# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:** 

203496Orig1s000

**OTHER REVIEW(S)** 



## Project Manager Overview

NDA 203496 for Orenitram (treprostinil) extended-release tablets proposed indication: treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity

PDUFA goal date: February 16, 2014
Pharmacologic Class: prostacyclin analogue
Type 3 NDA: New Dosage Form
RPM: Wayne Amchin
Class 2 Resubmission
(6-month PDUFA review clock,
21 CFR 314.110(b)(1))

### **Regulatory Background**

Remodulin® (treprostinil) for subcutaneous (NDA 21272) and intravenous (NDA 21272/s-002) administration was originally approved under Subpart H on May 21, 2002 (NDA 21272) and November 24, 2004, respectively.

Tyvaso® (treprostinil) inhalation solution (NDA 22387) was approved on July 30, 2009.

NDA 203496 was submitted on December 24, 2011 and received on December 27, 2011seeking to market a third dosage form of treprostinil diolamine (fourth route of administration). The original submission was reviewed under a standard 10-month review clock. Complete response actions on this NDA were taken on October 23, 2012 and on March 22, 2013.

The previous Complete Response was based on the finding that oral treprostinil had an effect on exercise capacity that was, by itself, too small to be clinically relevant when used alone. Orenitram had also failed to show even statistically significant effects on a background of another vasodilator in two studies of reasonable size.

On December 21, 2012, a meeting was held between the DCRP and the applicant to discuss the clinical, statistical, and clinical pharmacology issues noted in the October 23, 2012 Complete Response letter.

In addition, on May 3, 2013, a meeting was held between the DCRP and the applicant to discuss the clinical and statistical issues noted in the March 22, 2013 Complete Response Letter.

The Division Director's review, dated December 20, 2013, states that those findings are still true and labeling reflects this. Oral administration avoids adverse consequences and inconveniences of currently approved intravenous, subcutaneous, and inhaled routes of administration, so replacing these uses—for which the efficacy data are no more compelling—seems useful. Thus labeling suggests such substitution while denying there are study data to support it. The current proposed label states to titrate the dose to tolerability, so getting the oral dose right should not be particularly difficult in such a



203496 Orenitram (treprostinil) extended-release tablets change of route of administration.

Study number 302, conducted under IND number 71537

Protocol Number	Study Description	Sample Size	Dose of UT- 15C	Duration of Dosing
Study of UT-15C as Monotherapy				
TDE-PH-302	Randomized, multi-center, placebo-controlled study in subjects with PAH NOT receiving approved background therapy	349	0.25-1 mg BID starting dose with dose increasing over time	12 weeks

The sponsor proposes the following four strengths of treprostinil *extended-release tablets*, 0.125, 0.25, 1, and 2.5 mg.

An orphan designation was granted on 02 November 1999 for the use of treprostinil in the treatment of pulmonary arterial hypertension. Pursuant to 21 CFR 314.55(d), drugs seeking approval for an orphan indication are exempt from PREA. Therefore, PeRC review was not necessary.

The December 10, 2013 Product Quality review states on page 8 that the Office of Compliance has provided a final overall acceptable recommendation on December 9, 2013, for all manufacturing and testing facilities for this NDA. The Office of Compliance Summary report is attached to the Product Quality report as pages 13-16.

#### **NDA Reviews and Memos**

### Class 2 Resubmission (received August 16, 2013)

#### **Division Director/CDTL Memo**

Norman Stockbridge: December 20, 2013 Dr. Stockbridge will sign the *Approval* letter.

### **Product Quality Review**

Shastri Bhamidipati, December 10, 2013

This was the only primary review for the current submission. It reaffirms approvability from the product quality perspective. No new data were reviewed

### **DMEPA Proprietary Name Review**

Loretta Holmes and Irene Chan's November 27, 2013 review deemed the proposed name acceptable.

#### **Labeling Reviews**

SEALD PI Review December 13, 2013 OPDP/Patient Labeling PPI Joint Review on November 21, 2013 DMEPA CCL Review, November 21, 2013 OPDP CCL and PI reviews November 13, 2013 and October 18, 2013



## 203496 Orenitram (treprostinil) extended-release tablets

### Class 1 Resubmission (January 31, 2013)

#### **Division Director's Memo**

Norman Stockbridge: March 22, 2013

Dr. Stockbridge signed the complete response letter.

#### CDTL Memo

Abraham Karkowsky: March 5, 2013

Dr. Karkowsky recommended taking a complete response.

#### Clinical Review

Maryann Gordon: June 17, 2013 (archived 9/16/13)

This review highlighted the findings from previous reviews about the monotherapy and combination studies of treprostinil. No recommendation was made in this review.

## **Product Quality Review**

Shastri Bhamidipati: March 22, 2013

In response to labeling issues identified by DMEPA

and communicated in the CR letter, the sponsor has proposed to eliminate

and change the color film-coat

for 0.125 mg strength tablet to white. These changes were deemed acceptable.

#### **Nonclinical Review**

Thomas Papoian: March 21, 2013

This review summarized the carcinogenicity considerations and findings. It did not make an approvability recommendation.

#### **OSI Inspection Review**

Sharon Gershon, February 20, 2013

This review of a foreign inspection concluded that the regulatory violations observed are minor and isolated, and unlikely to importantly impact the efficacy or safety of this study. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

#### Original Submission (December 27, 2011)

**Division Director's Memo** 

Norman Stockbridge: October 23, 2012

Dr. Stockbridge signed the complete response letter.

#### **CDTL Memo**

Abraham Karkowsky: October 18, 2012

Dr. Karkowsky recommended taking a complete response.

#### Clinical

Maryann Gordon: October 3, 2012



# 203496 Orenitram (treprostinil) extended-release tablets

### **Biometrics**

John Lawrence: October 3, 2012 and October 10, 2012 Dr. Lawrence recommended taking a complete response action.

APPEARS THIS WAY ON ORIGINAL



# DOCKET

# Explore Litigation Insights



Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

# **Real-Time Litigation Alerts**



Keep your litigation team up-to-date with **real-time** alerts and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

# **Advanced Docket Research**



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

# **Analytics At Your Fingertips**



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

#### **LAW FIRMS**

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

#### **FINANCIAL INSTITUTIONS**

Litigation and bankruptcy checks for companies and debtors.

## **E-DISCOVERY AND LEGAL VENDORS**

Sync your system to PACER to automate legal marketing.

