CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208276Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Integrated Review

NDA or BLA Number	208276
Link to EDR	//Cdsesub1/evsprod/NDA208276/208276.enx
Submission Date	16th December 2015
Submission Type	Standard
Brand Name	Remodulin Implantable System (RIS)
Generic Name	Treprostinil
Dosage Form and Strength	1, 2.5, 5, and 10 mg/mL (approved formulations)
Route of Administration	Programmable pump delivering continuous intravenous infusion (iv) infusion
Proposed Indication	Pulmonary Arterial Hypertension (PAH)
Applicant	United Therapeutics Corporation
Associated IND	None
OCP Review Team	Ju-Ping Lai, Ph.D.; Sudharshan Hariharan, Ph.D.

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1. EXECUTIVE SUMMARY

Remodulin (treprostinil) Injection was approved on May 21, 2002 for the treatment of pulmonary arterial hypertension (PAH). It is a sterile sodium salt formulated for continuous subcutaneous or intravenous (IV) administration. Remodulin Injection is administered via an external infusion pump and surgically placed central venous catheter.

The applicant submitted NDA 208276 on December 16, 2015 and is seeking approval of Remodulin Implantable System (RIS), which consists of an approved drug (treprostinil) with its approved formulation (1, 2.5, 5, and 10 mg/mL) through an approved dosing route (IV infusion), for the same PAH indication in the same patient population, yet delivered by a new programmable and implantable drug delivery system.

The submission includes a multi-center, prospective, single arm, non-randomized, open label study designed to evaluate the safety of RIS in the treatment of PAH. From the clinical pharmacology perspective, two plasma samples were collected in each patient, one at baseline and the other at one week post-implant to assess maintenance of treprostinil steady state after switching of delivery system. For the safety evaluation, please refer to the clinical review by Drs. Gordon and Garnett (DARRTS date: 8/3/2016).

The use of Remodulin in the RIS does not change the drug's indication, subject population, drug dosage, formulation or route of administration for which the drug has already received FDA approval. However, a non-approvable letter was issued by Center for Devices and Radiological Health (CDRH) on March, 11, 2016 for the implantable device. A comprehensive summary of the issues pertaining to non-approvability of the device is summarized that letter.

The key review question focuses on evaluation of pharmacokinetic (PK) data collected pre- and post-implantation of RIS.

1.1 Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology I has reviewed the information contained in NDA 208-276. This NDA is considered approvable from a clinical pharmacology perspective pending approval of the device by CDRH. The key review issue with specific recommendations/comments is summarized below:

Review Issue	Recommendations and Comments
Evaluation of treprostinil plasma concentration collected pre- (baseline) and post-implantation (1-week) of RIS	The plasma samples collected from the trial provides evidence that the drug was delivered using the proposed RIS. The intra-subject variability estimate is within the past clinical experience with the oral product of treprostinil. The utility of PK data collected 1-week post-device implantation may be limited at least in terms of predicting the long term performance of the device.

1.2 Post-Marketing Requirements and Commitments

None (for the infused drug, Remodulin).

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Treprostinil acts by direct vasodilation of pulmonary and systemic arterial vascular beds. The current submission does not contain any new clinical pharmacology information and would not lead to any changes in the label of Remodulin. Therefore no additional clinical pharmacology information is summarized in this review. Please refer to the USPI and the clinical pharmacology review (DARRTS date: 3/12/2001) of Remodulin for the ADME information.

2.2 Dosing and Therapeutic Individualization

Not applicable for the infused drug, Remodulin. The studied dose in the clinical trial followed the USPI of Remodulin and dose titrations were within what is prescribed in the USPI. There is no proposal to change the doses or dose titration steps. Therefore, no additional evaluation was performed to assess dosing from the submitted study report.

2.3 Outstanding Issues

None for the infused drug, Remodulin. For the implantable device, the CDRH issued a non-approvable letter on March 11, 2016. A comprehensive summary of the issues pertaining to non-approvability of the device is summarized that letter.

2.4 Summary of Labeling Recommendations

Not applicable for the infused drug, Remodulin.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

This is a drug-device combination product. The original NDA was submitted to CDER and Premarket Approval Application (PMA) to CDRH on January 26, 2015 but was issued a refusal to file letter on March 26, 2015 by CDER. The resubmission was sent in on December 16, 2015. A non-approvable letter was issued by CDRH on March, 11, 2016 for the implantable device while the review clock within CDER for the infused drug has continued.

3.2 General Pharmacological and Pharmacokinetic Characteristics

Please refer to the USPI and clinical pharmacology review of Remodulin as there is no new clinical pharmacology information from this submission.

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