

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208276Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Office of Clinical Pharmacology Integrated Review

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| NDA or BLA Number | 208276 |
| <u>Link to EDR</u> | //Cdsesub1/evsprod/NDA208276/208276.enx |
| Submission Date | 16 th 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.

3.3 Clinical Pharmacology Questions

3.3.1 Evaluation of PK data pre- and post-implantation of Remodulin Implantable System

Study G100017 enrolled subjects who were receiving IV Remodulin via an external infusion pump. Patients need to be on stable dose of Remodulin for at least 4 weeks to enroll. The delivery system delivered drug at the subject's prescribed infusion rate, and the subject was transitioned off the external delivery system to the RIS when the implantation procedure was completed.

Plasma treprostinil concentrations were measured to ensure the RIS maintained the steady state levels of treprostinil that the patient was previously stabilized on. The time points were at baseline (where patients were on stable dose of Remodulin) and at one week post-implant of the proposed delivery system. The infusion rate of the drug was kept constant until the one-week PK sample was obtained. Drug plasma concentrations were available in 58 patients. The mean change (\pm standard deviation) in the drug concentration between two delivery systems is 2.3 % (\pm 41%), however the drug concentration between the two occasions on a patient level were more variable ranging from -60.5% to 235.5%. Eight out of 58 patients (~14%) exhibited concentration change of greater than -25% or +50% (Table 1).

Table 1: Subjects with concentration change of greater than -25% or +50%.

| No | Patients | Plasma concentration (ng/ml) | | % change |
|----|----------|------------------------------|--------------------------|----------|
| | | Baseline | 1 week post implantation | |
| 1 | (b) (6) | 3.01 | 10.1 | 235.5 |
| 2 | (b) (6) | 6.35 | 2.51 | -60.5 |
| 3 | (b) (6) | 1.47 | 2.57 | 74.8 |
| 4 | (b) (6) | 9.74 | 5.37 | -44.9 |
| 5 | (b) (6) | 13.2 | 8.67 | -34.3 |
| 6 | (b) (6) | 4.95 | 2.69 | -45.7 |
| 7 | (b) (6) | 1.92 | 3.81 | 98.4 |
| 8 | (b) (6) | 11.5 | 5.65 | -50.9 |

The within-subject variability estimate from this study is ~25%. This variability is within the past clinical experience with the oral formulation of treprostinil (Orenitram®) where the estimated within-subject variability were 31% and 25% for C_{max} and AUC, respectively. There are a few patients with greater plasma concentration changes than expected in this study (as shown in Table 1), however, in the absence of a control arm it is not known if similar extent of variability would have been observed following Remodulin external infusion pump at two

different occasions within the same individual. Nevertheless, PAH symptoms in these patients did not deteriorate significantly over time. Treprostinil infusion rates increased over time in this study, but it may be more reflective of the clinical practice with prostacyclins. Therefore, evaluation of PK data following one-week post implantation is not really indicative of device performance over the long-term. Instead, device accuracy ratio and long-term clinical experience, which are discussed in detail in the clinical review, are more reflective of the long-term performance of the device.

3.3.2 Is the proposed general dosing regimen appropriate?

Not applicable for the infused drug, Remodulin.

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

Not applicable for the infused drug, Remodulin.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Not applicable for the infused drug, Remodulin.

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

Not applicable for the infused drug, Remodulin.

4. Appendices

4.1 Summary of Bioanalytical Method Validation

The assay validation for treprostinil is within the specifications and acceptable. Concentrations of treprostinil in plasma were determined using validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method. The lower limit of quantitation (LLOQ) for treprostinil in the plasma was 0.01 ng/mL. Accuracy and precision for the Quality Control (QC) samples are < 7.7 % and < 14%, respectively, and is acceptable according to the specification listed in ‘Guidance for Industry: Bioanalytical Method Validation’.

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/s/

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09/21/2016

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09/21/2016