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

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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

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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 (b) (4) and communicated in the CR letter, the sponsor has proposed to eliminate (b) (4) and change the color film-coat for 0.125 mg strength tablet (b) (4) 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

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

APPEARS THIS WAY ON ORIGINAL

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