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

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
Dr. Gordon recommended taking a complete response action.

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

APPEARS THIS WAY ON ORIGINAL

Clinical Pharmacology
Sudharshan Hariharan: October 2 , 2012
Dr. Hariharan recommended a thrice-daily dosing regimen, a regimen not used in the clinical studies.

Nonclinical
Xavier Joseph: October 3, 2012
Dr. Joseph had no approvability issues.

Biopharmaceutics
Akm Khairuzzman: August 30, 2012
Dr. Khairuzzaman had no approvability issues.

CMC
Shastri Bhamidipati: August 28, 2012 and October 19, 2012
Dr. Bhamidipati had no approvability issues. The exclusion from environmental assessment was acceptable and facility inspections were acceptable.

DMEPA
Forest Ford, Irene Chan, and Kimberly Defronzo
DMEPA rejected the following 3 proposed proprietary names: (b) (4) The sponsor submitted a fourth, Orenitram, that is under review. DMEPA provided comments on all aspects of labeling (e.g., carton, container, PI).

Action Items:
Approve the NDA

Overview by Wayne Amchin
December 20, 2013

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/s/

WAYNE S AMCHIN
12/20/2013

Division of Cardiovascular and Renal Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 203496

Name of Drug: Orenitram (Treprostinil) Extended Release Tablets

Applicant: United Therapeutics Corporation

Labeling Reviewed

Submission Date: December 18, 2013

Receipt Date: December 18, 2013

Background and Summary Description: NDA 203496 was originally submitted December 27, 2011. A complete response action was taken on October 23, 2012. A class 1 resubmission was received on January 31, 2013, and a complete response action was taken on March 22, 2013. A class 2 resubmission was received on August 16, 2013.

In response to the class 2 resubmission, labeling comments were conveyed to the applicant on November 5, 2013, by email. The applicant submitted a revised PI and PPI in response to those comments on November 12, 2013. The changes to the PPI were deemed acceptable and no further changes were requested.

On December 13, 2013, SEALD completed their sign-off review of the End-of-Cycle Prescribing Information (PI). The SEALD review identified PLR format deficiencies and some other issues for DCRP to consider revisions to the Dosage and Administration Section and the Patient Counseling Information Section.

On December 17, 2013, DCRP sent an information request to the applicant to request submission of an amended PI to address the PLR format deficiencies and additional edits DCRP requested to the Dosage and Administration Section and the Patient Counseling Information Section.

Review

On December 18, 2013, the applicant submitted an amendment with revisions to the PI to incorporate the changes requested by DCRP on December 17, 2013. This review compares the applicant's December 18, 2013 PI submission to the PLR format changes requested and the PI with track changes provided in DCRP's December 17, 2013 Information Request.

The applicant made all the changes requested by DCRP. The applicant also proposed additional

minor formatting changes for consistency within the label. These changes involved header formatting case changes. The only issues I find in the 12/18/13 proposed PI are:

1. In section 12.3, Pharmacokinetics, Subsection Special Populations, subheader Hepatic Impairment and Subheader Renal Impairment, the I in the word Impairment was changed to lower case i.
2. In Section 17, Patient Counseling Information, a period is missing at the end of the opening statement "See FDA-approved patient labeling (Patient Package Insert)".

Recommendations

I recommend approval of the labeling with correction to the two items above.

Wayne Amchin	12-19-13
Regulatory Project Manager	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WAYNE S AMCHIN
12/20/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title[1]	**Orenitram (treprostinil) Extended Release Tablets for oral administration**
Applicant	United Therapeutics
Application/Supplement Number	NDA 203496
Type of Application	Original
Indication(s)	Treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity
Office/Division	ODE I/DCRP
Division Project Manager	Wayne Amchin
Date FDA Received Application	August 16, 2013
Goal Date	February 16, 2014
Date PI Received by SEALD	December 11, 2013
SEALD Review Date	December 13, 2013
SEALD Labeling Reviewer	Elizabeth Donohoe
Acting SEALD Division Director	Sandra Kweder

1 Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word "must" denotes that the item is a regulatory requirement, while the word "should" denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item **(deficiency)**.
- **YES:** The PI meets the requirement for this item **(not a deficiency)**.
- **N/A**: This item does not apply to the specific PI under review (**not applicable**).

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

NO 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *The top margin is less than 1/2 inch.*

YES 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period:**
  - *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of-Cycle Period:**
  - Select "**YES"** in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

NO 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *White space is missing before most major headings (it is present before I&U, DFS)*

NO 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *A reference is missing for the last paragraph under I&U.*

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: *The statement is not bolded and the name of the drug product is not in UPPER CASE.*

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Selected Requirements of Prescribing Information

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Selected Requirements of Prescribing Information

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

NO 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment: *The proposed statement includes an email address; this should be deleted. See the Labeling Review Tool, page 10.*

Patient Counseling Information Statement in Highlights

NO 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment: *The statement is not bolded and the words "PATIENT COUNSELING INFORMATION" are not in UPPER CASE.*

Revision Date in Highlights

NO 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment: *The date is missing and should state: 12/2013*

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment: *Consider revising so the two columns are of equal length for improved readability.*

NO 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment: *The heading is not bolded.*

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

NO 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment: *Subsection headings 16.1 and 16.2 are in UPPER CASE and should be in Title Case.*

NO 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment: *The heading for subsection 7.3 includes "on Treprostinil" in the TOC; this is missing from the FPI. Also, there is a dash "-" after 5.3 in the TOC that should be removed..*

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "*[see Warnings and Precautions (5.2)]*" or "[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

ELIZABETH A DONOHOE
12/13/2013

ERIC R BRODSKY
12/13/2013
I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, acting SEALD Division Director.

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Office of Medication Error Prevention and Risk Management

Final Label Memorandum

Date:	November 21, 2013
Reviewer:	Janine Stewart, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Drug Name and Strengths:	Treprostinil Extended-release Tablets 0.125 mg, 0.25 mg, 1 mg, 2.5 mg
Application Type/Number:	NDA 203496
Applicant:	United Therapeutics Corporation
OSE RCM #:	2013-2118

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION

This memorandum evaluates the revised container labels for Treprostinil Extended- release Tablets, NDA 203496, submitted on October 29, 2013 (Appendix A). DMEPA previously reviewed the proposed labels and labeling under OSE Review # 2013-1345 dated October 17, 2012.

2 MATERIAL REVIEWED

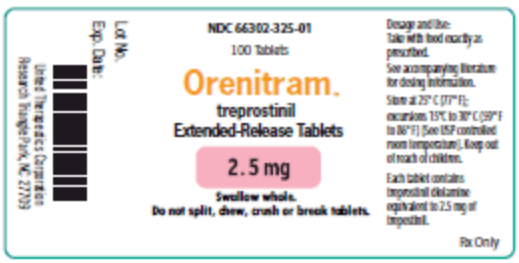
DMEPA reviewed the container labels submitted on October 29, 2013. We compared the revised labels against the recommendations contained in OSE Review # 2013-1345 dated October 17, 2012.

3 CONCLUSIONS AND RECOMMENDATIONS

The revised labels adequately address our concerns from a medication error perspective. We have no additional comments at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Cherye Milburn, at 301-796-2048.

Appendix A: Retail Preferred Container Labels



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/s/

JANINE A STEWART
11/21/2013

IRENE Z CHAN
11/21/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 13, 2013

To: Wayne Amchin
Regulatory Project Manager
Division of Cardiovascular and Renal Products(DCRP)

From: Emily Baker, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 203496**
OPDP Labeling Comments for Orenitram (treprostinil) Extended Release Tablets for oral administration

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OPDP has reviewed the proposed carton and container labeling submitted for consult on February 7, 2012, for Orenitram (treprostinil) Extended Release Tablets for oral administration. Our comments are based on the proposed labeling emailed to us on October 29, 2013.

OPDP has no comments on the proposed carton and container labeling at this time.

Thank you for the opportunity to comment on the proposed materials.

If you have any questions, please contact Emily Baker at 301.796.7524 or emily.baker@fda.hhs.gov.

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/s/

EMILY K BAKER
11/13/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 21, 2013
To:	Norman Stockbridge, MD, PhD Director **Division of Cardiovascular and Renal Products (DCRP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Emily Baker, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	Orenitram (treprostinil)
Dosage Form and Route:	Extended Release Tablets for oral administration
Application Type/Number:	NDA 203496
Applicant:	United Therapeutics Corp.

1 INTRODUCTION

On August 16, 2013, United Therapeutics Corp. resubmitted for the Agency's review their original New Drug Application (NDA) 203496 for Orenitram (treprostinil) Extended Release Tablets in response to a Complete Response letter dated March 22, 2013. The Applicant also previously received a Complete Response letter on October 23, 2012 for this NDA. The proposed indication for Orenitram (treprostinil) Extended Release Tablets is for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Cardiovascular and Renal Products (DCRP) on October 4, 2013, and February 7, 2012, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for Orenitram (treprostinil) Extended Release Tablets.

2 MATERIAL REVIEWED

- Draft Orenitram (treprostinil) Extended Release Tablets PPI received on January 31, 2013.
- Draft Orenitram (treprostinil) Extended Release Tablets Prescribing Information (PI) received on January 31, 2013, revised on June 17, 2013, and further revised by the Review Division throughout the review cycle, and received by DMPP OPDP on October 4, 2013.
- Approved TYVASO (treprostinil) inhalation solution comparator labeling dated April 30, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
10/21/2013

EMILY K BAKER
10/21/2013

BARBARA A FULLER
10/21/2013

LASHAWN M GRIFFITHS
10/21/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: October 18, 2013

To: Wayne Amchin
Regulatory Project Manager
Division of Cardiovascular and Renal Products(DCRP)

From: Emily Baker, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 203496**
OPDP Labeling Comments for Orenitram (treprostinil) Extended Release Tablets for oral administration

---

OPDP has reviewed the proposed Package Insert (PI) submitted for consult on February 7, 2012, for Orenitram (treprostinil) Extended Release Tablets for oral administration. Our comments on the PI are based on the proposed labeling emailed to us on October 4, 2013. OPDP's comments are provided directly on the attached marked-up copy of the proposed PI.

Thank you for the opportunity to comment on the proposed material.

If you have any questions, please contact Emily Baker at 301.796.7524 or Emily.Baker@fda.hhs.gov.

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/s/

EMILY K BAKER
10/18/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label Review

Date:	October 17, 2012
Reviewer:	Kimberly DeFronzo, RPh, MS, MBA Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z. Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Drug Name:	Treprostinil Extended-release Tablets 0.125 mg, 0.25 mg, (b) (4) 1 mg, and 2.5 mg
Application Type/Number:	NDA 203496
Applicant:	United Therapeutics, Inc.
OSE RCM #:	2012-1345

***** This document contains proprietary and confidential information that should not be released to the public.*****

Contents

1 INTRODUCTION

This review evaluates the revised container labels for Treprostinil Extended-release Tablets submitted on September 20, 2012 under the Request for Proprietary name Review for (b) (4) (see Appendix A). The Division of Medication Error Prevention and Analysis (DMEPA) previously reviewed the proposed container labels and insert labeling under OSE Review 2012-534, dated July 26, 2012.

2 MATERIALS REVIEWED

DMEPA evaluated the following:

- Revised container labels submitted on September 20, 2012 (Appendix A)

Additionally, our recommendations in OSE Review 2012-534 were reviewed to assess whether the revised labels adequately address our concerns from a medication error perspective.

3 CONCLUSIONS AND RECOMMENDATIONS

Review of the revised documents show that the Applicant has implemented all of DMEPA's recommendations under OSE Review 2012-534. However, we have identified additional areas of vulnerability that require revision to help mitigate potential medication errors. Therefore, we have the following recommendations which should be conveyed to the Applicant and implemented prior to approval.

3.1 COMMENTS TO THE APPLICANT

A. Container Labels

1. (b) (4) Therefore, (b) (4) we recommend removing this

2. We acknowledge you have attempted to differentiate the (b) (4) strengths within your product lin (b) (4) Therefore, (b) (4) utilize an alternate color for differentiation of the strength to minimize the risk of selection error.

3. Decrease the prominence of the "Rx Only" statement by debolding its font and relocating it away from the center to either side of the principal display panel to avoid crowding of important information.

4. Decrease the prominence of the net quantity "100 Tablets" statement by debolding its font and relocating it away from the statement of strength.

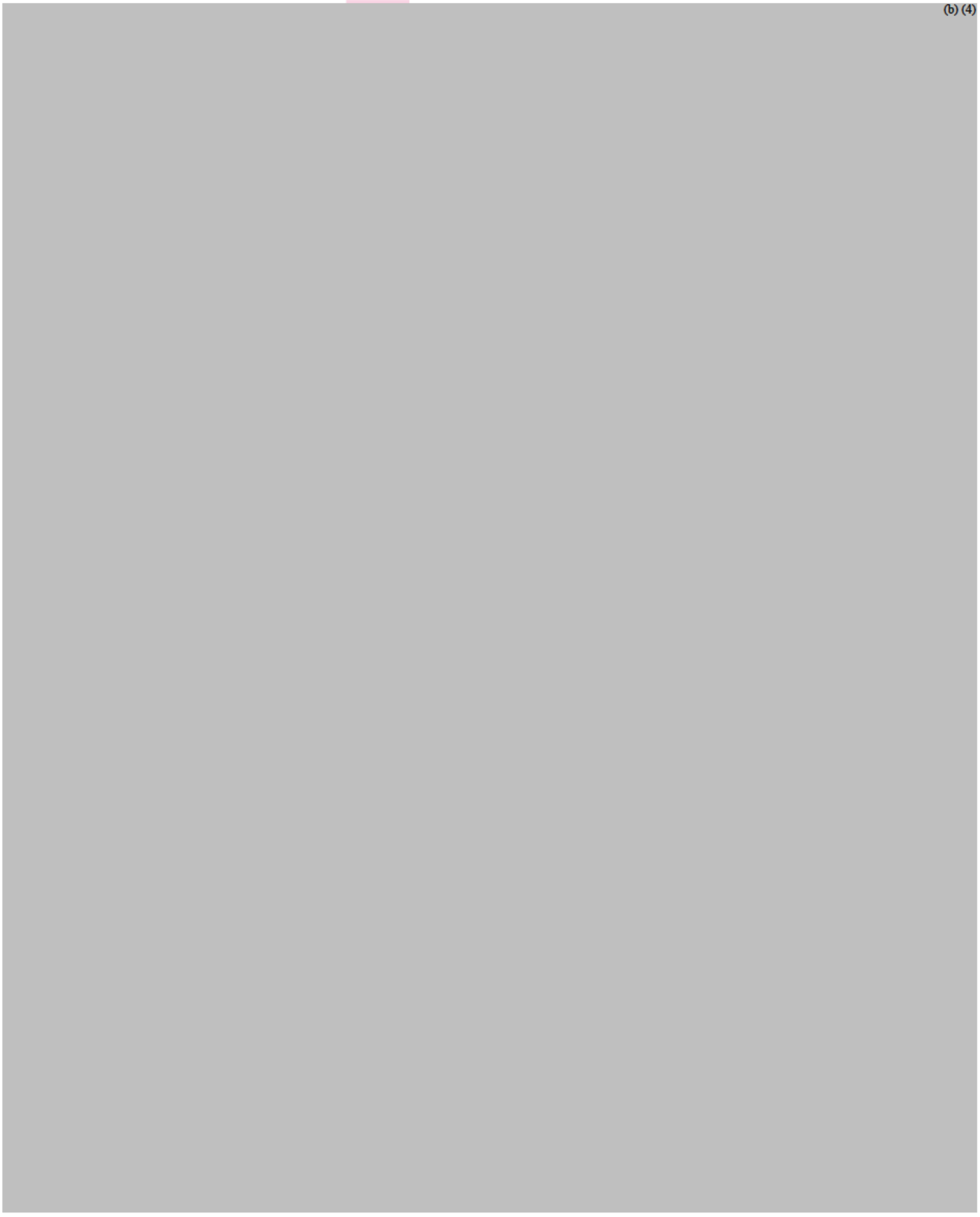
5. Increase the prominence of the [redacted] (b) (4) statement by bolding its font and relocating it from the side panel to the bottom of the principal display panel. Consider relocating the manufacturer information from the principal display panel to the side panel to accommodate this change.

6. Revise the storage statement to read: "Store at 25°C (77°F); excursions 15°C to 30°C (59°F to 86°F) [See USP controlled room temperature]. Keep out of reach of children." We recommend dashes not be used in order to provide clarity and prevent the potential for misinterpretation of the "-" symbol as a negative sign, especially for a temperature designation.

If you have further questions or need clarifications, please contact Cherye Milburn, OSE Project Manager, at 301-796-2084.

APPENDICES

Appendix A: Container Labels



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/s/

KIMBERLY A DE FRONZO
10/17/2012

IRENE Z CHAN
10/17/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: October 3, 2012

TO: Maryann Gordon, Medical Officer
Abraham Karkowsky, Cross Discipline Team Leader
Daniel Brum, Regulatory Project Manager
Division of Cardio-Renal Drug Products

FROM: Sharon K. Gershon, Pharm. D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203496

APPLICANT: United Therapeutics Corporation

DRUG: (b) (4) (treprostinil diethanolamine) sustained-release tablet

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of patients with pulmonary arterial hypertension (PAH)

CONSULTATION REQUEST DATE: April 20, 2012

INSPECTION SUMMARY GOAL DATE: September 28, 2012

DIVISION ACTION GOAL DATE: October 25, 2012

PDUFA DATE: October 27, 2012

PROTOCOL: TDE-PH-302: A 12-Week, International, Multicenter, Double-blind, Randomized, Placebo-Controlled Comparison of the Efficacy and Safety of Oral UT-15C Sustained Release Tables in Subjects with Pulmonary Arterial Hypertension

I. BACKGROUND:

United Therapeutics Corp. seeks approval of NDA 203496 for treatment of patients with pulmonary arterial hypertension (PAH). Pulmonary arterial hypertension is a rare disorder of the pulmonary microvasculature defined as a sustained elevation in pulmonary arterial pressure greater than or equal to 25 mmHg with a mean pulmonary capillary wedge pressure of less than or equal to 15 mmHg. Treprostinil is a chemically stable prostacyclin analog that has shown clinical effectiveness previously when administered by continuous subcutaneous, intravenous, and inhaled routes of administration. Treprostinil as a sodium salt, is available for clinical use in the approved drug products Remodulin® injection and Tyvaso® inhalation solution. Development of the new diethanolamine salt as a sustained-release, 12-hour tablet, builds upon the all-ready known safety and efficacy of Remodulin® injection and Tyvaso® inhalation solution.

This application is supported by data from the single Study TDE-PH-302, which was a 12-week, international, multi-center, randomized, double-blind, placebo-controlled, comparison of the efficacy and safety of oral treprostinil diethanolamine (UT-15C) sustained-release (SR) tablets in subjects with PAH, who were not receiving approved oral therapy for the treatment of PAH. The primary endpoint was the change from baseline in the 6-Minute Walk Distance (6MWD) at Week 12. The 6MWD was to be assessed between 3 and 6 hours after the morning dose of study drug.

Of the 349 subjects randomized (233 active, 116 placebo), 228 subjects (151 active, 77 placebo) comprised the primary analysis population. Subjects were randomly allocated 2:1 to receive either UT-15C or matching placebo.

One domestic clinical site, and two foreign clinical sites were chosen for inspection. These sites were chosen due to high enrollment numbers and significant primary efficacy results pertinent to decision making.

II. RESULTS (by Site):

Name of CI	Protocol # and # of Subjects	Inspection Dates	Final Classification
R. James White Mary Parkes Asthma Center 400 Red Creek Drive Suite 110 Rochester, NY 14623	Protocol: TDE-PH-302 Site #46 15 subjects	June 14, 2012 – 26, 2012	NAI
Keyur Harshadray Parikh Care Institute of Medical Sciences Opp. Panchamrut Bungalows, Nr. Shukan Mall Off Science City Road Sola, Ahmedabad 380060 Gujarat, India	Protocol: TDE-PH-302 Site #174 44 subjects	September 17 – 21, 2012	Preliminary VAI (EIR not yet received)
Zhicheng Jing Shanghai Pulmonary Hosp Respiratory Medicine Dept No, 507 Zhengmin Road Yangpu District, Shanghai China 200433	Protocol: TDE-PH-302 Site #200 51 subjects	September 25 – 28, 2012	Preliminary NAI (EIR not yet received)

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **R. James White (Site #46)**
Mary Parkes Asthma Center
400 Red Creek Drive
Suite 110
Rochester, NY 14623

a. **What was inspected**: The inspection was conducted in accordance with

Compliance Program (CP) 7348.811. At this site, eighteen subjects were screened, fifteen subjects randomized, and fourteen subjects completed the study. An audit of fifteen subjects' records was conducted, including a review of the source documents, Case Report Forms, Informed Consent Documents, corroboration of the information and data in these documents with the data provided in the background materials. The field investigator audited laboratory records, all adverse events, primary and secondary efficacy endpoints, protocol deviations, discontinuations and concomitant medications. The field investigator also looked at test article accountability records and control.

b. **General observations/commentary**: The source documents appeared organized, complete and legible. No significant regulatory violations were noted. At the end of the inspection, no Form FDA 483 was issued. However, the field investigator discussed one instance of a reported protocol violation concerning Subject 046211. This subject was randomized to the placebo arm on June 29, 2009, approximately 26 days after discontinuing sildenafil 20 mg BID, a PDE-5 inhibitor. this drug. Per the protocol, the patient must not have received a PDE-5 inhibitor for 30 days prior to randomization. This subject ultimately experienced an SAE and died (b) (6) Because this protocol violation had been reported to the sponsor as a protocol violation, and was listed in the data listings as a protocol violation, no Form FDA 483 was issued, and the inspection was classified as NAI.

c. **Assessment of data integrity**: No significant regulatory violations were noted. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.
.

2. **Keyur Harshadray Parikh (Site #174)**
Care Institute of Medical Sciences
Opp. Panchamrut Bungalows, Nr. Shukan Mall
Off Science City Road
Sola, Ahmedabad 380060
Gujarat, India

Note: Observations noted for this site are based on preliminary communications with the FDA investigator and review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

a. **What was inspected:** The inspection was conducted in accordance with Compliance Program (CP) 7348.811. At this site, 51 subjects were screened, 44 subjects enrolled, and 39 subjects completed the study. A total of three subjects died during the study, but none of these deaths were attributed to the investigational product. Two subjects withdrew from the study (reasons not provided by the FDA field investigator).

The FDA field investigator conducted a 100% review of all Informed Consent Documents and all adverse events, including the serious adverse events. She corroborated the data in the source records and data listings for 22 subjects (50% of enrolled subjects) for demographics, primary efficacy endpoints, protocol violations, dosing, concomitant medications, study discontinuations and laboratory data.

b. **General observations/commentary**: There was no evidence of underreporting of adverse events, and the primary efficacy endpoint data was verifiable. The FDA field investigator observed that some subjects were randomized into the study before all screening tests and procedures were completed.

At the conclusion of the inspection a 2-observational, Form FDA 483 was issued for: 1) an investigation was not conducted in accordance with the signed statement of investigator and investigational plan; and 2) failure to prepare and maintain adequate case histories with respect to observations and data pertinent to the investigation.

For Observation 1: The protocol required that, for women of childbearing potential, a negative serum pregnancy test will be obtained at Screening. The FDA field investigator found that four subjects (174232, 174234, 174240 and 174241) were randomized into the study and received investigational product before their serum pregnancy test results were reviewed, and one subject (174244) was randomized into the study without a serum pregnancy test performed. The protocol also required that diuretics not be discontinued or added within 14 days of Baseline. The FDA field investigator found that for Subject 174242, a diuretic was added within 14 days of the baseline visit.

For Observation 2, the FDA field investigator found that for Subject 174233, the source document for the grading of PAH symptoms of dyspnea and fatigue was "1" whereas the eCRF grading was "0". This finding was isolated, and not considered significant because efficacy outcome would not be changed.

c. **Assessment of data integrity**: 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.

Note: Observations noted for this site are based on preliminary communications with the FDA investigator and review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

3. **Zhicheng Jing (Site #200)**
Shanghai Pulmonary Hosp
Respiratory Medicine Dept
No, 507 Zhengmin Road
Yangpu District
Shanghai, China 200433

Note: Observations noted for this site are based on preliminary communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

a. **What was inspected:** The inspection was conducted in accordance with Compliance Program (CP) 7348.811. At this site, 52 subjects were screened, 51 subjects enrolled, and 42 subjects completed the study. A total of nine subjects withdrew from the study, including four subjects who died during study participation and one subject who died after completing the study. No deaths were attributable to the investigational product.

The FDA field investigator completed a 100% review of all source records against the eCRFs and data listings for demographics, primary and secondary efficacy parameters, adverse events, protocol violations, concomitant medications, and study discontinuations. A total of 17 subject records were reviewed for clinical laboratory results (to ensure consistency between source documents and data listings) and ten subject records were reviewed in detail for dosing. The FDA field investigator also reviewed the log of monitoring visits, and other regulatory documents including financial disclosure statements, Form 1572's and IRB review reports.

b. **General observations/commentary**: The data in the source records corroborated with reviewed data in the eCRFs and data listings, with respect to demographics, primary efficacy endpoints, adverse events, clinical worsening, concomitant medications, protocol violations and study discontinuations. There was no evidence of underreporting of adverse events, and the primary efficacy endpoint data was verifiable. The serious adverse events (SAEs) of right heart failure and death were documented as not attributable to the study drug.

Although no Form FDA 483 was issued following the inspection, the following discussion took place at the end of the inspection: According to and starting with Protocol Amendment #6, the dose of study drug should continue to be increased every 3 days as tolerated. The FDA field investigator noted that the subjects were not increased every 3 days and many subjects were on the same dose for an average of 5 to 10 days before increasing their dosage. Most subjects ended the study at the 2-4 mg dose range at 12 weeks. According to the clinical investigator, the dosages were

determined according to the medical interests of the subjects at all times during their participation in the study and were not tied to any strict schedule.

c. **Assessment of data integrity**: No significant regulatory violations were noted. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

Note: Observations noted above are based on the Form FDA 483 and communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigator sites were inspected in support of NDA 203496. No regulatory violations were found during the inspections at two clinical investigator sites (Dr. James White, U.S. and Dr. Zhicheng Jing, China) and no Form FDA-483 was issued. The inspection of Dr. Paikh (India) is classified preliminarily, as VAI, and a two-observational FDA-483 was issued for the failure to follow the protocol and failure to maintain accurate records. Although regulatory violations were noted as described above they are unlikely to significantly impact primary safety and efficacy analyses for Study TDE-PH-302. Therefore, the data from these studies, submitted in support of NDA 203496 may be considered reliable based on available information.

Note: Observations noted above are based in part on the preliminary communications provided by the FDA field investigators and preliminary review of available Form FDA 483, inspectional observations. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

{See appended electronic signature page}

Sharon K. Gershon, Pharm.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
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Susan D. Thompson, M.D.
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/s/

SHARON K GERSHON
10/03/2012

SUSAN LEIBENHAUT
10/03/2012

SUSAN D THOMPSON
10/03/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Review

Date:	July 26, 2012
Reviewer:	Ray Ford, RPh Division of Medication Error Prevention and Analysis
Team Leader:	Irene Z Chan, PharmD, BCPS Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength(s):	Treprostinil Extended-release Tablets 0.125 mg, 0.25 mg, (b) (4) 1 mg, and 2.5 mg
Application Type/Number:	NDA 203496
Applicant/Sponsor:	United Therapeutics
OSE RCM #:	2012-534

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Contents

1 INTRODUCTION

This review evaluates the proposed container label and insert labeling for Treprostinil Extended-release Tablets, NDA 203496, for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

The active ingredient, Treprostinil, is already marketed in an oral inhalation formulation (Tyvaso) and an injectable formulation (Remodulin); however, there is no immediate-release or extended-release, solid, oral formulation of this drug marketed by this firm or any other firm. Therefore, Treprostinil Extended-release tablets will be the first oral treprostinil product if approved.

The product Remodulin was approved under NDA 021272 on May 21, 2002 as a solution for subcutaneous or intravenous infusion. Tyvaso was approved under NDA 022387 on July 30, 2009 as a solution for inhalation. This product, Remodulin, and Tyvaso are all owned by United Therapeutics.

The proposed proprietary name, [redacted] (b) (4), was evaluated under separate cover in OSE 2012-533 and found to be unacceptable [redacted] (b) (4)

1.2 PRODUCT INFORMATION

The following product information is provided in the December 29, 2011 submission.

- **Active Ingredient:** The active ingredient was submitted as Treprostinil Diethanolamine; however, the salt 'diethanolamine' will be removed since the salt form does not determine the strength per the Office of New Drug Quality Assessment (ONDQA).
- **Indication of Use:** Treatment of pulmonary arterial hypertension (PAH) World Health Organization (WHO) group 1 to improve exercise capacity.
- **Route of Administration:** Oral
- **Dosage Form:** The formulation was submitted as Sustained-release tablets. However, upon consultation with the Office of New Drug Quality Assessment (ONDQA) on April 10, 2012 we found that this product will be characterized as an Extended-release formulation and the Applicant will be required to comply with this designation.
- **Strength:** 0.125 mg, 0.25 mg, [redacted] (b) (4) 1 mg, and 2.5 mg
- **Dose and Frequency:** 0.25 mg twice daily with food. Titration is in the increment of 0.25 mg twice daily every 3 to 4 days as tolerated. If the 0.25 mg dose is not tolerated, an increment of 0.125 mg is recommended. The maximum dose studied was 12 mg twice daily. In hepatic impairment, Child Pugh Class A, the initial dose is 0.125 mg twice daily titrating every 3 to 4 days by 0.125 mg [redacted] (b) (4) In Child Pugh Class C patients, this drug is

contraindicated. [redacted]

- **How Supplied:** Bottles of 100 tablets for each strength.
- **Storage:** Store at 25ºC (77ºF). Excursions permitted 15ºC to 30ºC (59ºF to 86ºF).
- **Container and Closure Systems:** Treprostinil Extended-release Tablets are packaged in 45-cc white square high-density polyethylene (HDPE) bottles. Each bottle also contains an [redacted] desiccant in an HDPE canister and a pharmaceutical-grade [redacted] coil to prevent the tablets from being damaged. The cap used is [redacted] an induction seal insert manufactured by [redacted].

2 METHODS AND MATERIALS REVIEWED

Using the principals of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted February 28, 2012 (Appendix A)
- Insert Labeling submitted February 28, 2012

Additionally, we compared the proposed label and labeling against the currently marketed labels and labeling for Remodulin, and Tyvaso (see Appendices B and C) to identify any potential safety issues.

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the deficiencies identified in our label and labeling risk assessment.

3.1 CONTAINER LABELS 100 COUNT (0.125 MG, 0.25 MG, [redacted] 1 MG, AND 2.5 MG)

- Overly prominent net quantity statement, NDC number, Rx Only statement, [redacted]
- Lack of instruction regarding swallowing the tablet whole and not manipulating
- Inappropriate active ingredient and dosage form designation per ONDQA

3.2 INSERT LABELING

- Numbers are presented without the corresponding unit of measure in the Highlights of Prescribing Information.
- Section 17 Patient Counseling Information can be revised to improve readability of important information.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI: 2004.

3.3 PATIENT PACKAGE INSERT

- [redacted]

4 CONCLUSIONS

DMEPA concludes that the proposed strengths are supported by the proposed dosage for this product; however, the proposed labels and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product, to mitigate any confusion, and to clarify information.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. General Comment

The proposed proprietary name, [redacted] was evaluated under separate cover and found to be unacceptable [redacted] Your revised labels and labeling should be updated to reflect a new proposed proprietary name.

B. Container Label

1. Decrease the prominence of the "Rx Only" statement by debolding its font. Additionally, the upper case lettering should be changed to title case to improve readability.
2. The net quantity statement is too close to the statement of strength which may lead to confusion. Move the net quantity statement away from the strength statement. Consider placing the net quantity statement on the lower or upper portion of the principal display panel away from, and with less prominence than, the proprietary name, established name, and strength statement.
3. The [redacted] is overly prominent and distracts [redacted]. Remove or relocate and minimize [redacted]
4. The [redacted] is overly prominent. Remove or minimize [redacted]
5. Per consultation with the Office of New Drug Quality Assessment (ONDQA), revise the active ingredient [redacted] to 'treprostinil' [redacted]
6. Per consultation with the Office of New Drug Quality Assessment (ONDQA), the dosage form for this product should be 'Extended-release Tablets.' Replace the dosage form and ensure it is presented in title case font to improve readability.

7. The established name appears to be half the height of the proprietary name; however, the thin font lacks prominence commensurate with the proprietary name. Increase the prominence of the established name to account for all pertinent factors including typography, layout, contrast and other printing factors in accordance with 21 CFR 201.10 (g) (2). Additionally, the established name is comprised of the active ingredient, Treprostinil, and the dosage form, Extended-release Tablets, and the entire established name should be presented with the same font style and color.

8. If space permits, move the dosage form 'Extended-release Tablets' so it appears on the same line as the active ingredient 'Treprostinil' for improved readability.

9. As currently presented, the middle portion of the NDC product codes for the 0.125 mg and 1 mg strengths are (b) (4) and 310 respectively (b) (4) increasing the probability for medication error when the NDC numbers are utilized for strength selection within a product line. Revise your NDC product codes to mitigate this risk.

C. Insert Labeling

1. In the Highlights of Prescribing Information under the Dosage Forms and Strengths section revise (b) (4) to read 'Extended-release Tablets: 0.125 mg, 0.25 mg, (b) (4) 1 mg, and 2.5 mg'.

2. In the Highlights of Prescribing Information under Dosage and Administration, revise the statement (b) (4)

3. Per consultation with the Office of New Drug Quality Assessment (ONDQA), the dosage form for this product should be 'Extended-release Tablets.' Throughout the insert labeling, update the dosage form to comply.

4. Under section 2.2 Recommended Dosing (b) (4) of the full prescribing information, increase the prominence of the statement (b) (4)

5. Section 3 Dosage Forms and Strengths is missing the dosage form information for this product. Include this information.

6. Revise Section 17 Patient Counseling Information to improve readability, optimize messages, and prioritize important information as follows:

(b) (4)

(b) (4)

(b) (4)

D. Patient Package Insert

1. Under the (b) (4) section:
   a. Revise the statement from (b) (4) to read "Swallow (b) (4) tablets Whole. (b) (4)
   b. Postmarketing experience indicates that patients may take additional tablets when they see ghost tablets in their stool. Therefore, consider adding a statement similar to (b) (4)
2. Under the "How should I take (b) (4)" section:
   a. Revise the statement from (b) (4) to read "Swallow (b) (4) tablets Whole. (b) (4) Additionally, move this statement so it is the first bullet point in this section.

If you have further questions or need clarifications, please contact Nina Ton, project manager, at 301-796-1648.

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

IRENE Z CHAN on behalf of FOREST R FORD
07/26/2012

IRENE Z CHAN
07/26/2012

SCOTT M DALLAS
07/27/2012

CAROL A HOLQUIST
07/27/2012

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: June 11, 2012

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Dan Brum, RPM
DCRP

Subject: QT-IRT Consult to NDA 203496

This memo responds to your consult to us dated May 9, 2012 regarding sponsor's proposal to evaluate QT effects The QT-IRT received and reviewed the following materials:

- Your consult
- Summary of QTc Safety
- QT-IRT consult (February 2, 2011)
- NDA 203 496 eCTD 2.7. 2 (Summary of Clinical Pharmacology Studies)
- NDA 203 496 eCTD 2.7.4 (Summary of Clinical Safety)
- QT-IRT review for inhaled Trepostinil sodium (Tyvaso, NDA 22387)

QT-IRT Comments for DCRP

DCRP's question/request: Please evaluate the sponsor's proposal and determine if a TQT study should be performed as a requisite of approval.

QT-IRT response: No need to perform a TQT study because there is sufficient information with other formulations.

DCRP's question: Do you recommend any post-approval studies (e.g., TQT PMR)?

QT-IRT response: There is no need for a PMR. Sponsor may conduct a study to get a better label.

DCRP question/request: If you do not recommend a TQT study be done, discuss how you would label the drug.

QT-IRT response:

- **Overall the ECGs information submitted in the QT Briefing Document is sub-optimal for labeling:**

    - Single ECGs were read on-site instead of replicates ECGs being read centrally. Only one study had ECG collected with time-matched PK samples and still the sampling schedule was inadequate to capture a QT effect at Tmax.

- **A TQT study conducted with the inhaled formulation (Tyvaso) showed a QT effect above threshold at a systemic exposure of 1.8 ng/ml.**

    - This exposure is lower than the therapeutic exposures achieved after mean therapeutic dose of the oral formulation (3.9 ng/mL). It should be noted that Tyvaso systemic exposure does not reflect the local concentration in the heart, which is expected to be higher. When results of the TQT study are above the threshold of regulatory concern at therapeutic exposures, QT-IRT advises a warning and precaution statement to be placed in the label. Patients with PAH can be considered at risk for TdP in that they are predominantly female, have heart failure, may have chronic comorbidities and electrolyte disturbances, and may be on many other co-administered drugs. Therefore an appropriate label should be placed to mitigate risk in PAH patients.

    The following warning and precaution statement is a suggestion only.

    - "In a TQT study conducted in healthy volunteers with the inhaled formulation (Tyvaso) a mean effect of 8.5 ms and an upper bound of the 90% CI of 11.3 ms was reported at systemic exposures lower than the therapeutic exposures achieved with the oral formulation."

BACKGROUND

Treprostinil diethanolamine (UT-15C) is a prostacyclin analogue that exhibits antiplatelet aggregation and antiproliferative effects. The compound is under clinical development for the treatment of pulmonary arterial hypertension (PAH). The bioactive species of UT-15C SR is the same as the parenterally administered prostacyclin analogue treprostinil sodium (Remodulin®), treprostinil. The sponsor markets Tyvaso (treprostinil) inhalation solution and Remodulin (treprostinil) for injection (SQ/IV) under NDAs 22387 and 21272, respectively.

QT-IRT reviewed a TQT study of inhaled treprostinil sodium (Tyvaso, NDA 22387) and the results were above the regulatory threshold of regulatory concern (upper bound of 2-sided 90% ΔΔQTcF was 11.2 ms) five minutes post-dose with the 84 µg supra-therapeutic dose. The TQT study demonstrated a shallow but positive concentration-QT relationship.

The sponsor requested to waive a TQT study for UT-15C and QT-IRT granted the waiver and advised to conduct a dedicated QT assessment in patients (QT-IRT consult, February 3 2011).

The approved labeling for Remodulin® includes the following text: "Treprostinil produces vasodilation and tachycardia. Single doses of treprostinil up to 84 mcg by inhalation produce modest and short-lasting effects on QTc, but this is apt to be an artifact of the rapidly changing heart rate. Treprostinil administered by the subcutaneous or intravenous routes has the potential to generate concentrations many-fold greater than those generated via the inhaled route; the effect on the QTc interval when treprostinil is administered parenterally has not been established."

The approved labeling for TYVASO reads as follows: "In a clinical trial of 240 healthy volunteers, single doses of Tyvaso 54 mcg (the target maintenance dose per session) and 84 mcg (supratherapeutic inhalation dose) prolonged the corrected QTc interval by approximately 10 ms. The QTc effect dissipated rapidly as the concentration of treprostinil decreased."

CLINICAL EXPERIENCE

-Systemic Exposure with treprostinil

Figure 1: Treprostinil Comparative Pharmacokinetic in Subjects with PAH

Source: Adapted from sponsor's figure 1-5, eCTD 2.7.2, page 28

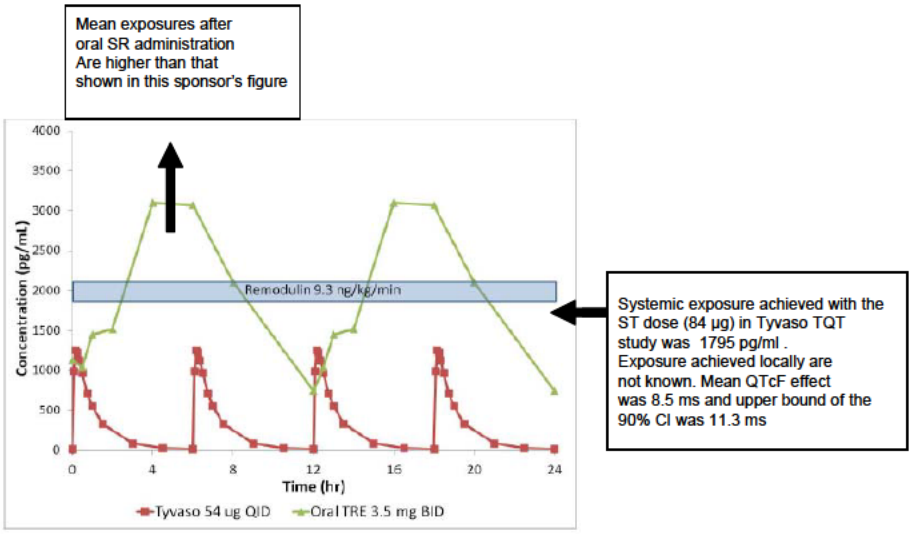
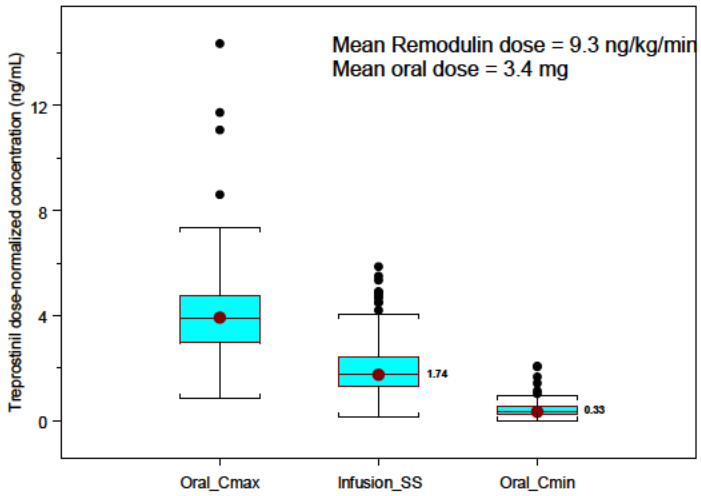


Figure 2. Systemic Exposures Achieved with Oral Tablet Span that Observed with Remodulin®

Source: Drs Hariharan and Brar, Clinical Pharmacology reviewers, Mid-cycle meeting presentation for NDA 203496



Reviewers' comments: Exposures after mean oral dose administration of 3.4 mg are higher than those reported for Remodulin®. Based on the TQT study conducted with the inhaled formulation (Tyvaso) a mean effect of 8.5 ms and an upper bound of the 90% CI of 11.3 ms for the supratherapeutic dose was reported. The systemic exposure achieved with the supratherapeutic dose of Tyvaso, 1.8 ng/mL is lower than the therapeutic exposures achieved after maximal therapeutic doses of the oral formulation. It should be noted that Tyvaso systemic exposure does not reflect local concentration in the heart, which is expected to be higher.

-Clinical Studies Presented in this Briefing Document

Table 1: Clinical Studies

Study Number Study Agent Phase Indication	Study Agent Methods/Dosing	Animal Model/ Subjects (mean age, range in years)	QT Interval/ECG Related Methods
RIN-PH-103† Treprostinil sodium (inhaled) Phase 1	Treatment A: 14 breaths treprostinil sodium placebo and moxifloxacin placebo Treatment B: 14 breaths treprostinil sodium placebo and moxifloxacin 400 mg Treatment C: 9 breaths (54 mcg) treprostinil sodium and moxifloxacin placebo Treatment D: 14 breaths (84 mcg) treprostinil sodium placebo and moxifloxacin placebo	n=241 Healthy adult volunteers (18 – 45)	12-lead ECGs were performed at Baseline (within five minutes prior to dosing and Day 1 at: 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 23.5 hours from dose. A blinded centralized ECG reading lab was used
P01:04/ P01:05‡ Treprostinil sodium (subcutaneous) Phase 3 PAH	UT-15 or placebo at ≤ 1.25 ng/kg/min sc After Week 1 through Week 4: dose escalation by ≤ 1.25 ng/kg/min/week After Week 4: dose escalation by ≤ 2.5 ng/kg/min/week Doses were escalated as clinically indicated based upon AEs and symptoms to a max outlined by week	n=469 Adult PAH patients (~ 45, 9 – 75)	12-lead ECGs were performed on Day 1 of Baseline prior to study drug and Week 12, continuously monitored on Day 2 of Baseline Patients remained hospitalized until a safe initial dose was established at Day 2 of Baseline
TDE-PH-104 UT-15C SR Phase 1	UT-15C SR or placebo BID (every 12 hours) with 240mL of water immediately after breakfast and dinner Cohort 1: 1 mg for 13 days Cohort 2: 1 mg for 7 days, then 2 mg for 6 days, if tolerated Cohort 3: 2 mg or placebo for 7 days, then 3 mg for 6 days, if tolerated	Adult healthy volunteers (28.6, 18-45)	12-lead ECGs were performed at Screening, Baseline (prior to study drug), 3.5 hours after study drug (approximate UT-15 C T_{max}) on days 1, 8, and 13, and on Day 15 Results of ECG were reviewed by the Investigator at Baseline prior to receiving study drug and Day 15 before CRU discharge
TDE-PH-201 UT-15C SR Phase 2 PAH	UT-15C SR after a ≥ 500 Calorie meal with 240 mL of water Cohort 1: 1 mg UT-15C SR x 1 Cohort 2: 2 mg UT-15C SR x 1 (two, 1 mg tablets)	Adult treatment naïve PAH patients (46.6, 35-57) responsive to vasodilator challenge	ECG via continuous telemetry for twenty-four hours following study drug, with parameters recorded at: -0.25 (pre-dose), 0.5, 2, 4, 8, 12, 16, 20, and 24 hours PK sampling completed within five minutes of scheduled time: -0.25 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 hours

TDE-PH-301 UT-15C SR Phase 3 PAH	UT-15C SR or placebo BID (every 12 hours) immediately after (~10 minutes) a breakfast and dinner of ≥ 500 Calories Initial: 1 mg UT-15C SR or placebo BID with dose escalation by 1 mg every 5 days Final: 0.5 mg UT-15C SR or placebo BID with dose escalation by 0.5 mg every 3 days Doses were escalated as clinically indicated based upon AEs and symptoms of PAH to a maximum of 16 mg BID	n=350 PAH subjects (50, 15 – 75) mainly treated (45%) with combination ERA and PDE5-I background therapy (for at least 90, and on stable dose [s] for at least 30 days)	12-lead ECGs were performed at Baseline (within 48 hours) prior to study drug and Week 16 (or at Premature Termination) Parameters collected included heart rate, PR and QT interval, QRS duration, and any abnormalities of at least 5 QRS complexes
TDE-PH-302 UT-15C SR Phase 3 PAH	UT-15C SR or placebo BID (every 12 hours) immediately after (~10 minutes) a breakfast and dinner of ≥ 500 Calories Initial: 1 mg UT-15C SR or placebo with dose escalation by 1 mg every 5 days Final: 0.25 mg UT-15C SR or placebo with dose escalation by 0.25 mg every 3 days; after first four weeks, dose escalation by either 0.25 or 0.5 mg every 3 days Doses were escalated as clinically indicated based upon AEs and symptoms of PAH to a maximum of 12 mg BID	n=349 Treatment naïve PAH patients (41.2, 12 – 73)	12-lead ECGs were performed at Baseline (within 48 hours) prior to study drug and Week 12 (or at Premature Termination) Parameters collected included heart rate, PR and QT interval, QRS duration, and any abnormalities of at least 5 QRS complexes

TDE-PH-304 UT-15C SR Phase 3 (open label) PAH	UT-15C SR BID (every 12 hours) immediately after (~10 minutes) a breakfast and dinner of ≥ 500 Calories Placebo previously, initial: 1 mg UT-15C SR with dose escalation by 1 mg Placebo previously, final: 0.25 mg UT-15C SR with dose escalation by either 0.25 or 0.5 mg every 3 days UT-15C SR previously: initiate at the same dose received at the final visit of the preceding study Doses were maximized with no upper dosing limit specified	n=824 PAH patients (47, 12-76) that completed participation in or were on placebo and discontinued due to clinical worsening during eligible study protocols	NA, ECG data were not collected outside of standard of care
TDE-PH-306 UT-15C SR Phase 3 PAH	One UT-15C SR dose immediately after (~10 minutes) a breakfast of ≥ 500 Calories	n=74 PAH patients (44.4, 16-67) on a stable UT-15C SR dose for at least five days with last dose taken 11 – 13 hours prior	Pharmacokinetic sampling was to be completed within five minutes of scheduled time: -10 minutes (pre-dose), 0.5, 1, 2, 4, 6, 8, and 12 hours
TDE-PH-308 UT-15C SR Phase 3 PAH	UT-15C SR or placebo BID (every 12 hours) immediately after (~10 minutes) a breakfast and dinner of ≥ 500 Calories Initial: 0.25 mg UT-15C SR or placebo with dose escalation by 0.25 or 0.5 mg every 3 days Doses were escalated as clinically indicated based upon AEs and symptoms of PAH to a maximum of 16 mg BID	n=310 PAH patients (51, 18-76) mainly treated (43%) with a PDE5-I alone as background therapy (taken for at least 90, and on stable dose[s] for at least 30 days)	12-lead ECGs were performed at Baseline (within 48 hours) prior to study drug and Week 16 (or at Premature Termination) Parameters collected included heart rate, PR and QT interval, QRS duration, and any abnormalities of at least 5 QRS complexes
TDE-DU-201 UT-15C SR Phase 2b Scleroderma Digital Ulcers	UT-15C SR or placebo BID (every 12 hours) immediately after (~10 minutes) morning and evening meals of ≥ 500 Calories Initial: 0.25 mg UT-15C SR or placebo with dose escalation by 0.25 every 2-3 days; may be escalated by 0.5 mg once 5 mg BID is reached Doses were escalated to a maximum of 16 mg BID or the patient's maximum tolerated dose	n=147 Adult (48.8, 19 – 82) systemic sclerosis patients with at least one active digital ulcer	12-lead ECGs were performed at Baseline prior to study drug and Week 20 (or at Premature Termination) Parameters collected included heart rate, PR and QT interval, QRS duration, and any abnormalities of at least 5 QRS complexes

*NDA 22-387, Sequence 0000, Module 4.2.1.3, WIL-583001
**NDA 22-387, Sequence 0000, Module 4.2.1.1, TPZZ-90-0085
†NDA 22-387, Sequence 0000, Module 5.3.4.1, RIN-PH-103
‡NDA 22-387, Sequence 0000, Module 5.3.5.1, P01-04-05
¤At the time of submission, 1259DU16.003 data were preliminary; a final report will be submitted when available and a draft report upon request

Source: QTc Briefing Document, Table 5-2

-Tolerability in Healthy Subjects

"Single doses between 1 and 2.5 mg UT-15C SR may be reasonably tolerated, but cause substantial prostacyclin-related systemic adverse effects in healthy volunteers that invariably limit dosing. A substantial number of dose decreases or dropouts may occur at doses starting at 2 mg BID or with dose escalation of 1 mg after seven days in healthy volunteers."

"TDE-PH-104: A 14-Day Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study Evaluating the Pharmacokinetics and Safety of a Sustained Release Tablet of UT-15C (treprostinil diethanolamine) Administered in Fixed and Escalating Doses in Healthy Volunteers

"This was a dose escalating study with ECGs collected at the approximate Tmax of UT-15C SR, 3.5 hours after dosing). UT-15C SR or placebo was administered BID for thirteen days to three cohorts of healthy volunteers (n=12, each). The number and severity of AEs reported increased with escalating dose. Specifically, 78%, 89%, and 100% of subjects receiving UT-15C SR reported AEs in Cohort 1 (1 mg administered BID for thirteen days), Cohort 2 (1 mg BID for seven days, followed by 2 mg BID for six days), and Cohort 3 (2 mg BID for seven days followed by 3 mg BID for six days), respectively. Furthermore, a dose reduction was required in six subjects in Cohorts 2 and 3 due to intolerable AEs including: headache, dizziness, nausea, and vomiting."

Source: QTc Briefing Document, page 17

"Intensive collection was to be as follows: on Day 1, PK sampling began with a pre-dose sample prior to study drug administration. After study drug was taken, 15 PK specimens were collected within the next 36 hours at the following time points: 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 30 and 36 hours after study drug administration. Study drug was not administered again until the evening dose on Day 2. The 36 hour PK collection time point was collected prior to the evening dose of study drug on Day 2. On Day 13, PK sampling began with a pre-dose sample prior to study drug administration. After study drug was taken, 17 PK specimens were collected within the next 48 hours at the following time points: 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 30, 36, 42 and 48 hours after study drug administration. The morning dose on Day 13 was the last dose of the study."

Source: QTc briefing document, page 30

Reviewer's comments:

- *Tolerability in healthy subjects limits the use of high therapeutic doses and supratherapeutic doses of treprostinil SR. Results from study TDE-PH-104: UT-15C SR suggest that 2 mg BID for seven days followed by 3 mg BID for six days is the maximal tolerated dose in healthy volunteers.*

- *ECGs were collected at day 1, 8 and 13 at the approximate Tmax of UT-15C SR, (only one time point: 3.5 hours after dosing). Despite intensive PK sampling was performed at day 1, 2 and 13 it was not time-matched with ECG collection. -*

"TDE-PH-201: A Dose-Range-Finding, Safety, and Pharmacokinetic Study Assessing the Hemodynamic Effects of UT-15C (treprostinil diethanolamine) SR in Subjects with Pulmonary Arterial Hypertension. This multi-center, open-label, dose-range finding study was designed to assess the safety, acute hemodynamic effects, dose response, and pharmacokinetic profile of UT-15C SR following a single dose in patients with PAH. Eight patients were enrolled into study Cohort 1 (n=5) or 2 (n=3), and all but one at the 1 mg dose level were included in the pharmacokinetic analyses. The mean AUC0-t (CV%) of treprostinil at the 2 mg dose level was approximately 2.6-fold higher than that achieved at the 1 mg dose level: 15.57 (17.4) and 6.09 ng•hr/mL (47.5), respectively. Similar results were observed for AUC0-24 (15.57 [17.4] and 6.13 ng•hr/mL [48.0], respectively). The mean Cmax (CV%) of treprostinil at the 2 mg dose level (1.95 ng/mL [24.3%]) was approximately 1.9-fold higher than that observed at the 1 mg dose level (1.05 ng/mL [66.7]). Also, median (range) Tmax occurred later at the 2 mg dose level (8 hours [2-16 hours]) than at the 1 mg dose level (6 hours [3-8 hours])."

"ECG monitoring was performed prior to administration of UT-15C SR and during the Treatment Phase via telemetry. Although monitored continuously for subject safety, ECG parameters were recorded at the following time points: pre-dose and 0.5, 2, 4, 8, 12, 16, 20, and 24 hours after the dose of UT-15C SR."

"As shown in Table 9-5, the mean change in QTcF interval from Baseline across time points ranged from -14.0 to 24.4 ms and -48.6 to 45.3 ms in Cohorts 1 and 2, respectively. Time-averaged mean changes were: -0.3, 24.5, and 9.0 ms for Cohort 1, 2, and combined, respectively."

"Of note, there were no discernable trends of QTcF interval prolongation when assessed at approximate Tmax or throughout the twenty-four-hour observation period."

Table 2: TDE-PH-201 QTcF Interval Analysis Summary Statistics

Time Point	QTcF Category (ms)	Cohort 1 n=3-5		Cohort 2 n=1-3		Combined n=4-8	
		QTcF	Change	QTcF	Change	QTcF	Change
Baseline	Mean	425.0	NA	346.7	NA	391.4	NA
	SD	59.7	NA	61.1	NA	69.1	NA
	Median	432.0	NA	404.3	NA	419.1	NA
30 minutes	Mean	445.5	2.9	426.7	-5.3	439.2	0.2
	SD	56.1	22.4	16.3	22.8	45.1	20.6
	Median	424.8	2.6	426.7	-5.3	424.8	2.6
2 hours	Mean	439.6	-14.0	435.0	3.1	438.1	-8.3
	SD	37.2	61.2	19.8	19.3	30.2	49.0
	Median	444.5	-20.0	435.0	3.1	440.9	1.6
4 hours	Mean	453.6	10.5	424.0	-8.0	445.2	5.2
	SD	35.1	44.7	2.0	41.1	32.1	41.2
	Median	454.4	25.5	424.0	-8.0	425.4	21.1
8 hours	Mean	450.5	7.4	411.0	-48.6	444.0	-1.9
	SD	29.6	42.9	NA	NA	31.0	44.7
	Median	451.0	12.8	411.0	-48.6	448.7	9.6
12 hours	Mean	444.4	-9.2	386.6	3.3	419.6	-3.8
	SD	13.2	58.3	53.4	45.2	44.6	49.3
	Median	441.4	7.5	412.1	18.2	432.5	18.2
16 hours	Mean	445.3	-8.3	402.5	19.2	427.0	3.5
	SD	22.8	47.4	25.1	65.1	31.5	52.5
	Median	442.7	10.8	416.6	12.3	421.7	12.3
20 hours	Mean	445.0	24.4	428.6	45.3	436.8	34.9
	SD	17.9	8.2	5.8	94.4	14.9	61.0
	Median	437.9	20.6	426.8	22.5	433.4	21.5
24 hours	Mean	444.4	-12.1	416.6	12.3	437.5	-6.0
	SD	36.2	48.3	NA	NA	32.7	41.2
	Median	424.0	4.0	416.6	12.3	423.5	8.2
Time-averaged	Mean	NA	-0.3	NA	24.5	NA	9.0
	SD	NA	38.9	NA	63.7	NA	46.8
	Median	NA	7.3	NA	16.3	NA	11.8

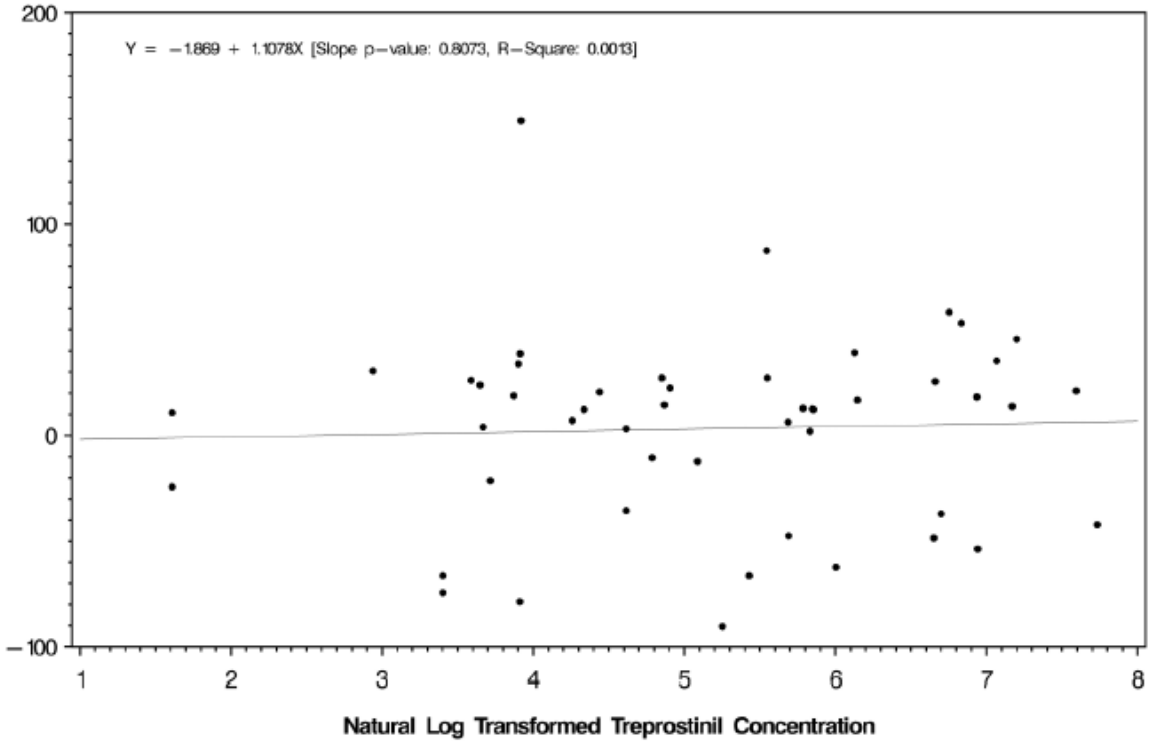
Source: Table 9-5, QTc Briefing Document, Page 56

Table 3: TDE-PH-201 QTcF Interval Categorical Summaries

Time Point	QTcF Category (ms)	Cohort 1 n n=3-5	Cohort 2 n n=1-3	Combined n n=4-7
Baseline	≥ 500	1	0	1
0.5 – 24 hours	≥ 500	1	0	1
	< 30 change from Baseline	25	14	39
	30 ≤ change from Baseline < 60	7	1	8
	≥ 60 change from Baseline	0	2	2

Source: Table 9-6, QTc Briefing Document, Page 57

Figure 3: TDE-PH-201 Change from Baseline in QTcF Interval (ms) as a Function of Natural Log Transformed Treprostinil Plasma Concentration (pg/mL)



Source: QTc briefing document, Figure 9-1, page 57.

Reviewer's comments: Study TDE-PH-201 is a multi-center dose-range, open-label study. Single ECGs were collected with time-matched PK samples at pre-dose and 0.5, 2, 4, 8, 12, 16, 20, and 24 hours after administration of a 1- or 2-mg dose of UT-15C SR. Assuming a T_{max} for the 1-mg dose between 4 to 6 hours, time-points of ECG collection may not be adequate to capture a QT effect at C_{max}. Eight subjects were enrolled in this study and single ECGs were read on-site. Doses tested were low/intermediate (1 and 2 mg, mean oral dose is 3.4 mg).

"TDE-PH-301: A 16-Week, International, Multicenter, Double-Blind, Randomized, Placebo-Controlled Comparison of the Efficacy and Safety of Oral UT-15C Sustained Release Tablets in Combination with an Endothelin Receptor Antagonist and/or a Phosphodiesterase-5 Inhibitor in Subjects with Pulmonary Arterial Hypertension.

"This sixteen-week, multicenter, double-blind, randomized, parallel-group study was designed to assess the effect of UT-15C SR on exercise capacity in PAH patients compared to placebo.

"Twelve-lead ECGs were recorded after at least 5 minutes rest in the semi-recumbent position at Baseline prior to starting study drug and at the end of the Treatment Phase at Week 16. Recordings included lead II as a rhythm strip and contained at least 5 QRS complexes. Electrocardiogram parameters collected (after at least 5 minutes rest) included heart rate, PR interval, QT interval, QRS duration and any clinically significant abnormalities.

“Three-hundred fifty subjects received a dose of study drug during the course of this study and were included in the safety evaluation.

“The majority of subjects received an initial starting dose of 1 mg twice daily (255 subjects). With the implementation of Amendment 4, 94 subjects received a starting dose of 0.5 mg twice daily and one subject received a starting dose of 0.25 mg twice daily. The mean dose ± SD of UT-15C achieved during the study at Week 16 was 3.5 ± 2.9 mg (range of 0.25 – 16 mg) twice daily as compared to 11.0 ± 5.3 (range of 0.5 – 23 mg) in the placebo group.

Table 4: Summary of ECG Results

Variable	Statistic or Category	Treatment: Active	Treatment: Placebo
Heart Rate	n	173	174
	Mean	77.9	78.6
	SD	13.0	12.2
	SE	1.0	0.9
	Median	77.0	78.5
	Lower Qrtl	69.0	71.0
	Upper Qrtl	85.0	86.0
	Min.	46	51
	Max.	120	116
PR Interval	n	168	171
	Mean	169.3	172.5
	SD	28.0	29.3
	SE	2.2	2.2
	Median	169.0	168.0
	Lower Qrtl	151.0	152.0
	Upper Qrtl	182.5	188.0
	Min.	91	80
	Max.	278	294
QT Interval	n	173	174
	Mean	397.7	399.6
	SD	44.0	43.6
	SE	3.3	3.3
	Median	400.0	400.0
	Lower Qrtl	370.0	376.0
	Upper Qrtl	428.0	422.0
	Min.	220	104
	Max.	496	500
QTc (Fridericia)	n	173	174
	Mean	431.3	435.0
	SD	42.9	42.0
	SE	3.3	3.2
	Median	429.6	433.6
	Lower Qrtl	408.8	416.2
	Upper Qrtl	456.2	455.3
	Min.	220	102
	Max.	600	582
QTc (Bazett)	n	173	174
	Mean	449.7	454.3
	SD	47.4	45.5
	SE	3.6	3.4
	Median	451.8	455.1
	Lower Qrtl	425.8	432.0
	Upper Qrtl	468.1	475.8
	Min.	220	100
	Max.	659	641
QRS Duration	n	173	174
	Mean	98.0	102.0
	SD	24.0	36.5
	SE	1.8	2.8
	Median	94.0	94.0
	Lower Qrtl	86.0	85.0
	Upper Qrtl	102.0	108.0
	Min.	28	43
	Max.	225	416

Source: CSR, Table 14.3.6

Reviewer's comments: Mean dose at week 16 was 3.5 mg b.i.d.. Although there is no QT signal reported, data are sub-optimal i.e., single ECGs were obtained, without centrally reading and ECG sampling was sparse (baseline and week 16).

"TDE-PH-302: A 12-Week, International, Multicenter, Double-Blind, Randomized, Placebo-Controlled Comparison of the Efficacy and Safety of Oral UT-15C Sustained Release Tablets in Subjects with Pulmonary Arterial Hypertension.

"Three hundred forty-nine subjects (233 UT-15C and 116 placebo) were randomized and subsequently received at least one dose of study drug. UT-15C treated patients (of the ITT population) achieved a Week 12 mean ± SD dose of 3.6 ± 2.2 mg BID, a median dose of 3.25 mg BID (range of 0.25 to 12 mg BID), and a most common maximum dose of 2.125 to 4 mg BID. Patients were exposed to UT-15C SR for a mean ± SD of 76.1 ± 24.5 days (range of 2 to 146 days). Pharmacokinetic data were not collected during the study

"Table 9-15 and Table 9-16 display results from central tendency and categorical QTcF analyses of TDE-PH-302 ECG safety data, respectively. ECG data collected forty eight hours prior to dosing and at Week 12 of UT-15C SR treatment were utilized to create change from Baseline assessments. Mean, median, and variability of the QTcF interval were similar in both treatment groups and remained relatively unchanged following twelve weeks of treatment. Categorical threshold changes were consistent across groups. There were no discernable differences or trends seen between treatment groups.'

Table 5: TDE-PH-302 QTcF Interval Analysis Summary Statistics

QTcF Interval Category (ms)	UT-15C n=182		Placebo n=97	
	Baseline	Week 12	Baseline	Week 12
Mean (SD)	424.1 (39.2)	426.7 (36.2)	423.2 (34.6)	427.4 (34.5)
Median (range)	424.2 (175-554)	424.0 (340-591)	422.0 (306-526)	426.3 (360-594)
Mean change from Baseline (SD)	NA	2.6 (38.9)	NA	4.2 (39.6)
Median change from Baseline (range)	NA	1.2 (-156-244)	NA	0.2 (-89-189)

Source: QTc Briefing document, Table 9-15

Table 6: TDE-PH-302 QTcF Interval Categorical Summaries

QTcF Interval Category (ms)	UT-15C n (%) n=182		Placebo n (%) n=97	
	Baseline	Week 12	Baseline	Week 12
≥ 500	5 (3%)	9 (5%)	2 (2%)	3 (3%)
< 30 change from Baseline	NA	156 (86%)	NA	81 (84%)
30 ≤ change from Baseline < 60	NA	18 (10%)	NA	9 (9%)
≥ 60 change from Baseline	NA	8 (4%)	NA	7 (7%)

Source: QTc Briefing document, Table 9-16

Mean dose at week 12 was 3.6 mg BID. Although there is no QT signal reported, data are sub-optimal i.e., single ECGs were obtained, without centrally reading and ECG sampling was sparse (baseline-8 hours before dosing- and week 12).

"TDE-PH-306: A Pharmacokinetic Study of UT-15C in Subjects with Pulmonary Arterial Hypertension

The objective of this multicenter, open-label, TDE-PH-304 substudy was to evaluate the pharmacokinetic profile of UT-15C SR in PAH patients. Seventy-four patients on chronic therapy with UT-15C were selected to have serial plasma sampling over a twelve-hour period following a dose of UT-15C, seventy of which were included in the analysis. The median dose of UT-15C SR administered was 3.6 mg BID, with a range of 0.5 to 16 mg BID. Ninety percent of patients were on a dose ≤ 7 mg BID.'

Reviewer's comments: ECG data were not collected.

Thank you for requesting our input into the development of this product under NDA. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONICA L FISZMAN
06/11/2012

NITIN MEHROTRA
06/11/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 203496 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: [redacted] (b) (4) (proposed) Established/Proper Name: treprostinil diethanolamine Dosage Form: sustained release tablets Strengths: 0.125, 0.25, [redacted] (b) (4) 1, and 2.5 mg		
Applicant: United Therapeutics Agent for Applicant (if applicable):		
Date of Application: December 24, 2011 Date of Receipt: December 27, 2011 Date clock started after UN:		
PDUFA Goal Date: October 27, 2012 (Saturday)	Action Goal Date (if different): October 26, 2012	
Filing Date: February 25, 2012	Date of Filing Meeting: February 7, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 2, 3		
Proposed indication(s)/Proposed change(s): pulmonary arterial hypertension		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 71537	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	X			Treprostinil is orphan-designated for PAH. Both Remodulin and

				Tyvaso were orphan designated and both received orphan exclusivity. United Therapeutics is the sponsor of both products.

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	Note: United Therapeutics is the sponsor of this NDA.
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: **3 years** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			X	Assumes diethanolamine has no abuse potential.

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		X		Orphan designation
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***			X	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]				
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			(b) (4)
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the DCRMSRMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			Will include labeling comments in filing letter.

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP (formerly DDMAC)?	X			
MedGuide, PPI, IFU (plus PI) consulted to OMP/Patient Labeling Team? (*send WORD version if available*)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X			IRT QT
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** November 9, 2005 (EOP 1 meeting) ***If yes, distribute minutes before filing meeting***				EOP 1 meeting minutes dated 11/23/05

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** November 16, 2011 ***If yes, distribute minutes before filing meeting***	X			pre-NDA meeting minutes dated 11/30/11
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 7, 2012

BLA/NDA/Supp #: NDA 203496

PROPRIETARY NAME: (b) (4) (proposed)

ESTABLISHED/PROPER NAME: treprostinil diethanolamine

DOSAGE FORM/STRENGTH: sustained-release tablets

APPLICANT: United Therapeutics

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): pulmonary arterial hypertension (PAH)

BACKGROUND: On December 27, 2011, we received NDA 203496 for a new dosage form (new salt form) of treprostinil diethanolamine SR tablets. The proposed trade name is (b) (4)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Daniel Brum	Y
	CPMS/TL:	Edward Fromm	Y
Cross-Discipline Team Leader (CDTL)	Abraham Karkowsky		Y
Clinical	Reviewer:	Tsvi Aranoff	Y
	TL:	Abraham Karkowsky	CDTL
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Sudharshan Hariharan	Y
	TL:	Raj Madabushi	Y
Pharmacometrics	Reviewer:	Satjit Brar	Y
	TL:	Pravin Jadhav	
Biostatistics	Reviewer:	John Lawrence	Y
	TL:	Jim Hung	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Xavier Joseph	
	TL:	Tom Papoian	Y
Statistics (carcinogenicity)	Reviewer:	To be determined	N
	TL:	TBD	
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Shastri Bhamidipati	Y
	TL:	Kasturi Srinivasachar	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA	Reviewer:	Forest (Ray) Ford	N
	TL:	Irene Chan	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		

	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	Sharon Gershon	N
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Pharmaceutics	Akm Khairuzzaman		Y
Office of Prescription Drug Products (OPDP)	Emily Baker and Zarna Patel		N
Patient Labeling Review (OMP)	Latonia Ford Barbara Fuller (TL)		N
Other attendees	Norman Stockbridge, Monica Fiszman (IRT-QT)		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**:	☐ YES Date if known: ☒ NO

If no, for an original NME or BLA application, include the reason. For example: o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☒ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Norman Stockbridge

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐ The application is unsuitable for filing. Explain why:

☐ The application, on its face, appears to be suitable for filing.

Review Issues:

☐ No review issues have been identified for the 74-day letter.

☒ Review issues have been identified for the 74-day letter. List (optional):

Alcohol-induced dose dumping testing

Please evaluate the alcohol-induced dose dumping of your modified-release (MR) product using the highest and lowest strengths. Conduct the alcohol-induced dose dumping testing *in vitro*, and depending on the results you may need to follow-up with an *in vivo* alcohol-induced dose dumping study. Please consider the following points:

- Dissolution testing should be conducted using the optimal dissolution apparatus and agitation speed. Dissolution data should be generated from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.
- The following alcohol concentrations for the *in vitro* dissolution studies are recommended: 0%, 5%, 10%, 20%, and 40%.
- The shape of the dissolution profiles should be compared to determine if the modified-release characteristics are maintained, especially during the first 2 hours.
- The f2 values assessing the similarity (or lack thereof) between the dissolution profiles should be estimated using 0% alcohol as the reference standard.

The report with the complete data (e.g., individual, mean, SD, comparison plots, f2 values) collected during the evaluation of the *in vitro* alcohol-induced dose dumping study should be provided to FDA for review and comment.

	Nonclinical testing for pharmacobezoar formation We recommend that you examine the potential for treprostinil diethanolamine sustained-release tablets to cause local irritation if it is trapped in a diverticulum or is otherwise non-motile. Given that treprostinil sustained-release tablets produced severe GI lesions in dogs, similar to that seen with other prostacyclins (Wohrmann T et al., Exp. Toxic. Pathol. 1994; 46:71-73), it is possible that if such a concretion of tablets were to form in the GI tract in patients and release treprostinil locally over a prolonged period, then the potential for GI irritation or toxicity may be substantially increased. Options for such a study may include using a rabbit ligated intestinal loop model or other appropriate model. The study should be placebo-controlled and include a known gastric irritant as a positive control (e.g., potassium chloride sustained-release tablets). *Clinical pharmacology* Please submit the analysis datasets used to generate the dose- and concentration-response information and plots presented in section 1.2.5.1 within the "Summary of Clinical Pharmacology Studies". All analysis codes or control streams, output listings and scripts used to generate plots should be provided. Files should be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt). *Labeling* Several deficiencies will be included in filing letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)

☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Daniel Brum	February 16, 2012
Regulatory Project Manager	Date
Edward Fromm	
Chief, Project Management Staff	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DANIEL BRUM
02/16/2012