit, maintenance, and titration kit carton labels) were included.

❖ REVIEWS

The following is a list of discipline reviews obtained during this review. For more detail on reviews completed from the previous review cycle, refer to RPM review in DARRTS dated 10/15/21.

Clinical/Decisional Memo (May 23, 2022 – Southworth, Stockbridge)

Recommended Action: Approval

During the original review cycle, the clinical reviewer recommended approval based on the submitted data (Psotka, September 23, 2021). No new clinical data were included within the resubmission; however, DCN became aware of a CP submitted during the original review cycle (regulations.gov; FDA-2021-P-0714) which raised concerns about 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.

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), the drug substance in Tyvaso DPI. Several cases of acute bronchospasm shortly after Tyvaso IS use were identified (see postmarketing review dated 5/3/2022). Another prostaglandin (Ventavis, NDA 21779) is associated with bronchospasm. Despite the absence of clinical cases with Tyvaso DPI at this time, bronchospasm has been identified as a potential risk for the class of inhaled prostaglandins; therefore, language to address bronchospasm was included into the Warnings and Precautions section of labeling. Both the Applicant and FDA agreed to include this new warning statement.

OPQ - Integrated Quality Review (January 31, 2022 - Multiple reviewers)

Recommended Action: Approval

OPQ provided an integrated review and concluded the complete response issues are now adequately resolved from a quality perspective; therefore, recommending approval of this NDA. Their review detailed the withdrawal of (b) (4) drug substance testing facility and replacement with two new testing facilities, (b) (4) and United Therapeutics Corporation (Silver Spring, MD). In addition, their review states "These two new facilities will now be responsible to conduct the drug substance testing for (b) (4) content, endotoxin, and microbial limits. All these three compendial (USP) tests and their methods were appropriately transferred. The tests were conducted on the new drug substance batches at these new testing sites. The testing data demonstrated acceptable results."

The review also stated that an expiration period of **18 months** for the product, when refrigerated at controlled temperature of **2°C to 8°C (36°F to 46°F)** in the commercial packaging is granted. In addition, the drug product in unopened blister cards/strips is permitted to be stored up to 5 weeks at room temperature.

UTC claimed categorical exclusion and OPQ found the exclusion acceptable.

For additional information, please refer to the OPQ integrated review for the previous NDA review cycle, dated September 30, 2021.

❖ CONCLUSION

After taking into consideration all primary and consult reviews during the original and resubmission review, the Division issued an approval letter, signed by Norman Stockbridge, Division Director for NDA 214324 on May 23, 2022.

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