CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208276Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 208276
Resubmission After 2017 Complete Response
Review #1

Drug Name/Dosage Form	Treprostinil Injection
Strength	10 mg/mL
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	United Therapeutics Corporation
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Amendment	*19-JUN-2018*	*Quality Labeling*
Resubmission	*30-JAN-2018*	*All*

Quality Review Team

DISCIPLINE	REVIEWER	OPQ OFFICE
Drug Substance	Thomas Wong	ONDP
Drug Product		
Process		
Environmental Analysis		
Microbiology	John Metcalfe	OPF
Facility	Christina Capacci-Daniel	OPF
Regulatory Business Process Manager	Grafton Adams	OPRO
Application Technical Lead	Wendy Wilson-Lee	ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

None.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21272	Treprostinil Injection
PMA	(b) (4)	Implantable Pump Device

2. CONSULTS

No consults requested.

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 208276 for Remodulin (treprostinil) Injection, 10 mg/mL drug product with the implantable infusion pump.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	Treatment of pulmonary arterial hypertension
Duration of Treatment	16 weeks
Maximum Daily Dose	2.5 ng/kg/min per week
Alternative Methods of Administration	Initial administration will be via external infusion system until implantation.

NDA 208276 seeks approval of the use of Remodulin (treprostinil) Injection with a fully implanted, programmable infusion system for the chronic intravenous delivery of treprostinil. The NDA is a sister application to Medtronic, Inc. Premarket Approval Application (PMA) P140032 for the device components of the implantable system. The applicant references approved NDA 21272 for all relevant chemistry, manufacturing, and controls (CMC) information for the treprostinil drug substance and drug product. The chemical and physical compatibility of the drug product with the implantable system was reviewed under PMA P140032.

This NDA was initially submitted in February 2015. Due to Refuse to File status, the applicant resubmitted this NDA in December 2015. The December 2015 resubmission was recommended for Complete Response due to insufficient data to evaluate the risk of potential patient exposure to microbial contaminants when the treprostinil injection drug product is used in the proposed implantable pump system.

In December 2016, the applicant resubmitted this NDA, addressing all deficiencies. Changes provided in the December 2016 resubmission were in response to the Complete Response Letter deficiencies (October 2016) and the elimination of the 2.5 mg/mL and 5.0 mg/mL drug product strengths listed in the initial filing and first resubmission (December 2015). The applicant retained only the 10.0 mg/mL strength for proposed commercialization and use with the implantable pump in the December 2016 resubmission. There are no changes made to any of the CMC information filed in the referenced NDA 21272. An approval recommendation was made by OPQ at the end of the review cycle. However, due to deficiencies identified under the PMA and insufficient human factors data, a Complete Response letter was issued (June 2017).

The 2018 resubmission did not include any new CMC information. All referenced CMC information under NDA 21272 remained unchanged as well. **Therefore, OPQ recommends approval of NDA 208276.**

B. Quality Assessment Overview

Treprostinil is a tricyclic benzindene analog of prostacycline (PGI2). It is a white to cream-colored powder, and is insoluble in water. There are five chiral centers in treprostinil and the drug substance is a single enantiomer. **The retest date of the drug substance is (b) (4) months (b) (4) (b) (4):**

The drug product, Remodulin® (treprostinil injection), is a sterile, 10 mg/mL, ready to use, solution packaged in a 20-mL vial for intravenous injection administered by continuous infusion. The vial and carton labels for the 10 mg/mL strength include the following statement: "When used with the Implantable System for Remodulin, no dilution is required." Other strengths of Remodulin are approved but will not be indicated for use with the implantable pump system. Since the drug in the newly proposed drug-device combination product is the identical drug as the approved Treprostinil injection in NDA 021272, a Biopharmaceutics review is not needed. **An expiration dating period of (b) (4) months will be granted for the drug product when stored at 25ºC. The categorical exclusion is granted based on compliance with both 21 CFR 25.31(a) and 25.15 (d).**

There appears to be no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history, and relevant experience. There is no change to the proposed facilities, responsibilities, or assessment outcomes in the resubmission. **All facilities are acceptable to support approval of NDA 208276.**

C. Special Product Quality Labeling Recommendations (NDA only)

None.

Wendy Wilson- Lee

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CHAPTERS: Primary Quality Assessment

History of submission:

Initial submission and first resubmission: This NDA was initially submitted in 2/13/2015. Due to Refuse to File status, the applicant resubmitted this NDA in 12/16/2015 (Seq. #0007). The applicant references their approved NDA (NDA 21272) and all subsequent supplements for all relevant drug substance and drug product CMC information in both submissions. The resubmission dated 12/16/2015 was recommended for Complete Response. One of the reasons for CR is due to insufficient data to evaluate the risk of potential patient exposure to microbial contaminants when the Remodulin drug product is used in the proposed implantable pump system.

Second resubmission: In 12/15/2016 (Seq. #0014), the applicant resubmitted this NDA to address all deficiencies. There are no changes made to any of the CMC information filed in the referenced NDA 21272. The only changes provided in this resubmission are:

- Provided justification for insufficient microbial data to support the use of the proposed implantable pump system.
- Eliminated the strengths of 2.5 mg/mL and 5.0 mg/mL proposed in the initial filing and resubmission dated 12/16/2015 and retains only 10.0 mg/mL for commercialization in this submission dated 12/15/2016.

This second resubmission was recommended for Complete Response on 6/2/17 due to:

- A Not Approvable letter on the PMA for the device component on March 11, 2016.
- Insufficient human factors data to demonstrate that the Implantable System for Remodulin (ISR) user interface supports safe and effective use for the intended users, uses and use environments.

Third resubmission: In 1/30/2018 (Seq. #0019), the applicant resubmitted this NDA to address the above deficiencies.

Evaluation and Recommendation:

CMC information on both drug substance and drug product is found adequate and this NDA is recommended for approval.

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Expiry Dating (NDA 21272 Supplement #14 dated 12/30/2010):

In Supplement #14, the applicant stated that the current shelf life is (b) (4) months and proposes to continue to use the established shelf life of (b) (4) months based on the primary and supporting stability data contained in this submission. This supplement was approved.

Evaluation: There has been no change in the drug product information in the cross-referenced NDA 21272 since the last resubmission of this NDA 208276 (Seq. # 0014) dated 12/16/2015. The review of Seq. #0014 was found adequate.

Recommendation: This NDA 208276 is recommended for approval.

CHAPTER III: Environmental Analysis

Firm has submitted a request on 2/9/2017 for a categorical exclusion under 21 CFR 25.31 (a). And further states to their knowledge there exist no extraordinary circumstances [21 CFR 25.15(d)], and no increased use of active moiety. Since there is no change in the proposed commercial batch size, manufacturing process, patient populations and additional indication, it is not necessary to resubmit the request for a categorical exclusion.

Evaluation: Acceptable

Recommendation: This NDA 208276 is recommended for approval.

CHAPTER IV: Labeling

There is no change in labeling from the Package Insert and container labels since the last resubmission (Seq. #0014).

Evaluation: Acceptable

Recommendation: This NDA 208276 is recommended for approval.

CHAPTER V: Process

There is no change made to the manufacturing process.

Thomas Wong

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Wendy Wilson- Lee

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