CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203496Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2013
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER: 203-496

NAME OF APPLICANT/NDA HOLDER: United Therapeutics Corporation

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME): To Be Determined

ACTIVE INGREDIENT(S)	STRENGTH(S)
treprostinil diolamine	0.125mg, 0.25mg, 1.0mg, 2.5mg

DOSAGE FORM: Extended Release Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
8,497,393	07/30/2013	12/15/2028

d. Name of Patent Owner	Address *(of Patent Owner)*	
United Therapeutics Corporation	55 T.W. Alexander Drive	
	City/State: Research Triangle Park, North Carolina	
	ZIP Code: 27709	FAX Number *(if available)*: (919) 313-1298
	Telephone Number: (919) 485-8350	E-Mail Address *(if available)*: dbunce@unither.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☐ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☒ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☒ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
dbunce@unither.com Digitally signed by dbunce@unither.com DN: cn=dbunce@unither.com, email=dbunce@unither.com Date: 2013.08.19 15:43:05 -04'00'	19 August 2013

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Dean Bunce, Executive Vice President Regulatory Affairs and Compliance, United Therapeutics Corporation	
Address 55 TW Alexander Drive	City/State Research Triangle Park/NC
ZIP Code 27709	Telephone Number (919)485-8350
FAX Number *(if available)* (919) 313-1298	E-Mail Address *(if available)* dbunce@unither.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html.*

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 203496 SUPPL # HFD # 110

Trade Name Orenitram

Generic Name Treprostinil diethanolamine

Applicant Name United Therapeutics Corporation

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES X NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES X NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES X NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years.

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO X

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO X

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES X NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 22387 Tyvaso

NDA# 21272 Remodulin

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO X

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES X NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES X NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO X

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES ☐ NO X

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study #302

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO X

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO X

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study #302

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 71537 YES X ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in

interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO X

If yes, explain:

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Name of person completing form: Wayne Amchin
Title: Senior Consumer Safety Officer, Division of Cardiovascular and Renal Products
Date: 12-19-13

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

APPEARS THIS WAY ON ORIGINAL

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

NORMAN L STOCKBRIDGE
12/20/2013

DEBARMENT CERTIFICATION

NDA 203496

(b) (4) (treprostinil diethanolamine) Sustained Release Tablets

United Therapeutics Corporation 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.

{See Appended Electronic Signature Page}

Dean Bunce
EVP, Regulatory Affairs and Compliance

Debarment Certification Orginal NDA

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
Dean Bunce	Regulatory Affairs Approval	21-Dec-2011 19:25 GMT-05

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 203496 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Orenitram Established/Proper Name: treprostinil Dosage Form: Tablets		Applicant: United Therapeutics Corporation Agent for Applicant (if applicable):
RPM: Wayne Amchin		Division: DCRP

NDAs and NDA Efficacy Supplements:

NDA Application Type: X 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(For additional information regarding 505(b)(2)s, please refer to http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/RegulatoryAffairsTeam/ucm027499.htm)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 2/16/2014	X AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR on 10/23/12, CR on 3/22/13

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: X Standard ☐ Priority
Chemical classification (new NDAs only): 3

☐ Fast Track
☐ Rolling Review
X Orphan drug designation
☐ Breakthrough Therapy designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
- ☐ Accelerated approval (21 CFR 314.510)
- ☐ Restricted distribution (21 CFR 314.520)

Subpart I
- ☐ Approval based on animal studies

BLAs: Subpart E
- ☐ Accelerated approval (21 CFR 601.41)
- ☐ Restricted distribution (21 CFR 601.42)

Subpart H
- ☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS:
- ☐ MedGuide
- ☐ Communication Plan
- ☐ ETASU
- ☐ MedGuide w/o REMS
- ☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	X Yes ☐ No
• Press Office notified of action (by OEP)	☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	**X** None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	X No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	X No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	X No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	**X** Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[4]	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	X Included
Documentation of consent/non-consent by officers/employees	X Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) : AP 12/20/13, CR on 10/23/12, CR on 3/22/13
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	12/18/13 (sponsor submission)
• Original applicant-proposed labeling	12/27/11
• Example of class labeling, if applicable	Included

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide X Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	11-12-13
• Original applicant-proposed labeling	12-27-12
• Example of class labeling, if applicable	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	10-29-13
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	Granted 12-12-13; Reviewed 11/27/13, 9/4/12, 5/18/12; Denied 9/4/12. 5/25/12
❖ Labeling reviews *(indicate dates of reviews and meetings)*	X RPM 12/20/13 X DMEPA 11/21/13, 10/17/12, 7/26/12 X DMPP/PLT (DRISK) 11/21/13 X OPDP (DDMAC) 11/13/13, 11/21/13; 10/18/13 X SEALD 12/13/13 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	RPM Filing Review 2/16/12; Statistics Filing Review 2/15/12; Clinical Filing Review 2/9/12; Clinical Pharmacology Filing Review 2/9/12; Product Quality Filing Review 1/19/12; Pharmacology/Toxicology Filing Review 1/20/12 X Not a (b)(2) X Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	X Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes X No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes X No ☐ Not an AP action

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: treprostinil is orphan designated • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☐ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	X Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	Included
❖ Internal memoranda, telecons, etc.	N/A
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	X No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	X N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 11/16/2011
• EOP2 meeting *(indicate date of mtg)*	X No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	11/9/2005 (EOP 1)
❖ Advisory Committee Meeting(s)	X No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	X None
Division Director Summary Review *(indicate date for each review)*	☐ None 12/20/2013, 3/22/2013, 10/23/2012
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 3/5/2013, 10/18/2012
PMR/PMC Development Templates *(indicate total number)*	X None
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See CDTL memo
• Clinical review(s) *(indicate date for each review)*	9/16/13, 3/05/13, 10/18/12, 10/12/12 (joint w/stats)
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	X None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See 10/03/12 joint Clinical/Stats Review page 9.
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	X None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	X Not applicable

[6] Filing reviews should be filed with the discipline reviews.

❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	X None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 2/20/13, 12/5/12, 10/31/12, 10/3/12
Clinical Microbiology X None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	X None
Clinical Microbiology Review(s) *(indicate date for each review)*	X None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None 10/10/12, 10/3/12 (joint with Clinical)
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None 10/10/12, 10/3/12 (joint with Clinical)
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	X None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None 10/28/12, 10/2/12
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 10/28/12, 10/2/12
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	X None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	X None
• Supervisory Review(s) *(indicate date for each review)*	☐ None 3/21/13, 10/3/12
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 10/3/12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	X None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc 6/1/12
❖ ECAC/CAC report/memo of meeting	☐ None 6/28/12 Included in P/T review, pages 46-59
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	X None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	X None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 12/10/13, 3/22/13, 10/19/12, 8/28/12, 1/19/12
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 12/10/13, 3/22/13, 10/19/12, 8/28/12, 1/19/12
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	X Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None Biopharm 8/30/12
❖ Environmental Assessment (check one) (original and supplemental applications)	
X Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See CMC review 12/10/13, page 7
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: See 12/10/13 CMC Review, page 16 and 12/9/13 EES email **X** Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested X Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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/s/

WAYNE S AMCHIN
12/20/2013

NORMAN L STOCKBRIDGE
12/20/2013

PLR format and language edits
to PI for NDA 203496

We are reviewing your NDA, and we have the following edits to the PI to address PLR format requirements and language changes to the PI. By noon, December 19, 2013, submit an amendment to your NDA that addresses the PLR format issues discussed below and the track change edits shown in the attached PI.

1. Highlights (HL):
    a. Highlights 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. The top margin is less than ½ inch. Correct the top margin to ½ inch.
    b. White space should be present before each major heading in HL. There must be no white space between the HL Heading and the HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approvoal. The white space is missing before most major headings in the HL, except Indications and Usage and Dosage Forms and Strenghts. Add in the white space before all the other major headings in the HL.
    c. 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 reference to (1.1) is missing for the last paragraph under Indications and Usage in the HL.
    d. The name of the drug product in the bolded HL Limitation Statement must appear in UPPER CASE letters. Correct the drug name to all UPPER CASE.
    e. In the ADVERSE REACTIONS section of HL, delete the language "via e-mail at drugsafety@unither.com, or contact".
    f. In the statement in HL "***See 17 for Patient Counseling Information and FDA-approved patient labeling", change the words Patient Counseling Information to all UPPER CASE***.
    g. At the end of HL, change the date to ***Revised: 12/2013***.

2. In the **TABLE OF CONTENTS (TOC):**
    a. The header FULL PRESCRIBING INFORMATION: CONTENTS* should be bolded.
    b. All subsection headings should be in indented and not bolded and in title case (first letter of all words are capitalized except the first letter of prepositions, articles, or conjunctions. Change subsection headings 16.1 and 16.2 from UPPER CASE to Title Case.
    c. The section and subsection headings in the TOC must match the section and subsection headings in the FPI. The headings for subsection 7.3 includes "on Treprostinil" in the TOC, but this phrase is not in the subsection heading in the FPI.
    d. The subsection heading 5.3 in the TOC has a dash after 5.3. Delete the dash.

Provide your response by email to me at wayne.amchin@fda.hhs.gov, followed in close proximity by an official submission to NDA 203496.

If you have any questions me at (301) 796-0421.

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/s/

WAYNE S AMCHIN
12/17/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 203496

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

United Therapeutics Corporation
55 TW Alexander Drive
PO Box 14186
Research Triangle Park, NC 27709

Attention: Rex Mauthe, MBA
Associate Vice President, Regulatory Affairs

Dear Mr. Mauthe:

Please refer to your resubmission of your new drug application dated and received August 16, 2013, submitted under section 505 (b)(1) of the Federal Food, Drug, and Cosmetic Act for Treprostinil Extended-Release Tablets, 0.125 mg, 0.25 mg, 1mg, and 2.5 mg.

We also refer to your correspondence, dated and received September 13, 2013, requesting review of your proposed proprietary name, Orenitram. Also refer to your amendment, dated and received November 27, 2013, with a response to our request for product characteristic information. We have completed our review of the proposed proprietary name, Orenitram and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your September 13, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cherye Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Wayne Amchin at (301)796-0421.

Sincerely,

{See appended electronic signature page}
Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
12/12/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203496

MEETING MINUTES

United Therapeutics Corp.
Attention: Mr. Dean Bunce
EVP, Regulatory Affairs & Compliance
55 TW Alexander Drive
P.O. Box 14186
Research Triangle Park, NC 27709

Dear Mr. Bunce:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for treprostinil diolamine 0.125 mg, 0.25 mg, (b) (4) 1 mg, and 2.5 mg extended-release tablets.

We also refer to the meeting between representatives of your firm and the FDA on December 21, 2012. The purpose of the meeting was to discuss the clinical, statistical, and clinical pharmacology issues noted in the complete response letter dated October 23, 2012.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301)796-0578.

Sincerely,

{See appended electronic signature page}

Daniel Brum, PharmD, MBA, BCPS, RAC
Senior Regulatory Project Manager
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting minutes
Sponsor's slide presentation

MEMORANDUM OF MEETING MINUTES

Meeting Type:	A
Meeting Category:	End of review conference
Meeting Date and Time:	December 21, 2012
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1415 Silver Spring, Maryland 20903
Application Number:	NDA 203496
Product Name:	treprostinil diolamine extended-release tablets
Indication:	pulmonary arterial hypertension
Sponsor/Applicant Name:	United Therapeutics
Meeting Chairs:	Ellis Unger and Robert Temple
Meeting Recorder:	Dan Brum

FDA ATTENDEES

CDER: Robert Temple (Deputy Center Director for Clinical Science)

ODE I: Ellis Unger (Director)

DCRP: Norman Stockbridge (director), Steve Grant (deputy director), Abraham Karkowsky (cross discipline team leader), Maryann Gordon (clinical), Edward Fromm (chief, project management staff), Dan Brum (regulatory project manager)

Office of Clinical Pharmacology: Sudharshan Hariharan (clinical pharmacology reviewer), Sreedharan Sabarinath (clinical pharmacology reviewer)

Office of Biometrics I: James Hung (director, division of biometrics I), John Lawrence (biometrics reviewer)

SPONSOR ATTENDEES

United Therapeutics

Carl Arneson – Vice President, Biostatistics and Data Management
Dean Bunce – Executive Vice President, Compliance and Regulatory Affairs
Roger Jeffs – President and Chief Scientific Officer
Kevin Laliberte – Senior Director, Product Development
Rex Mauthe – Senior Director, Regulatory Affairs
David Zaccardelli – Executive Vice President, Manufacturing

Consultants for United Therapeutics

(b) (4) – Regulatory Consultant
(b) (4) – Biostats Consultant

1.0 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.

On December 27, 2011, NDA 203496 was submitted to market a third dosage form of treprostinil diolamine (fourth route of administration). The sponsor plans to manufacture the following (b) (4) strengths of treprostinil *extended-release tablets*, 0.125, 0.25, (b) (4) 1, and 2.5 mg.

The sponsor planned to market the three dosage forms separately i.e., separate proprietary names and separate package inserts.

On October 23, 2012, DCRP sent the sponsor a **Complete Response Letter** that included the following comments:

> You were able to demonstrate an effect on 6-minute walk only in study 302. The effect in that study was quite small and of dubious clinical importance. The estimated mean effect probably exaggerates the true effect, as much of the effect seems to be attributable to how values are imputed to subjects missing week 12 data. (This appears to have been less of an issue with inhaled treprostinil. In addition, we note our disagreement about how some subjects in study 302 were categorized for the purposes of imputation.)
>
> You were unable to demonstrate an effect on time to clinical worsening in three phase 3 studies.
>
> You were unable to demonstrate an effect on 6-minute walk in two well-powered studies (301 and 308) in which subjects were on background therapy with other, possibly more effective but certainly better tolerated vasodilators. Given the meager effect of treprostinil and its poor tolerability, it is difficult to name a clinical scenario in which use of oral treprostinil is appropriate.
>
> We are unsure whether an additional clinical study can alter these impressions, but if you undertake an additional study, we advise you to consider
>
> - a fixed-dose design (titration to different target doses), so that you have the ability to generate data to support exposure-response analysis,
> - more frequent dosing, to reduce the large peak-to-trough ratio you get with twice daily dosing and maybe reduce the impact of exposure-related tolerability issues, and
> - a setting in which you think you can defend the context of use as standalone therapy.

The sponsor requested this meeting to gain additional insight as to what steps may be required to increase the likelihood of approvability of NDA 203496. Note there was no internal premeeting and the meeting request/package did not contain a list of questions. Rather, in an email the sponsor requested that the Division provide the clinical and statistical reviews. In lieu of providing reviews that are unredacted and not publically available, the Division provided portions of the statistical analyses (see FDA correspondence dated December 4, 2012).

Bold, black font reflects the main discussion points during the meeting. The sponsor submitted a slide deck on December 4, 2012, and presented those slides during the meeting (attached).

Discussion

The sponsor responded to various points in FDA's Complete Response Letter with the aid of a slide presentation (enclosed).

The Division emphasized that the sponsor was unable to demonstrate an effect on 6-minute walk in two well-powered studies (301 and 308) in which subjects were on background therapy, the clinical scenario in which the Division anticipates the drug (if approved) to be most likely used. The Division raised the issue during the pre-NDA meeting on November 16, 2011, wherein it is states in the minutes: ***With respect to the three phase 3 studies conducted with oral treprostinil, two studies with background therapy (both $p > 0.05$)) and one without ($p < 0.05$), Dr. Brum asked the sponsor to speculate on this product's therapeutic role given the efficacy data and its safety profile relative to approved first-line therapies. The sponsor said both studies that missed the primary endpoint trended in the right direction.***

There was discussion about factors the sponsor may wish to consider if they perform a new clinical trial, e.g., enrichment design stratified by background PAH therapies and a run-in period to reduce the number of dropouts because of adverse reactions.

Dosing of treprostinil diolamine extended-release tablets in trials 301, 302, and 308 entailed administering study drug twice daily; however, the Division noted twice daily dosing was associated with substantial peak-to-trough ratios. The Division said thrice daily dosing would be expected to provide smaller peak-to-trough ratios, which may improve tolerability and lead to fewer subjects dropping out.

The sponsor had the following comments/questions:

Oral treprostinil might be used first-line in some patients. Development programs for the other approved routes of administration of treprostinil provide support for the oral development program. Would the Division consider approving NDA 203496 with a postmarketing commitment to conduct the new trial? The Division recognized that the activity of other routes of treprostinil administration was encouraging, but emphasized the need to show that the drug worked in this dosage form at the dose recommended. The Division did not agree to this approval suggestion during the meeting.

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/s/

DANIEL BRUM
01/10/2013

ELLIS F UNGER
01/11/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203496

ACKNOWLEDGE –
CLASS 2 RESPONSE

United Therapeutics Corporation
Attention: Dean Bunce, RAC
Executive Vice President,
Regulatory Affairs and Compliance
55T. W. Alexander Drive
P.O. Box 14186
Research Triangle Park, NC 27709

Dear Mr. Bunce:

We acknowledge receipt of your August 16, 2013, resubmission of your new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Treprostinil Extended Release Tablets, 0.125 mg, 0.25 mg, 1mg, and 2.5 mg.

We consider this a complete, class 2 response to our March 22, 2013, action letter. Therefore, the user fee goal date is February 16, 2014.

If you have any questions, call Wayne Amchin, Regulatory Project Manager, at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Edward Fromm, RPh, RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM
09/11/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203496

MEETING MINUTES

United Therapeutics Corp.
Attention: Mr. Dean Bunce
EVP, Regulatory Affairs & Compliance
55 TW Alexander Drive
P.O. Box 14186
Research Triangle Park, NC 27709

Dear Mr. Bunce:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for treprostinil diolamine 0.125 mg, 0.25 mg, 1 mg, and 2.5 mg Extended-ReleaseTablets.

We also refer to the meeting between representatives of your firm and the FDA on May 3, 2013. The purpose of the meeting was to discuss the clinical and statistical issues noted in the complete response letter dated March 22, 2013.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Edward Fromm, Regulatory Project Manager, at (301) 796-1072.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Deputy Director for Clinical Science
Center for Drug Evaluation and Research
Food and Drug Administration

Enclosure:
Meeting minutes
Sponsor's slide presentation

MEMORANDUM OF MEETING MINUTES

Meeting Type:	A
Meeting Category:	End of review conference
Meeting Date:	May 3, 2013
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	NDA 203496
Product Name:	treprostinil diolamine extended-release tablets
Indication:	pulmonary arterial hypertension
Sponsor/Applicant Name:	United Therapeutics
Meeting Chair:	Robert Temple
Meeting Recorder:	Edward Fromm

FDA ATTENDEES

Center for Drug Evaluation and Research
Robert Temple, M.D., Deputy Director for Clinical Science

Office of Drug Evaluation I
Ellis Unger, M.D., Director

Office of Drug Evaluation 1, Division of Cardiovascular and Renal Products
Norman Stockbridge, M.D., Ph.D., Director
Maryann Gordon, M.D., Medical Officer
Edward Fromm, R.Ph., RAC, Chief, Project Management Staff

Office of Biostatistics, Division of Biometrics I
James Hung, Ph.D., Team Leader

Office of Clinical Pharmacology, Division of Clinical Pharmacology I
Sudarshan Hariharan, Ph.D., Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

United Therapeutics
Carl Arneson – Vice President, Biostatistics and Data Management
Dean Bunce – Executive Vice President, Compliance and Regulatory Affairs
Roger Jeffs – President and Chief Scientific Officer
Kevin Laliberte – Senior Director, Product Development
Rex Mauthe – Senior Director, Regulatory Affairs
David Zaccardelli – Executive Vice President, Manufacturing

Consultants for United Therapeutics
(b) (4) – Regulatory Consultant
(b) (4) – Biostats Consultant

1.0 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.

On December 27, 2011, NDA 203496 was submitted to market a third dosage form of treprostinil diolamine (fourth route of administration). The applicant plans to manufacture the following 4 strengths of treprostinil extended-release tablets, 0.125, 0.25, 1, and 2.5 mg.

The applicant planned to market the three dosage forms separately i.e., separate proprietary names and separate package inserts.

On October 23, 2012, FDA sent United Therapeutics a Complete Response Letter. Following a meeting with the Agency on December 21, 2012, the firm resubmitted their application on January 31, 2013. FDA issued a second Complete Response Letter on March 22, 2013; the meeting today (May 3, 2013) is to discuss the clinical and statistical issues enumerated in the action letter.

Meeting Discussion

United Therapeutics responded to various points in FDA's Complete Response Letter with the aid of a slide presentation (attached).

Regarding slide #6 (Distribution of change at Week 12 – Study 302), Dr. Temple encouraged the applicant to explore further the distribution of treatment effects on 6 minute walk distance (6MWD).

Duration of Effect and Post-Marketing Study

United Therapeutics presented slide #16 (Peak to Trough Stability of 6MWD) and noted that variability of the peak to trough ratio was lower in the active group completers in the trial. The Agency said that using completers of the study for this analysis was inherently biased as it did not include subjects who dropped out of the study. The firm believed that subjects who dropped out of the study (around 20%) were relatively well-balanced between the treatment arms of study 302. They also noted that their analysis of the active group completers in the Ventavis labeling showed a 60% variability rate, somewhat lower than the same comparison with the oral treprostinil group.

Dr. Temple expressed concern about the duration of the effect of the drug, given the variability in the peak to trough concentrations and that the drug is proposed as monotherapy. He suggested a TID or QID dosing regimen that would provide more

consistent drug levels throughout the day. The firm replied that even continuous infusion of treprostinil produced a similar effect on 6MWD, and so they were skeptical that a more frequent dosing regimen would result in better efficacy. They also noted that about 80% of subjects were taking the drug for over a year, and these patients were hesitant to switch to a more frequent dosing regimen.

United Therapeutics stated that although they believe the data submitted to date are sufficient to support approval, they are open to conducting a post-marketing study (b) (4)

Dr. Stockbridge asked the firm whether they have identified acute models (e.g., pharmacodynamic) that would justify an additive effect on other drugs used in the PAH setting (e.g., bosentan, sildenafil). United Therapeutics replied that although treprostinil is a vasodilator, inhibition of smooth cell proliferation has been shown when the drug was tested in human smooth muscle cell cultures. They noted that although treprostinil did not show a statistically significant effect on dual PAH background therapy, there was a positive trend. The firm also said that the dual background therapy may have limited the capacity of some subjects to show improvement in the study.

United Therapeutics presented a slide (Comparison of Remodulin Transition Data) comparing the effects of placebo, Remodulin, and oral treprostinil when patients were transitioned from Remodulin to oral treprostinil. They stated that there appears to be little drop off in efficacy in subjects transitioned to oral treprostinil.

PET Scan and Drug Levels

Dr. Unger asked if a PET (Positron Emission Tomography) scan had been done with labeled drug to show levels in the lung. United Therapeutics said that a PET scan was not done with treprostinil. Dr. Unger said that if trough drug levels of treprostinil in the lung were higher than blood levels, it could lessen our concern regarding the large peak to trough ratio of the drug when given twice daily.

Summary

United Therapeutics presented arguments on the clinically meaningful benefit of the drug and noted that the variability in the peak to trough ratio was not unlike other drugs used to treat this disease. They proposed (b) (4) The Agency said that they would carefully consider the applicant's proposal for the post-marketing study and provide a response in the context of these minutes.

Addendum to meeting minutes: The Agency is discussing the applicant's proposal (b) (4) **but has yet to reach a final decision on how to move forward. We will keep you updated on the progress of our internal discussions** (b) (4)

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/s/

ROBERT TEMPLE
05/31/2013

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 1, 2013
TIME: 1:00 PM-1:30 PM
LOCATION: WO Bldg 22,
DRUG NAME: NDA 203496 Orenitram
TYPE OF MEETING: Teleconference with United Therapeutics.
MEETING RECORDER: Cherye Milburn, SRPM, OSE

FDA ATTENDEES:
Irene Z. Chan, TL DMEPA, OSE
Kimberly DeFronzo, Safety Evaluator, DMEPA, OSE

EXTERNAL ATTENDEES:
Dean Bunce, EVP, Regulatory Affairs and Compliance
Hilary Hafeken, Associate Director, Regulatory Informatics
Kevin Laliberte, AVP, Product Development
Rex Mauthe, AVP, Regulatory Affairs
Scott Moomaw, AVP, Marketing
David Zaccardelli, EVP, Pharmaceutical Development

Background:
On February 27, 2012, the Applicant submitted a request for the review of the proposed proprietary name (b) (4) In OSE Review # 2012-533 dated May 17, 2012, the Division of Medication Error Prevention and Analysis (DMEPA) found the name unacceptable (b) (4)

On June 6, 2012, the Applicant submitted a request for the review of the second proposed proprietary name, (b) (4) In OSE Review # 2012-1321 dated September 4, 2012, the Division of Medication Error Prevention and Analysis (DMEPA) found the name unacceptable (b) (4)

On September 20, 2012, the Applicant submitted a request for the review of the third proposed proprietary name, (b) (4) which was found to be unacceptable (b) (4)

On October 16, 2012, the Applicant submitted a request for the review of the fourth proposed proprietary name, Orenitram. However, the Application received a Complete Response (CR) letter on October 23, 2012. Therefore, on November 6, 2012, a teleconference call was scheduled between DMEPA and the Applicant to discuss how to proceed with review of the name given the CR. DMEPA advised the Applicant to consider withdrawing the proposed proprietary name until product characteristics for the product could be fully characterized based on the advice in the CR letter. The company withdrew the Orenitram name on November 27, 2012.

On January 31, 2013, the Applicant submitted a resubmission after complete response, and on February 15, 2013, the Applicant submitted a second request for the review of the same proposed proprietary name, Orenitram. However, the application received another

Complete Response (CR) on March, 22, 2013. Therefore, this teleconference call was scheduled to discuss how to proceed with the review of the proposed proprietary name Orenitram.

Meeting Objectives:
DMEPA requested a teleconference with the Applicant to discuss the review of the proposed proprietary name, Orenitram.

Discussion:
DMEPA find this submission incomplete given that the product characteristics are not fully characterized based on the reasons cited for the Complete Response action taken by the Agency on March, 22, 2013. Because the Agency does not hold names for companies, and the findings of our review are based on the product characteristics for the product, we recommend you withdraw the proprietary name request from the NDA at this time. In the future, when you have the product characteristics fully characterized after additional clinical development, you can submit a request for proprietary name review under the IND.

Regulatory Options:
1. Wait for DMEPA to complete the review and issue a denial letter for the trade name request by the OSE PDUFA goal date.
2. Withdraw the proposed name, Orenitram.

Action Items:
United Therapeutics will send in a withdrawal letter for the proposed name Orenitram.

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/s/

IRENE Z CHAN
04/18/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203496

ACKNOWLEDGE --
CLASS 1 COMPLETE RESPONSE

United Therapeutics Corporation
Attention: Mr. Dean Bunce
Executive Vice President,
Regulatory Affairs & Compliance
55 TW Alexander Drive, P.O. Box 14186
Research Triangle Park, NC 27709

Dear Mr. Bunce:

We acknowledge your January 31, 2013 resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Treprostinil Extended Release Tablets, 0.125 mg, 0.25 mg, 1 mg, and 2.5 mg.

We consider this a complete, class 1 response to our October 23, 2012, action letter. Therefore, the user fee goal date is March 31, 2013.

If you have any questions, please contact:

Dan Brum, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0578

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM
02/13/2013

10/17/12

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	October 16, 2012
TIME:	10:00 AM-10:30 AM
LOCATION:	WO Bldg 22,
DRUG NAME:	(b) (4) (Treprostinil) Extended-release Tablets
TYPE OF MEETING:	Teleconference with United Therapeutics
MEETING RECORDER:	Cherye Milburn, SRPM, OSE
FDA ATTENDEES:	Irene Chan, TL DMEPA, OSE
EXTERNAL ATTENDEES:	Dean Bunce, EVP, Regulatory Affairs and Compliance Greg Bottorff, Marketing Product Manager Kevin Laliberte, Sr. Director, Product Development Kerry McKenzie, Assoc. Director, Regulatory Affairs Rex Mauthe, Sr. Director, Regulatory Affairs

Background:
On February 27, 2012, the Applicant submitted a request for the review of the proposed proprietary name, (b) (4). In OSE Review # 2012-533 dated May 17, 2012, the Division of Medication Error Prevention and Analysis (DMEPA) found the name unacceptable (b) (4).
On June 6, 2012, the Applicant submitted a request for the review of the second proposed proprietary name, (b) (4). In OSE Review # 2012-1321 dated September 4, 2012, the Division of Medication Error Prevention and Analysis (DMEPA) found the name unacceptable (b) (4).
On September 20, 2012, the Applicant submitted a request for the review of the third proposed proprietary name, (b) (4) which is the subject of this review.

Meeting Objectives:
DMEPA requested a teleconference with the Applicant to discuss safety concerns with the primary proposed proprietary name, (b) (4) and to provide recommendations in consideration of the NDA PDUFA goal date of October 27, 2012.

Discussion Points:
Our preliminary review identified that the proposed proprietary name, (b) (4) is unacceptable (b) (4)

(b) (4)

[redacted] (b) (4)

[redacted] (b) (4)

[redacted] (b) (4)

Therefore, [redacted] (b) (4) we conclude there is a potential for confusion [redacted] (b) (4) that can lead to wrong drug errors.

[redacted] (b) (4) However, if the second name application is approved prior to your application, then you will be requested to submit another name.

Regulatory Options:

1. Wait for DMEPA to complete our review within our 90-day OSE PDUFA goal date and issue a denial letter.
2. You may wish to withdraw the proposed name, [redacted] (b) (4) and submit an alternate name for review as soon as possible, preferably by the close of business today. The proprietary name review cycle is 90 days, which would exceed the overall NDA PDUFA goal date of October 27, 2012; however, DMEPA will make our best efforts to complete a review sooner. Your NDA can be approved with the established name Treprostinil if a name is not approved prior to the NDA approval. If you choose this regulatory path, we would advise you to submit more than one name to the Agency.

---

[1]Chi-Ming Tu, et al., "Use of Proprietary Names by Prescribers for Discontinued Brand Drug Products With Existing Generic Equivalents," *Drug Information Journal*, August 21, 2012, pp. 1-6. Published online before print August 21, 2012, doi: 10.1177/0092861512456282.

Action:

Sponsor will send name withdrawal letter to the FDA by close of business today and include another request for a review of a new proprietary name.

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/s/

CHERYE D MILBURN
10/17/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203496

GENERAL ADVICE

United Therapeutics Corp.
Attention: Mr. Dean Bunce
EVP, Regulatory Affairs & Compliance
55 TW Alexander Drive
P.O. Box 14186
Research Triangle Park, NC 27709

Dear Mr. Bunce:

Please refer to your New Drug Application (NDA) dated December 24, 2011, received December 27, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for treprostinil 0.125 mg, 0.25 mg, (b) (4) 1 mg, and 2.5 mg tablets.

We also refer to the complete response letter dated October 23, 2012, your correspondence requesting a Type A meeting dated October 25, 2012, our correspondence granting the meeting dated October 30, 2012, and Mr. Rex Mauthe's email dated October 26, 2012 wherein United Therapeutics requested FDA analyses relating to the following items in the complete response letter (bold for emphasis):

> You were able to demonstrate an effect on 6-minute walk only in study 302. The effect in that study was quite small and of dubious clinical importance. **The estimated mean effect probably exaggerates the true effect, as much of the effect seems to be attributable to how values are imputed to subjects missing week 12 data.** (This appears to have been less of an issue with inhaled treprostinil. **In addition, we note our disagreement about how some subjects in study 302 were categorized for the purposes of imputation.**)

We have reviewed your request for additional information and have the following comments:

A greater percentage of subjects randomized to UT-15C stopped study drug early (22%, 51/233) compared to subjects randomized to placebo (16%, 18/116). Overall, a higher percentage of placebo subjects (88%) agreed to rollover into the open label follow up study compared to UT-15C subjects (76%). (from table 14.1.3.1.2.)

Of the subjects who stopped drug prematurely, eleven UT-15C subjects and 2 placebo subjects were reported to have discontinued for other/lost to follow up/consent withdrawn. The CRFs for these subjects were reviewed and the findings are discussed below.

UT-15C subjects

Subject 200232 Reason given: lost to follow up week 8 (last visit week 4). Adverse events reported were lower extremity edema, facial edema, weakness of legs. PAH related events that appeared or worsened between randomization and end of study included general edema, hypoxia, and loss of consciousness. 6MWD went from 350 m at baseline to 337 week 4. Fatigue score went from 0 at baseline to 2 at week 4. Dizziness and syncope went from 1 to 0 and chest pain went from 0 to 1. Dose was decreased from 1.75 mg BID to 0.25 mg BID and then increased to 2.0 BID up to 2.75 BID. Revise reason for study drug discontinuation to clinical worsening. Reviewer assessment: clinical worsening.

Subject 200225 Reason given: lost to follow up. Adverse events reported were headache, fatigue, rash. WHO class went from II to III, dyspnea-fatigue index went from7 to 6, PAH symptoms did not change, 6MWD went from 390 m baseline to 450 m week 8 to 440 week 11. Dose was decreased and then increased three times. Reviewer assessment: adverse events/drug intolerability.

Subject 200245 Reason given: lost to follow up. No adverse events reported. PAH symptoms no change, dyspnea/fatigue index improved (6 to 8), WHO class improved (III to II). Drug titrated without interruption up to 2.5 BID. Reviewer assessment: lost to follow up.

Subject 060204 Reason given: lost to follow up. Subject did not return after baseline visit. Reported "upset stomach" when dose was increased from 0.25 mg bid to 0.5 mg bid. Reviewer assessment: adverse event/drug intolerability.

Subject 174223 Reason given: other (subject decided to go for non-medical alternative treatment). Adverse events reported were dizziness, restlessness, headache, dyspnea on exertion, dry skin, decreased memory, dry throat, numbness of extremities, loss of taste, loss of appetite. Dose was decreased and then increased three times. WHO classification was unchanged from baseline and walk distance increased from 297 m to 360 m. Reviewer assessment: adverse events/drug intolerability. Subject 115207 Reason given: consent withdrawn. Adverse events reported were abdominal pain, diarrhea, leg pain, nausea. Dose down titrated and then increased then stopped. Reviewer assessment: adverse events/drug intolerability.

Subject 013201 Reason given: other. Subject had unblinded study drug (peeled back label) prior to week 4 assessment. Adverse events reported lung cramps (sic), sinusitis, left knee pain, headache, nausea, rash, left ear pain, tinnitus, diarrhea, vomiting. Reviewer assessment: adverse events/drug intolerability.

Subject 020210 Reason given: consent withdrawn. Adverse events reported were headache, vomiting, dizziness, facial redness, muscle pain, flatulence, diarrhea, insomnia. Reviewer assessment: adverse events/drug intolerability.

Subject 041204 Reason given: consent withdrawn. On day of withdrawal, subject complained of chest pain and was admitted to hospital. Adverse events included body aches, constipation, asthma exacerbated, chest wall strain. Dyspnea developed but fatigue improved at week 4. Walk

distance went from 432 m to 473 m week 4. Dose was stopped and restarted. Reviewer assessment: adverse events/drug intolerability.

Subject 171201 Reason given: other (mistakenly unblinded during ivrs, labels are undisturbed). No adverse events reported. Dyspnea-fatigue index became less severe at week 12 (magnitude of pace went from major to moderate), symptom of dyspnea improved, 336 m at baseline to 400 m week 12. Reviewer assessment: subject should not be classified as premature discontinuation.

Subject 026204 Reason given: other. Subject stopped taking study drug for "unknown reason." WHO class went from III at baseline to IV at week 8. Two days later the subject died (listed as pulmonary embolism/pulmonary edema). Adverse events include headache, dizziness, nausea, facial flushing, jaw pain, abdominal cramping, diarrhea, restless legs, metallic taste, renal insufficiency. Reviewer assessment: clinical worsening/death.

Placebo subjects

Subject 036214 Reason given: other. Subject mistakenly stopped study drug early but completed last visit. Subject has week 12 values. Reviewer assessment: subject should not be classified as premature discontinuation.

Subject 041205 reason given: other. Clinical worsening was recorded as reason for drop out on CRF page 37. Walk distance went from 301 m at baseline to 91 m week 8. Nearly all symptoms of CHF grew worse at week 8. Reviewer assessment: clinical worsening.

59 subjects in the UT-15C group did not have the week 12 walk test compared to 18 subjects in the placebo group (the number without a walk test differs slightly from the number who discontinued early because some subjects did not discontinue study drug yet did not have a week 12 walk test measurement).

The primary analysis was complicated, but essentially all subjects were assigned a score between 0 and 1 based on their change from baseline walking distance. Higher scores indicate better change in walking distance. The average imputed score for the 59 treprostinil subjects with missing Week 12 data is 0.36 while the average score for the 18 placebo subjects is 0.11.

Because of the imbalance in the percentage of subjects with missing data, the observation that imputed scores were higher in the treprostinil group, and the subjectivity about the reason for missing data, we looked at other sensitivity analyses. For example, when the 59 UT-15C subjects are given worst rank, the p-value for the primary analysis becomes 0.92. When the missing placebo subjects are assigned worst rank as well, the p-value becomes 0.21.

If you have any questions, please call Dan Brum, Pharm.D., RAC, Regulatory Project Manager, at (301)796-0578.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
12/04/2012

Bouie, Teshara

From: Bouie, Teshara
Sent: Monday, October 01, 2012 2:22 PM
To: 'Rex Mauthe'
Cc: Brum, Dan
Subject: RE: NDA 203496 - Request for TCON

Hi Rex,

Based on your responses below, there is no need for a tcon tomorrow.

Regards,

Teshara G. Bouie

From: Rex Mauthe [mailto:RMauthe@unither.com]
Sent: Monday, October 01, 2012 11:22 AM
To: Bouie, Teshara
Cc: Brum, Dan
Subject: RE: NDA 203496 - Request for TCON

Hi Teshara,

See our responses to the issues below.

We believe our responses clarify these issues; however, if the teleconference is still necessary, please use the following for the call:

(b) (6)

Please let us know if anything else is needed at this time and if the teleconference is needed to further address any of the issues.

Thanks,
Rex

From: Bouie, Teshara [mailto:Teshara.Bouie@fda.hhs.gov]
Sent: Friday, September 28, 2012 3:31 PM
To: Rex Mauthe
Cc: Brum, Dan
Subject: NDA 203496 - Request for TCON

Hi Rex,

As discussed, the CMC team would like to have a tcon on Tuesday, October 2, 2012 at 11:00 am.

We would like to discuss the following:

Please identify the testing laboratory for diethanolamine content for release of UT-15C since (b) (4) was not included in the original list of establishments for this NDA or in this CMC amendment. Provide particulars of establishment information for (b) (4) Alternatively, provide supporting documentation or the plan for implementing this method at any of the previously identified establishments for cGMP use of UT-15C.

Response: The initial method development was outsourced to (b) (4). We will complete full method transfers with appropriate qualifications to the previously submitted laboratories in our NDA (United Therapeutics, (b) (4) prior to testing and release of future lots of drug substance. (b) (4) will not be used for GMP testing for commercial production.

Revise the acceptance criterion for diethanolamine content in UT-15C drug substance specification from a limit of (b) (4)

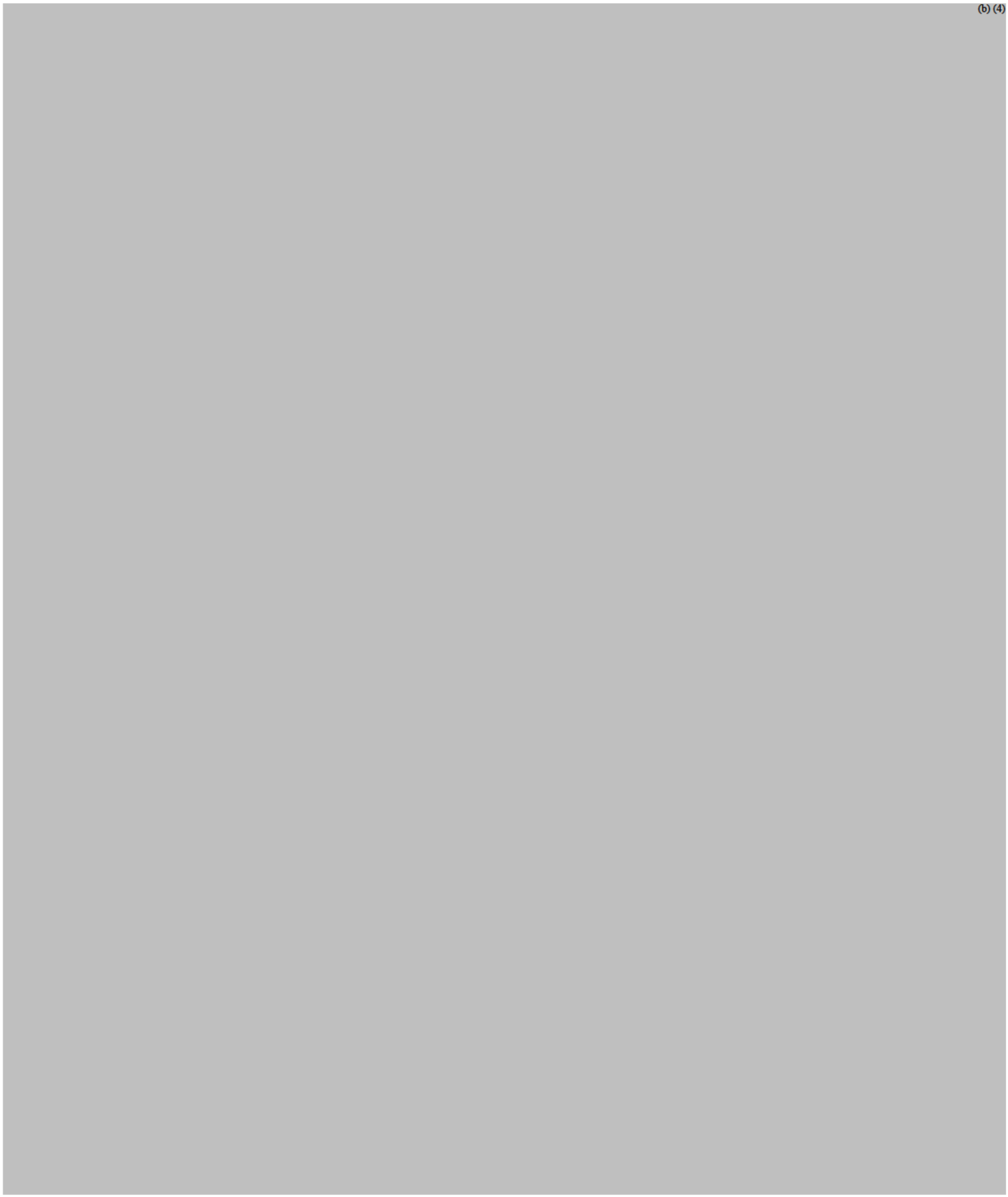
Response: We will revise the Specification to reflect the acceptance limits of (b) (4)

The labeling information submitted with revised chemical name and structural representation of the salt form are consistent with approved USAN statement. However, the representation of stereochemistry for hydroxyl group on octylchain is not consistent between the information submitted in the NDA and approved USAN statement.

Response: Although depicted differently, the stereochemistry of the hydroxyl groups in the NDA submission and in the USAN statement are the same. (b) (4)

(b) (4)


(b) (4)


(b) (4)

Please provide a call-in number for the meeting.

Thanks,

Teshara

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/s/

TESHARA G BOUIE
10/01/2012

MEMORANDUM OF TELECON

DATE: September 20, 2012

APPLICATION: NDA 203496 for treprostinil diolamine for pulmonary arterial hypertension

BETWEEN:

United Therapeutics:
Kevin Laliberte, Senior Director, Product Development
Carl Arneson, VP, Biostatistics and Data Management
Jeff Sigman, Senior Director, Clinical Operations
Dean Bunce, EVP, Regulatory Affairs and Compliance
Wayne DellaMaestra, Director, Clinical Data Systems
Rex Mauthe, Senior Director, Regulatory Affairs

AND

Division of Cardiovascular and Renal Products:
Abraham Karkowsky, M.D., Ph.D., Cross-Discipline Team Leader
Maryann Gordon, M.D., Medical Officer
Dan Brum, Pharm.D., RAC, Project Manager
Division of Biometrics I:
John Lawrence, Ph.D., Biometrics Reviewer

SUBJECT: Points of discussion from the teleconference

For study -302, Dr. Karkowsky noted that the difference in 6MWD between the placebo and treatment arms was largest between the W8 and W12 visits. He asked the sponsor about how blinding was maintained at the end of the 12-week controlled portion of the trial. At that point blinding was broken and subjects could enter the open-label extension. The sponsor said patients were unblinded *after* the W12 6MWD was entered into the IVRS. Dr. Karkowsky asked about the precise timing of these events and the sponsor said they would follow-up on this issue.

Dr. Karkowsky mentioned several adverse events related to prostacyclin therapy (e.g., jaw pain, bone pain, flushing, nausea, vomiting) that may have unblinded the study. In light of this concern, Dr. Karkowsky requested that the sponsor provide an analysis of time to first prostacylin-related AE.

Regarding the sponsor's primary analysis (referred to modified intent to treat mITT), the sponsor said they submitted an amendment ("Amendment 4") to IND 71537 following the unblinding of study -301. Study -302 began about the same time as study -301, and approximately one-half (171) of the total patients enrolled (N=349) in -302 were unblinded at the time of that amendment. Dr. Karkowsky asked the sponsor to submit an analysis of 6MWD both pre- and post-amendment 4 (i.e., analysis with the first 171 patients and a separate analysis for the remaining 178.

Daniel Brum
Regulatory Project Manager

APPEARS THIS WAY ON ORIGINAL

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/s/

DANIEL BRUM
09/21/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 203496

PROPRIETARY NAME REQUEST
UNACCEPTABLE

United Therapeutics Corporation
55 TW Alexander Drive
P.O. Box 14186
Research Triangle Park, NC 27709

ATTENTION: Rex Mauthe
Senior Director, Regulatory Affairs

Dear Mr. Mauthe:

Please refer to your New Drug Application (NDA) dated December 24, 2011, received December 27, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Treprostinil Extended-release Tablets, 0.125 mg, 0.25 mg, (b) (4) 1 mg, and 2.5 mg.

We also refer to your correspondence dated and received June 6, 2012, requesting review of your proposed proprietary name, (b) (4). We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

(b) (4)

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cherye Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
09/04/2012

MEMORANDUM OF TELECON

DATE: August 28, 2012

APPLICATION NUMBER: NDA 203496

BETWEEN:

United Therapeutics:
Rex Mauthe, Sr. Director, Regulatory Affairs
Dean Bunce, EVP, Regulatory and Compliance
Ken Phares, VP Pharmaceutical Development
Michael Scannell, Director, Analytical Sciences
Raju Penmasta, SVP, R&D
Liang Guo, VP Manufacturing

AND

Office of New Drug Quality Assessment:
Ramesh Sood, Ph.D., Branch Chief
Kasturi Srinivasachar, Ph.D., CMC Lead
Shastri Bhamidpati, Ph.D., Review Chemist
Teshara G. Bouie, Project Manager

SUBJECT: Request for Information

On July 27, 2012 the Agency sent the applicant requests for information. The applicant provided a response on August 10, 2012, however additional information was needed for following requests:

Drug Substance Question # 2: Revise the drug substance specification to include testing for diethanolamine content and provide details of analytical method and its validation for quantitation of diethanolamine content.

The sponsor agreed to include testing for diethanolamine content and revise the drug substance specification once an appropriate method is developed and validated for its quantitation. The sponsor also offered an explanation for not including the testing (not included here).

> *Tcon Discussion: The applicant stated method validation should be complete by mid September. They will amend the NDA in the third week of September 2012 with the method, validation, and revised specification. The sponsor will also submit diethanolamine content data for drug substance batches.*

Drug Product Question # 2: Provide data to show that (b) (4) in the drug product batches at (b) (4) will be below the levels that support any microbial growth.

Alternatively, include testing for microbial content in drug product specification.

The sponsor agreed to include testing for microbial content in the drug product batches and revise the drug product specification when an appropriate method is developed and validated. Simultaneously, the sponsor will also test the drug product batches with (b) (4) to determine if (b) (4) will support any microbial growth. If the results show that (b) (4) does not support microbial growth, the sponsor will exclude microbial limits testing.

Tcon Discussion: The applicant will include microbial content testing in the final updated specifications and provide data. This will be provided in the amendment planned for the third week of September 2012.

On August 27, 2012, the Agency sent the applicant the following additional request for information:

1. Please submit strength specific tabulated form of drug listing data elements (DLDE) as stipulated in SPL Revision 4 for evaluation.

   Tcon Discussion: The applicant agreed and will update accordingly.

2. Revise the information presented for treprostinil diolamine in Description section of drug product labeling text and the SPL XML file in terms of chemical name, structural representation of the salt form and the stereochemistry of the hydroxyl group on octylchain to be consistent with approved USAN Statement.

   Tcon Discussion: The applicant will confirm naming and make appropriate corrections.

3. The stability data submitted for registration batches for 0.25 mg and 2.5 mg support only 30 month expiration period for these two strengths. Please revise the current stability protocol and the post approval stability protocols accordingly to include a 30 month testing interval for these strengths.

   Tcon Discussion: The applicant concurred with the request above. It was noted that some batches have already pasted the 30 month time point, however all future batches will include a 30 month testing interval. The sponsor agreed to provide these responses also in a timely manner for evaluation before PDUFA date.

Teshara G. Bouie
Regulatory Health Project Manager

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/s/

TESHARA G BOUIE
08/31/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203496

DISCIPLINE REVIEW LETTER

United Therapeutics Corp.
Attention: Mr. Dean Bunce
EVP, Regulatory Affairs & Compliance
55 TW Alexander Drive
P.O. Box 14186
Research Triangle Park, NC 27709

Dear Mr. Bunce:

Please refer to your New Drug Application (NDA) dated December 24, 2011, received December 27, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for treprostinil 0.125 mg, 0.25 mg, (b) (4) 1 mg, and 2.5 mg tablets.

The Division of Medication Error Prevention and Analysis (DMEPA) review of the proposed label and labeling section of your submission is complete, and they have identified the following deficiencies:

A. General Comment

The proposed proprietary name (b) (4) was evaluated under separate cover and found to be unacceptable (b) (4) 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 (b) (4) is overly prominent and distracts (b) (4) Remove or relocate and minimiz (b) (4)
4. The (b) (4) is overly prominent. Remove or minimize (b) (4)

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 [redacted] and 310 respectively [redacted] 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 [redacted] to read 'Extended-release Tablets: 0.125 mg, 0.25 mg, [redacted], 1 mg, and 2.5 mg'.
2. In the Highlights of Prescribing Information under Dosage and Administration, revise the statement [redacted]
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 [redacted] increase the prominence of the statement [redacted]
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:

[redacted]

(b) (4)

D. Patient Package Insert

1. Under the (b) (4) section:
   a. Revise the statement from (b) (4) to read "Swallow Proprietary Name 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 Proprietary Name tablets whole. (b) (4) Additionally, move this statement so it is the first bullet point in this section.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Dan Brum, Pharm.D., RAC, Regulatory Project Manager, at (301)796-0578.

Sincerely,

{See appended electronic signature page}

Abraham Karkowsky, M.D., Ph.D.
Cross Discipline Team Leader
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

ABRAHAM M KARKOWSKY
08/06/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203496

INFORMATION REQUEST

United Therapeutics Corp.
Attention: Rex Mauthe, Senior Director, Regulatory Affairs
55 TW Alexander Drive
P.O. Box 14186
Research Triangle Park, NC 27709

Dear Mr. Mauthe:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Treprostinil Diethanolamine Sustained Release Tablets.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

1. Provide a description of the procedure employed for determination of [redacted] (b) (4) content from peak area ratio [redacted] (b) (4) since the specific peaks were not clearly identified in the development report (Chapter V in Dev. Report 0067)

2. Revise the drug substance specification to include testing for diethanolamine content and provide details of the analytical method and its validation for quantitation of diethanolamine content.

3. Review of the analytical method for UT-15C assay and related substances (SOP: TQC-110) provided as part of the method transfer report show inconsistencies in terms of system suitability acceptance criteria. For example, determination of %RSD of the peak area [redacted] (b) (4) Revise system suitability acceptance criteria to include determination of %RSD of peak area for [redacted] (b) (4) the main standard.

4. Provide a copy of the current version of the analytical method for UT-15C assay and related substances.

5. Provide Relative Response Factors used in calculations for all UT-15C related substances and degradants as applied in the analysis of the drug substance (and the drug product).

6. Provide reference standard information for the impurity, [redacted] which is used in the analytical method as a resolution solution.

7. In assessing the stability of the drug substance, UT-15C was packaged in [redacted] Confirm that drug substance packaged in [redacted] so that the actual commercial storage is same as used in the stability studies.

Drug Product

1. Revise the drug product specification for Appearance to include the presence of imprinted strength identification. .

2. Provide data to show tha [redacted] in the drug product batches at [redacted] will be below levels that support any microbial growth. Alternatively, include testing for microbial content in drug product specification.

3. As part of process optimization for [redacted] Revise the in-process specification for [redacted] to include an acceptable range with appropriate lower limit.

4. Identify the specific tablet strengths employed in Treprostinil Diolamine Extended Release tablets Aperture Size Dissolution Study (Doc# 2011-0002).

5. We recommend that you include in-process testing [redacted] with appropriate acceptance criteria.

6. We recommend that you include testing of tablet [redacted]

7. Provide current Analytical procedures for TM0004, TM0006, TM0007 & TM0008 in use at the commercial manufacturing facility (UTC, [redacted] testing labs.

8. In Section 3.2.P.5.3 (Validation of Analytical Procedures), the references provided for supplemental validation reports P7290-01-0-125, P6917-00-025 and P7096-00-205, contain only validation protocols. Provide the corresponding validation reports for treprostinil assay and related substances.

9. You have not provided a complete dissolution method development report and therefore we do not know whether or not the drug product's dissolution behavior is condition independent. Therefore, provide data to show:

   i) Whether or not the drug product's dissolution behavior is impacted at pH below 4.5 (recommended pH 1.2) and why pH 1.2 was not selected.
   ii) Discriminating capability of the selected dissolution method for tablet coating defect.

10. Your IVIVC cannot predict the C_{max} using the in vitro dissolution data. Additionally, you have generated IVIVC using in vitro mean dissolution data from the two identical batches that were used for the site equivalence. Such an approach is not sufficient as per the guidance for industry, **"Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations"** where it is recommended that a correlation be established using different formulations with different release rates such as medium, fast and slow release formulations. Therefore, your proposed dissolution limit is not justified as per the ICH Q6A which recommends a maximum of ±10% limit in absence of IVIVC. Therefore, you should follow one of the options given below:
    i) Provide appropriate IVIVC to support the proposed (b) (4) dissolution limit.
    ii) (b) (4) dissolution limit as follows:
    (b) (4)
    (iii) Conduct a bioequivalence study to show PK similarity between the batches with fast and slow dissolution rates..

11. Stability data presented for bulk storage of Treprostinil Extended Release tablets show noticeable changes (b) (4)
    i) Clarify if the bulk storage study is conducted (b) (4)
    ii) Specify the time limit for storage of bulk tablets based on the stability data prior to packaging.

12. While you have provided stability data for multiple batches of treprostinil extended release tablets of different strengths, you have not explicitly designated the primary stability batches. Identify the drug product batches of each strength designated as primary stability batches.

13. We recommend that you evaluate available data for the primary stability batches per Agency recommended acceptance criteria for dissolution (See Comment 10).

14. Provide complete summaries of analysis of the primary stability data along with justification for the expiration dating of the drug product.

15. Please be advised that Sustained Release is not a CDER standard for dosage form (see the link below). Revise the established name for the drug product throughout labeling from "[redacted] (b) (4) (treprostinil diolamine) Sustained Release Tablets" to [redacted] (b) (4) (treprostinil) Extended Release Tablets" to be consistent with the labeled strength of the drug product. http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162038.htm

16. Provide a copy of the approval of Treprostinil diolamine as USAN and ascertain that the chemical name and the structure of Treprostinil diolamine in drug product labeling are consistent with the USAN.

17. Provide a Structured Product Labeling (SPL) XML file for evaluation. Refer to the following link for information. http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

18. There is a potential for alcohol-induced dose dumping. Appropriate instruction should be included in the labeling.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
07/27/2012

Executive CAC
Date of Meeting: June 26, 2012

Committee: Abby Jacobs, Ph.D, OND IO, Acting Chair
Barbara Hill, Ph.D., DDDP, Alternate Member
Haleh Saber, Ph.D., DHOT, Alternate Member
Thomas Papoian, Ph.D., DCRP, Team Leader
Xavier Joseph, D.V.M., DCRP, Presenting Reviewer

Author of Draft: Xavier Joseph, D.V.M.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #:	203-496
Drug Name:	Treprostinil diethanolamine (UT-15C)
Sponsor:	United Therapeutics Corp., Research Triangle Park, NC

Background: UT-15C, the diethanolamine salt of treprostinil (UT-15), is being developed for oral administration in pulmonary arterial hypertension (PAH) patients. Treprostinil sodium (Remodulin®), a chemically stable analogue of prostacyclin (PGI_2), with potent vasodilatory as well as platelet antiaggregatory effects, has been approved for chronic administration either by continuous subcutaneous or intravenous infusion for the treatment of PAH. Tyvaso® (treprostinil) Inhalation Solution has also been approved for the treatment of PAH by the inhalation route. An oral formulation of treprostinil will allow patients to benefit from the ease of drug administration.

Tg.rasH2 Mouse Carcinogenicity Study: A 26-week oral carcinogenicity study was conducted in hemizygous Tg.rasH2 mice. For the main study, groups of mice (25/sex/group) were randomly assigned to receive the test drug by oral gavage at dose levels of 0 (water), 5, 10 and 20 mg/kg/day in males and 0, 3, 7.5 and 15 mg/kg/day in females (doses expressed as the free acid) once daily for 26 weeks. The positive control group animals (15/sex) received a total of 3 ip injections of urethane (1000 mg/kg/day) in saline on study Days 1, 3 and 5. For toxicokinetic (TK) evaluation, wildtype littermate mice (5/sex in the control group and 23/sex in the treated groups) were dosed with UT-15C by oral gavage once daily until blood collection on Days 176-177. In-life evaluation parameters included mortality, clinical signs of toxicity, body weight and food consumption. A complete necropsy was performed on all main study animals that were found dead or killed *in extremis* or sacrificed at study termination. All gross pathologic findings were recorded and protocol-specified organs were weighed. Tissues from all animals and all gross lesions were examined microscopically. All data were analyzed statistically.

There was no treatment-related increased incidence of mortality in either sex following treatment with the test drug compared to vehicle control. Oral administration of UT-15C in Tg.rasH2 male and female mice daily for 26 weeks did not significantly increase the

incidence of tumors in drug treated groups when compared to the vehicle control group. Statistically significant increases in mortality ($p<0.05$) were noted in both sexes of the positive control group when compared to vehicle control. The positive control group had statistically significant increased incidences ($p<0.05$) of pulmonary (adenoma, carcinoma and hemangiosarcoma) and splenic (hemangiosarcoma) tumors in both sexes.

Executive CAC Recommendations and Conclusions:

Tg.rasH2 mouse study:

- The Committee agreed that the study was adequate, noting prior Exec CAC concurrence with the protocol.

- The Committee concluded that there were no drug-related neoplasms.

Abigail Jacobs, Ph.D
Acting Chair, Executive CAC

cc:\
/Division File, DCRP
/TPapoian, DCRP
/XJoseph, DCRP
/DBrum, DCRP
ASeifried, OND IO

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/s/

ADELE S SEIFRIED
06/28/2012

ABIGAIL C JACOBS
06/28/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203496

PROPRIETARY NAME REQUEST
UNACCEPTABLE

United Therapeutics Corp.
55 TW Alexander Drive
P.O. Box 14186
Research Triangle Park, NC 27709

Attention: Hilary Hafeken
Regulatory Informatics Manager

Dear Ms. Hafeken:

Please refer to your New Drug Application (NDA) dated December 24, 2011, received December 27, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for treprostinil diethanolamine extended-release tablets, 0.125 mg, 0.25 mg, (b) (4) 1 mg, and 2.5 mg.

We also refer to your February 27, 2012, correspondence, received February 28, 2012, requesting review of your proposed proprietary name, (b) (4) We have completed our review of (b) (4) and have concluded that this name is unacceptable for the following reasons:

(b) (4)

(b) (4)

We note that you have proposed an alternate proprietary name in your submission dated February 27, 2012. In order to initiate the review of the alternate proprietary name, (b) (4) submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Cherye Milburn, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2084. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Dan Brum at (301) 796-0578.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
05/25/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203496

FILING COMMUNICATION

United Therapeutics Corp.
Attention: Mr. Dean Bunce
EVP, Regulatory Affairs & Compliance
55 TW Alexander Drive
P.O. Box 14186
Research Triangle Park, NC 27709

Dear Mr. Bunce:

Please refer to your New Drug Application (NDA) dated December 24, 2011, received December 27, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (treprostinil diethanolamine) 0.125 mg, 0.25 mg, (b) (4) 1 mg, and 2.5 mg sustained-release tablets.

We also refer to your amendments dated January 13, 26, and 31, and February 10, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 27, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 29, 2012.

During our filing review of your application, we identified the following potential review issues and we request that you submit the following information:

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
During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

Highlights (HL)

☒ HL should be limited in length to one-half page. If it is longer than one-half page, please shorten to one-half page or request a waiver. Note that all Warnings and Precautions listed in the Full Prescribing Information (FPI) do not need to be included

in Highlights. Therefore, clinical judgment should be used to ascertain which Warnings and Precautions to include in Highlights and which are not necessary. Some of the information in the Warnings and Precautions section may be more appropriately placed in Dosage and Administration e.g., dosage-related changes based on a drug-drug interaction.

☒ There is redundancy of information. Please revise the information to eliminate redundancy e.g., Warnings and Precautions and Drug Interactions has redundant information.

☒ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type. Note that in the submitted draft labeling, all text in column 1 is unbolded and all text in column 2 is bolded. Please revise.

☒ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information e.g., Contraindications.

Product Title

☒ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

Initial U.S. Approval

☒ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. Because treprostinil diethanolamine is not an NME, the year must correspond to that of Remodulin i.e., 2002.

Recent Major Changes (RMC)

☒ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions. Please delete this section.

Indications and Usage

☒ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)]." Identify the established pharmacologic class for the drug at:

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm

e.g., (b) (4) is a prostacyclin vasodilator indicated for…

Patient Counseling Information Statement

☒ Must include the verbatim statement: "**See 17 for Patient Counseling Information**" or if the product has FDA-approved patient labeling: "**See 17 for Patient Counseling Information and (insert either "FDA-approved patient labeling" or "Medication Guide")**.

e.g., **See 17 for Patient Counseling Information and FDA-approved patient labeling**

Revision Date

☒ A placeholder for the revision date, presented as "Revised: MM/YYYY or Month Year," must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Full Prescribing Information (FPI)

☒ A horizontal line must separate the TOC and FPI.

Adverse Reactions

☒ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided. Please provide explanation for any proposals to use a different terminology e.g., adverse event.

☒ For the "Clinical Trials Experience" subsection, 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 clinical practice."

Patient Counseling Information

☒ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:

"See FDA-approved patient labeling (Patient Information)"

We request that you resubmit labeling that addresses these issues by March 2, 2012. The resubmitted labeling will be used for further labeling discussions.

While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because treprostinil diethanolamine for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, please call Dan Brum, Pharm.D., RAC, Regulatory Project Manager, at (301)796-0578.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
02/17/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203496

NDA ACKNOWLEDGMENT

United Therapeutics Corp.
Attention: Mr. Dean Bunce
EVP, Regulatory Affairs & Compliance
55 TW Alexander Drive
P.O. Box 14186
Research Triangle Park, NC 27709

Dear Mr. Bunce:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: (b) (4) (treprostinil diethanolamine) Sustained Release Tablets, 0.125 mg, 0.25 mg, (b) (4) 1 mg and 2.5 mg

Date of Application: December 23, 2011

Date of Receipt: December 27, 2011

Our Reference Number: NDA 203496

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 25, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, please contact:

Dan Brum, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0578

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM
12/29/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: August 31, 2012

TO BE COMPLETED BY APPLICANT

The following information concerning See attachment to Form FDA 3455 (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study TDE-PH-301, TDE-PH-302 and TDE-PH-308 (*Name of clinical study*) is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable check boxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☒ any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest, as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Dean Bunce	EVP, Regulatory Affairs & Compliance
FIRM/ORGANIZATION: United Therapeutics Corporation	
SIGNATURE: {See Appended Electronic Signature Page}	Date (mm/dd/yyyy): 12/21/2011

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

0000 Form FDA 3455

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
Dean Bunce	Regulatory Affairs Approval	21-Dec-2011 19:25 GMT-05

28 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: August 31, 2012

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See attachment to Form FDA 3454	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Dean Bunce	EVP, Regulatory Affairs & Compliance
FIRM/ORGANIZATION	
United Therapeutics Corporation	
SIGNATURE	DATE *(mm/dd/yyyy)*
{See Appended Electronic Signature Page}	12/21/2011

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
1350 Piccard Drive, 420A
Rockville, MD 20850

0000 Form FDA 3544 Financial Certification

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
Dean Bunce	Regulatory Affairs Approval	21-Dec-2011 19:25 GMT-05

Form Approved: OMB No. 0910 - 0297 Expiration Date: January 31, 2013. See instructions for OMB Statement, below.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on FDA's website: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

1. APPLICANT'S NAME AND ADDRESS	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
UNITED THERAPEUTICS CORP Hilary Hafeken United Therapeutics Corp. 55 TW Alexander Drive PO Box 14186 Research Triangle Park NC 27709 US	203-496
2. NAME AND TELEPHONE NUMBER OF REPRESENTATIVE 919-4858350	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? [X] YES [ ] NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: [X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION [ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:
3. PRODUCT NAME treprostinil diethanolamine	6. USER FEE I.D. NUMBER PD3011988

7. ARE YOU REDEEMING A PRIORITY REVIEW VOUCHER FOR THE TREATMENT OF TROPICAL DISEASES? [ ] YES [X] NO

PRIORITY REVIEW VOUCHER NUMBER:

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.
[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)
[X] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION

736(a)(1)(F) of the Federal Food,Drug, and Cosmetic Act
[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY

9. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO
If a waiver has been granted, include a copy of the official FDA notification with your submission.

OMB Statement:
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Office of Information Management (HFA-710) 1350 Piccard Drive, 4th Floor Rockville, MD 20850	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

PRINTED NAME AND SIGNATURE OF AUTHORIZED REPRESENTATIVE	TITLE	DATE
Dean Bunce *{See Appended Electronic Signature Page}*	EVP, Regulatory and Compliance	

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
$0.00

Form FDA 3397 (01/10)

INSTRUCTIONS FOR COMPLETING PRESCRIPTION DRUG USER FEE COVER SHEET FORM FDA 3397

Form FDA 3397 is to be completed for and submitted with each new drug or biologic product original application or supplemental application submitted to the Agency on or after April 30, 2001, unless specifically exempted below. Form FDA 3397 should be placed in the first volume of the application with the application (FORM FDA 356(h)) form. Form FDA 3397 is to be completed on-line at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119184.htm. If you need assistance in completing the form call 301-796-7200 or email: userfees@fda.gov.

NOTE: Form FDA 3397 need not be submitted for:

CDER

505(j) applications
Supplements to 505(j) applications

CBER

Any supplement that does not require clinical data for approval.
Applications and supplements for:

* Products for further manufacturing use only
* Whole blood or blood components for transfusion
* Bovine blood product for topical application licensed before September 1, 1992
* A crude allergenic extract product
* An in vitro diagnostic biological product licensed under Section 351 of the PHS Act

ITEM NO.	INSTRUCTIONS
1-2.	**Self-explanatory**
3.	**PRODUCT NAME:** Include generic name and trade name, as applicable.
4.	**BLA STN / NDA NUMBER - FOR AN ORIGINAL BIOLOGIC LICENSE APPLICATION (BLA) -** Indicate the 6-digit BLA number (Submission Tracking Number (STN)) if pre-assigned, otherwise leave blank. For A **SUPPLEMENT** enter the BLA STN. **FOR DRUG PRODUCTS:** Indicate the new drug application (NDA) number. NDA numbers can be obtained by completing the information at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm114027.htm.
5.	**CLINICAL DATA:** The definition of 'clinical data' for the assessment of user fees is found in FDA's Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees. FDA's guidance on the definition of clinical data can be found on FDA's web site: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.
6.	**USER FEE I.D. NUMBER:** Please include the ID number (generated when completing Form FDA 3397) on the application payment check.
7.	**PRIORITY REVIEW VOUCHER:** If you are redeeming a priority review voucher awarded to a sponsor of a tropical disease product application (see section 524 of the Federal Food, Drug, and Cosmetic Act (FD&C Act)), please include the priority review voucher number assigned when the voucher was initially granted. See FDA's Guidance for Industry: Tropical Disease Priority Review Vouchers for further information. FDA's guidance can be found on FDA's web site: http://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
8.	**EXCLUSIONS:** The application is for an orphan drug product. Under section 736(a) (1) (F) of the FD&C Act, a human drug application is not subject to an application fee if the proposed product is for a rare disease or condition designated under section 526 of the FD&C Act (orphan drug designation) AND the application does not include an indication that is not so designated. A supplement is not subject to an application fee if it proposes to include a new indication for a rare disease or condition, and the drug has been designated pursuant to section 526 for a rare disease or condition with regard to the indication proposed in the supplement. A copy of the FDA letter granting orphan designation should be included with the BLA/NDA submission.
9.	**WAIVER:** Complete this section only if a waiver of user fees, including the small business waiver, has been granted for this application. *A copy of the official FDA notification that the waiver has been granted must be provided with the BLA/NDA submission.*

2011-12-16 PDUFA Cover Sheet

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
Dean Bunce	Regulatory Affairs Approval	20-Dec-2011 13:26 GMT-05