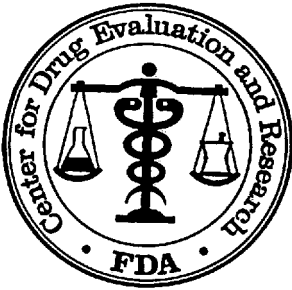


**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203496Orig1s000**

**SUMMARY REVIEW**



## DIVISION OF CARDIO-RENAL DRUG PRODUCTS

### *Divisional Memo*

**NDA:** 203496 Treprostinil extended-release tablets for pulmonary arterial hypertension.

**Sponsor:** United Therapeutics

**Review date:** 20 December 2013

**Reviewer:** N. Stockbridge, M.D., Ph.D., HFD-110

**Distribution:** NDA 203496

This memo conveys the Division's recommendation to approve treprostinil extended-release tablets.

This application was originally submitted 27 December 2011 and then resubmitted 31 January 2013 and again 16 August 2013 following Complete Response actions of 23 October 2012 and 22 March 2013.

The only primary review for the current submission is of CMC (Bhamidipati; 10 December 2013), which reaffirms approvability from the product quality perspective. No new data were reviewed.

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.

Those findings are, of course, still true, and labeling reflects this. Unquestionably, 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. Part of why I think this is reasonable is that dose is titrated to tolerability, so getting the oral dose right should not be particularly difficult in such a change of route of administration.

I should also note that the sponsor and the Division have attempted to review successes and failures to demonstrate that one vasodilator adds to the efficacy obtained with another. While there are a few successes, it is not clear how well the background was dosed to maximum effect. There may be little reason to expect much additivity.

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/s/  
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NORMAN L STOCKBRIDGE  
12/20/2013