CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203496Orig1s000

CHEMISTRY REVIEW(S)

NDA 203496

Orenitram (treprostinil) Extended Release Tablets 0.125, 0.25, 1 and 2.5 mg

United Therapeutics, Inc.

Division of Cardiology and Renal Products, HFD 110

Shastri Bhamidipati, Ph.D.
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

Submission Date : 16-AUG-2013
PDUFA Goal Date: 16-FEB-2014

Reference ID: 3419754

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1. NDA 203496

2. REVIEW #: 4

3. REVIEW DATE: 10-DEC-2013

4. REVIEWER: Shastri Bhamidipati, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 203496 Original Submission	27-DEC-2011
SD#15 Quality Information	10-AUG-2012
SD#18 Quality Information	24-SEPT-2012
SD# 21 Quality Information	19-OCT-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
SD#33 Class 2 Resubmission	16-AUG-2013
SD# 36 Labeling	08-OCT-2013
SD#37 Labeling/Container-Carton Draft	29-OCT-2013
SD#38 Labeling/PPI draft	12-NOV-2013
SD# 39 Proprietary Name	27-NOV-2013

7. NAME & ADDRESS OF APPLICANT:

Name: United Therapeutics, LLC

Address: 55 TW Alexander Drive
PO Box 14186
Research Triangle Park, NC 27709

Reference ID: 3419754

Chemistry Review Data Sheet

Representative: Dean Bunce,
Executive Vice President,
Regulatory Affairs & Compliance
55 TW Alexander Drive
PO Box 14186
Research Triangle Park, NC 27709

Telephone: 919-485-8350

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Treprostinil Extended Release Tablets (Trade name not finalized)
b) Non-Proprietary Name (USAN): Treprostinil Diolamine
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.50, 505(b)(1)

10. PHARMACOL. CATEGORY: Cardiology, Pulmonary Arterial Hypertension (PAH)

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 0.125, 0.25, 1.0 and 2.5 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___X__ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

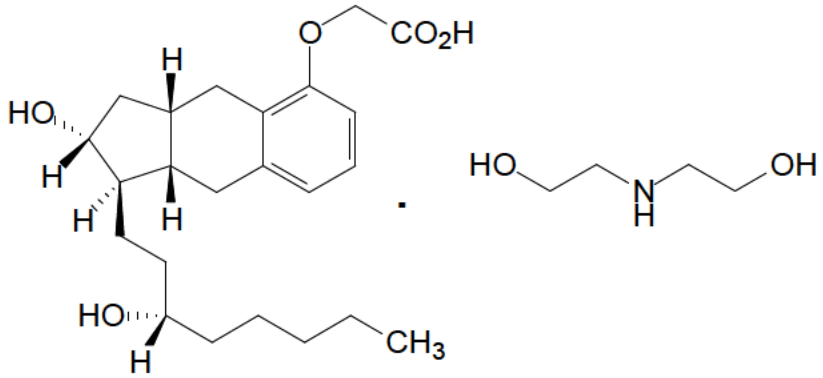
Reference ID: 3419754

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s):

1. Acetic acid, 2-[[(1*R*,2*R*,3a*S*,9a*S*)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-1*H*-benz[*f*]inden-5-yl]oxy]-, compd. with 2,2'-iminobis[ethanol] (1:1)

2. 2-hydroxy-*N*-(2-hydroxyethyl)ethanaminium 2-({(1*R*,2*R*,3a*S*,9a*S*)-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*]naphthalen-5-yl}oxy)acetate



Molecular Formula: $C_{23}H_{34}O_5.C_4H_{11}NO_2$
Molecular Weight: 495. 66 (salt form) 390.52 (acid form)
CAS: [830354-48-8]
Laboratory Code : UT-15C

17. RELATED/SUPPORTING DOCUMENTS*:

* Sponsor submitted pertinent DMF information (DMF holders and LOA) (b) (4) [redacted]

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4) [redacted]	II	[redacted]	[redacted]	[redacted]	(b) (4) [redacted]		
	II						

Reference ID: 3419754

(b) (4)			(b) (4)	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	71537	Treprostinil Diethanolamine

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER(S)
Biometrics			
EES	Acceptable	09-DEC-2013	
Pharm/Tox	Recommended Approval	03-OCT-2012	Joseph Xavier
Biopharmaceutics/ Clinical Pharmacology	Recommended approval.	30-AUG-2012 02-OCT-2012	Akm Khairuzzaman S.Hariharan
Methods Validation	Not requested. The methods are		

Reference ID: 3419754

	conventional and do not qualify for internal validation by FDA labs		
DMEPA	Proposed Trade names (b) (4) were duly reviewed and determined unacceptable. Newly proposed trade name, Orenitram, is acceptable.	Nov-29-2013	Loretta Holmes
EA	Categorical Exclusion granted		
Microbiology	Not Applicable		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

Chemistry Review for NDA 203496

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA 203496 for Orenitram (treprostinil) Extended Release Tablets (0.125, 0.25, 1 and 2.5 mg) is approvable from CMC perspective based on evaluation of labeling, container/carton draft information provided in the resubmission (SD#33 16-Aug-2013) and subsequent amendments. DMEPA has reviewed the proposed tradename, "Orenitram" for the drug product and deemed acceptable.

Please refer to Quality Reviews filed in DARRTS for additional information. Office of Compliance has provided a final overall acceptable recommendation for all manufacturing and testing facilities for this NDA (Summary report attached).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None applicable .

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The proposed drug product, Orenitram consists of the active Treprostinil , a tricyclic benzindene analogue of prostacyclin as a diethanolamine salt which is a new chemical entity (NCE) developed to treat Pulmonary Arterial Hypertension (PAH). Remodulin (treprostinil) Injection and Tyvaso (treprostinil) Inhalation Solution are currently marketed by the sponsor, United Therapeutics, for the same indication of PAH. This drug product is an alternate and new oral dosage form developed as a sustained release formulation designed to deliver the active over 12 hr period at zero-order kinetics employing , "EnSoTrol® Osmotic Technology platform". This technology entails coating of drug product tablet cores with a semi-permeable membrane agent and a single aperture is laser-drilled on one side of the tablet through which the drug is released upon administration. The drug product is a round biconvex tablet consisting of 0.125, 0.25, (b) (4) 1 and 2.5 mg of active treprostinil (acid form) with strength identifying (b) (4) green, white, yellow and pink (b) (4) coating respectively. The tablets are also printed on one side with, "UT" and the corresponding strength in black. The formulation consists of the pharmaceutical excipients, xylitol, maltodextrin, sodium lauryl sulfate, magnesium stearate, cellulose acetate, and triethyl citrate (b) (4) The drug product is intended to be marketed as 100 count tablets packaged in 40 cc HDPE opaque white plastic bottle and a (b) (4)

Reference ID: 3419754

(b) (4) closure with induction seal liner. Each bottle also contains (b) (4) desiccant pouch and (b) (4) coil.

Treprostinil sustained release tablet formulation was developed (b) (4) The stability of 33 batches of Treprostinil sustained release tablets manufactured at pilot and commercial scale and packaged in HDPE containers, (b) (4) stored at long term (25°C/60%RH), intermediate (30°C/75%RH) and accelerated (40°C/75%RH) storage conditions were evaluated for appearance, assay, impurities, dissolution and (b) (4) for stability per ICH guideline. Stability data obtained were statistically assessed by pooling of batches (including registration batches up to 18 months) and linear regression analysis was employed for estimation of expiration dating and proposed shelf-life (b) (4) The sponsor submitted evaluation of stability data (up to 24 months) for registration batches in terms of revised acceptance criteria for dissolution in response to information request (IR) letter in support of the proposed (b) (4) shelf-life. However, based on evaluation of the stability data, a 30 month shelf-life is recommended for 0.25 and 2.5 mg strength tablets. The drug product is recommended to be stored at 25 °C (77 °F) with excursions permitted to 15-30 °C (59-86 °F) (USP Controlled Room Temperature).

It should be noted that in response to labeling issues identified by DMEPA (b) (4) and communicated in the CR letter, the sponsor has proposed (b) (4) and change the color film-coat for 0.125 mg strength tablet (b) (4) to white.

Drug Substance:

Treprostinil Diethanolamine (UT-15C) is a white to cream-colored solid and consists of five chiral centers with a well-defined single enantiomer associated with each chiral center. The chemical structure of Treprostinil Diethanolamine was determined to be 2-hydroxy-*N*-(2-hydroxyethyl) ethanaminium 2-({(1*R*,2*R*,3a*S*,9a*S*)-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*]naphthalen-5-yl}oxy)acetate. Treprostinil diethanolamine has an aqueous solubility of 453 mg/mL in water. UT-15C is manufactured by United Therapeutics at Silver Spring , MD facility from [redacted] (b) (4) the starting material and the process was qualified by way of its use in manufacturing of two approved drug products namely, Remodulin and Tyvaso. The manufacturing process for the starting material , acquired from two different vendors, was adequately described in the application and appropriately referenced to respective DMFs through Letters of authorization. The final drug substance is obtained in relatively more stable [redacted] (b) (4) The sponsor revised the drug substance specification to include diethanolamine content in UT-15C. The stability of the drug substance is adequately evaluated and proposed retest dating of [redacted] (b) (4) for the drug substance lots is considered acceptable.

B. Description of How the Drug Product is Intended to be Used

The drug product is intended to be marketed as 100 count tablets packaged in 40 cc HDPE opaque white plastic bottle and a [redacted] (b) (4) closure with induction seal liner. Each bottle also contains [redacted] (b) (4) desiccant pouch and [redacted] (b) (4) coil. The recommended storage conditions for the drug product are:

"Store at 25 °C (77 °F) with excursions permitted to 15-30 °C (59-86 °F) (USP Controlled Room Temperature)."

C. Basis for Approvability or Not-Approval Recommendation

The recommendation for approvability of this NDA 203496 for T treprostinil Extended Release Tablets of 0.125, 0.25, 1 and 2.5 mg strengths is based on the evaluation of quality information submitted in the original application and the supporting documents with the recommended changes to the dissolution acceptance criteria, and revised specification for drug substance and the drug product. A shelf-life of 36 months for 0.125 and 1 mg strength tablets and 30 months for the remaining 0.25 and 2.5 mg strength tablets are recommended since the sponsor submitted no additional information.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

C. CC Block

Original NDA 203496
DNP (HFD-110)/NDA Division File
DNP(HFD-110)/CSO/W. Amchin
ONDQA/DNDQAI/Chemist/S. Bhamidipati

Reference ID: 3419754

ONDQA/DNDQAI /Lead/K.Srinivasachar
ONDQA/DNDQAI RPM/Y. Knight
ONDQA/DNDQAI /Branch Chief/O. Stephens

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/s/

SHASTRI P BHAMIDIPATI
12/10/2013

OLEN M STEPHENS
12/10/2013

NDA 203496

Treprostinil Extended Release Tablets
0.125, 0.25, (b) (4) 1 and 2.5 mg

OND Division: Division of Cardiovascular and Renal Products
Applicant: United Therapeutics Corp
Letter Date Jan 31, 2013
Stamp Date Jan 31, 2013
PDUFA Date Mar 31, 2013
Established Name: Treprostinil diethanolamine
Dosage Form: Sustained release tablets
Route of Administration: Oral
Indication: Pulmonary Arterial Hypertension
Quality Reviewer: Shastri Bhamidipati, Ph.D.

Summary:
In response to labeling issues identified by DMEPA (b) (4) and communicated in the CR letter, the sponsor has proposed (b) (4) and change the color film-coat for 0.125 mg strength tablet (b) (4) to white. If this change is acceptable to the Agency, the sponsor will place the first three commercial lots on stability and submit the data. No additional information was provided in the resubmission.

At the end of 1st review cycle, we have determined that the NDA is approvable from CMC perspective and recommended a shelf life of 36 months for 0.125, (b) (4) and 1 mg strengths and 30 months for 0.25 and 2.5 mg strengths based on stability data presented in the original NDA and the amendments.

This change in strengths is considered acceptable from ONDQA perspective and reportable in annual reports per SUPAC guidance. If the clinical division were to approve this NDA after completion of reviewing this resubmission, we will still recommend 36 months shelf for 0.125 and 1 mg strength tablets and 30 months for the remaining 0.25 and 2.5 mg strength tablets since the sponsor submitted no additional information.

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/s/

SHASTRI P BHAMIDIPATI
03/22/2013

RAMESH K SOOD
03/22/2013

NDA 203496

Treprostinil Extended Release Tablets
0.125, 0.25, (b) (4) 1 and 2.5 mg

United Therapeutics, Inc.

Division of Cardiology and Renal Products, HFD 110

Shastri Bhamidipati, Ph.D.
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

Submission Date : 27-DEC-2011
PDUFA Goal Date: 27-OCT-2012

Reference ID: 3205838

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- **A. Reviewer's Signature** 10
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- **C. CC Block** 10

Reference ID: 3205838

Chemistry Review Data Sheet

1. NDA 203496

2. REVIEW #: 2

3. REVIEW DATE: 19-OCT-2012

4. REVIEWER: Shastri Bhamidipati, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 203496 Original Submission	27-DEC-2011
SD#15 Quality Information	10-AUG-2012

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
SD#18 Quality Information	24-SEPT-2012
SD# 21 Quality Information	19-OCT-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	United Therapeutics, LLC
Address:	55 TW Alexander Drive PO Box 14186 Research Triangle Park, NC 27709
Representative:	Dean Bunce, Executive Vice President, Regulatory Affairs & Compliance 55 TW Alexander Drive PO Box 14186 Research Triangle Park, NC 27709
Telephone:	919-485-8350

Reference ID: 3205838

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Treprostinil Extended Release Tablets (Trade name not finalized)
b) Non-Proprietary Name (USAN): Treprostinil Diolamine
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.50, 505(b)(1)

10. PHARMACOL. CATEGORY: Cardiology, Pulmonary Arterial Hypertension (PAH)

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 0.125, 0.25, (b) (4) 1.0 and 2.5 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___X__ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

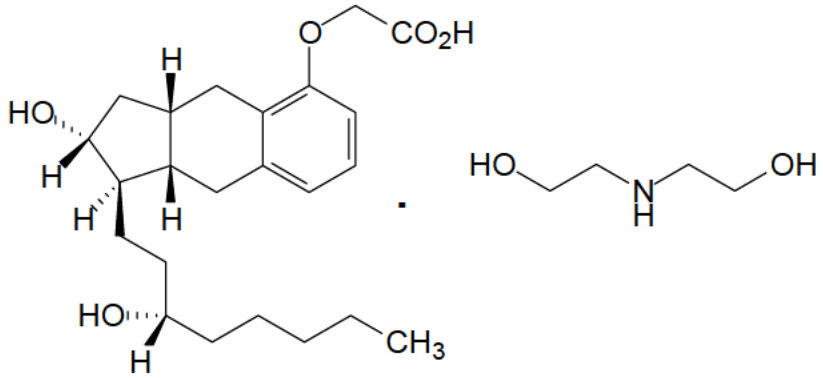
Reference ID: 3205838

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s):

1. Acetic acid, 2-[[(1*R*,2*R*,3a*S*,9a*S*)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-1*H*-benz[*f*]inden-5-yl]oxy]-, compd. with 2,2'-iminobis[ethanol] (1:1)

2. 2-hydroxy-*N*-(2-hydroxyethyl)ethanaminium 2-({(1*R*,2*R*,3a*S*,9a*S*)-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*]naphthalen-5-yl}oxy)acetate



Molecular Formula: $C_{23}H_{34}O_5.C_4H_{11}NO_2$
Molecular Weight: 495. 66 (salt form) 390.52 (acid form)
CAS: [830354-48-8]
Laboratory Code : UT-15C

17. RELATED/SUPPORTING DOCUMENTS*:

* Sponsor submitted pertinent DMF information (DMF holders and LOA) (b) (4) [redacted]

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4) [redacted]	II	[redacted]	(b) (4) [redacted]	3,4	Active and up to date		
	II			3,4	Active and up to date		
				4	N/A		

Reference ID: 3205838

(b) (4)		(b) (4)				
			4	N/A		
			4	N/A		
			4	N/A		
			4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	71537	Treprostinil Diethanolamine

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER(S)
Biometrics			
EES	Acceptable	16-OCT-2012	
Pharm/Tox	Recommended Approval	03-OCT-2012	Joseph Xavier
Biopharmaceutics/ Clinical Pharmacology	Recommended approval.	30-AUG-2012 02-OCT-2012	Akm Khairuzzaman S.Hariharan
Methods Validation	Not requested. The methods are		

Reference ID: 3205838

	conventional and do not qualify for internal validation by FDA labs		
DMEPA	Proposed Trade names, (b) (4) [redacted] were duly reviewed and determined unacceptable. Newly proposed trade name, Orenitram, is under evaluation.	July-26-2012	Forest Ford
EA	Categorical Exclusion granted		
Microbiology	Not Applicable		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

Chemistry Review for NDA 203496

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA 203496 for Treprostinil Extended Release Tablets (0.125, 0.25, (b) (4) 1 and 2.5 mg) is approvable from CMC perspective. This review includes evaluation of sponsor provided responses to the information request letter dated 28-August-2012, 24-Sept-2012 and 19-Oct-2012. Please refer to Quality Review #1 filed in DARRTS on 28-August-2012 for additional information. Office of Compliance has provided a final overall acceptable recommendation for all manufacturing and testing facilities for this NDA.

It should be noted that proposed tradenames, (b) (4) for the drug product were considered not acceptable by DMEPA and most recently proposed tradename, "Orenitram" is under evaluation. In addition, changes to labeling are not completed.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None applicable .

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The proposed drug product, Orenitram consists of the active Treprostinil , a tricyclic benzindene analogue of prostacyclin as a diethanolamine salt which is a new chemical entity (NCE) developed to treat Pulmonary Arterial Hypertension (PAH). Remodulin (treprostinil) Injection and Tyvaso (treprostinil) Inhalation Solution are currently marketed by the sponsor, United Therapeutics, for the same indication of PAH. This drug product is an alternate and new oral dosage form developed as a sustained release formulation designed to deliver the active over 12 hr period at zero-order kinetics employing , "EnSoTrol® Osmotic Technology platform". This technology entails coating of drug product tablet cores with a semi-permeable membrane agent and a single aperture is laser-drilled on one side of the tablet through which the drug is released upon administration. The drug product is a round biconvex tablet consisting of 0.125, 0.25, (b) (4) 1 and 2.5 mg of active treprostinil (acid form) with strength identifying (b) (4) green, white, yellow and pink (b) (4) coating respectively. The tablets are also printed on one side with, "UT" and the corresponding strength in black. The formulation consists of the pharmaceutical excipients, xylitol, maltodextrin, sodium lauryl sulfate, magnesium stearate, cellulose acetate, and triethyl citrate (b) (4)

Reference ID: 3205838

(b) (4) The drug product is intended to be marketed as 100 count tablets packaged in 40 cc HDPE opaque white plastic bottle and a (b) (4) closure with induction seal liner. Each bottle also contains (b) (4) desiccant pouch and (b) (4) coil.

Treprostinil sustained release tablet formulation was developed (b) (4) The stability of 33 batches of Treprostinil sustained release tablets manufactured at pilot and commercial scale and packaged in HDPE containers, (b) (4) stored at long term (25°C/60%RH), intermediate (30°C/75%RH) and accelerated (40°C/75%RH) storage conditions were evaluated for appearance, assay, impurities, dissolution and (b) (4) for stability per ICH guideline. Stability data obtained were statistically assessed by pooling of batches (including registration batches up to 18 months) and linear regression analysis was employed for estimation of expiration dating and proposed shelf-life (b) (4) The sponsor submitted evaluation of stability data (up to 24 months) for registration batches in terms of revised acceptance criteria for dissolution in response to information request (IR) letter in support of the proposed (b) (4) shelf-life. However, based on evaluation of the stability data, a 30 month shelf-life is recommended for 0.25 and 2.5 mg strength tablets. The drug product is recommended to be stored at 25 °C (77 °F) with excursions permitted to 15-30 °C (59-86 °F) (USP Controlled Room Temperature).

Drug Substance:

Treprostinil Diethanolamine (UT-15C) is a white to cream-colored solid and consists of five chiral centers with a well-defined single enantiomer associated with each chiral center. The chemical structure of Treprostinil Diethanolamine was determined to be 2-hydroxy-*N*-(2-hydroxyethyl)ethanaminium 2-({(1*R*,2*R*,3a*S*,9a*S*)-2-hydroxy-1-[(3*S*)-3-

Reference ID: 3205838

hydroxyoctyl]-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*]naphthalen-5-yl}oxy)acetate. Treprostinil diethanolamine has an aqueous solubility of 453 mg/mL in water. UT-15C is manufactured by United Therapeutics at Silver Spring , MD facility from [redacted] (b) (4) the starting material and the process was qualified by way of its use in manufacturing of two approved drug products namely, Remodulin and Tyvaso. The manufacturing process for the starting material , acquired from two different vendors, was adequately described in the application and appropriately referenced to respective DMFs through Letters of authorization. The final drug substance is obtained in relatively more stable [redacted] (b) (4) conditions. The sponsor revised the drug substance specification to include diethanolamine content in UT-15C. The stability of the drug substance is adequately evaluated and proposed retest dating of [redacted] (b) (4) for the drug substance lots is considered acceptable.

B. Description of How the Drug Product is Intended to be Used

The drug product is intended to be marketed as 100 count tablets packaged in 40 cc HDPE opaque white plastic bottle and a [redacted] (b) (4) closure with induction seal liner. Each bottle also contains [redacted] (b) (4) desiccant pouch and [redacted] (b) (4) coil. The recommended storage conditions for the drug product are:

"Store at 25 °C (77 °F) with excursions permitted to 15-30 °C (59-86 °F) (USP Controlled Room Temperature)."

C. Basis for Approvability or Not-Approval Recommendation

The recommendation for approvability of this NDA 203496 for T treprostinil Extended Release Tablets of 0.125, 0.25, [redacted] (b) (4) 1 and 2.5 mg strengths is based on the evaluation of quality information submitted in the original application and the supporting documents with the recommended changes to the dissolution acceptance criteria, and revised specification for drug substance and the drug product.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

C. CC Block

Original NDA 203496
DNP (HFD-110)/NDA Division File
DNP(HFD-110)/CSO/D. Brum
ONDQA/DNDQAI/Chemist/S. Bhamidipati
ONDQA/DNDQAI /Lead/K.Srinivasachar
ONDQA/DNDQAI RPM/T. Bouie
ONDQA/DNDQAI /Branch Chief/R. Sood

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Reference ID: 3205838

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/s/

SHASTRI P BHAMIDIPATI
10/19/2012

RAMESH K SOOD
10/19/2012

NDA 203496

[redacted] (b) (4) ™

(Treprostinil) Extended Release Tablets
0.125, 0.25, [redacted] (b) (4) 1 and 2.5 mg

United Therapeutics, Inc.

Division of Cardiology and Renal Products, HFD 110

Shastri Bhamidipati, Ph.D.
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment

Submission Date : 27-DEC-2011
PDUFA Goal Date: 27-OCT-2012

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Reference ID: 3181252

Chemistry Review Data Sheet

1. NDA 203496

2. REVIEW #: 1

3. REVIEW DATE: 20-AUG-2012

4. REVIEWER: Shastri Bhamidipati, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 203496 Original Submission	27-DEC-2011
SD#9 Quality Information	12-APR-2012
SD#12 Quality Information	06-JUN-2012
SD#15 Quality Information	10-AUG-2012

7. NAME & ADDRESS OF APPLICANT:

Name: United Therapeutics, LLC

Address: 55 TW Alexander Drive
PO Box 14186
Research Triangle Park, NC 27709

Reference ID: 3181252

Chemistry Review Data Sheet

Representative: Dean Bunce,
Executive Vice President,
Regulatory Affairs & Compliance
55 TW Alexander Drive
PO Box 14186
Research Triangle Park, NC 27709

Telephone: 919-485-8350

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4)
b) Non-Proprietary Name (USAN): Treprostinil Diolamine
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.50, 505(b)(1)

10. PHARMACOL. CATEGORY: Cardiology, Pulmonary Arterial Hypertension (PAH)

11. DOSAGE FORM: Extended Release Tablets

12. STRENGTH/POTENCY: 0.125, 0.25, (b) (4) 1.0 and 2.5 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___X__ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

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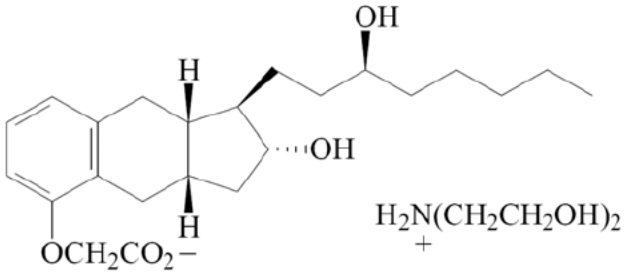
1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s):

1. Acetic acid, 2-[[(1*R*,2*R*,3a*S*,9a*S*)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-1*H*-benz[*f*]inden-5-yl]oxy]-, compd. with 2,2'-iminobis[ethanol] (1:1)

2. 2-hydroxy-*N*-(2-hydroxyethyl)ethanaminium 2-({(1*R*,2*R*,3a*S*,9a*S*)-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*]naphthalen-5-yl}oxy)acetate



Molecular Formula: $C_{23}H_{34}O_5.C_4H_{11}NO_2$
Molecular Weight: 495. 66 (salt form) 390.52 (acid form)
CAS: [830354-48-8]
Laboratory Code : UT-15C

Note : The above structure and chemical names are not consistent with USAN.

17. RELATED/SUPPORTING DOCUMENTS*:

* Sponsor submitted pertinent DMF information (DMF holders and LOA) (b) (4) [redacted]

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4) [redacted]	II	[redacted]	(b) (4) [redacted]	3,4	Active and up to date		
[redacted]	II	[redacted]	[redacted]	3,4	Active and up to date		
[redacted]	[redacted]	[redacted]	[redacted]	4	N/A		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	4	N/A		

		(b) (4)				
(b) (4)						
			4	N/A		
			4	N/A		
			4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	71537	Treprostinil Diethanolamine

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER(S)
Biometrics			
EES	Final Recommendation pending		
Pharm/Tox	Review pending		
Biopharmaceutics	Recommended changes to dissolution acceptance criteria were accepted by the sponsor. Review to be filed in DARRTS.		Akm Khairuzzaman
Methods Validation	Not requested. The methods are conventional and do not qualify for		

	internal validation by FDA labs		
DMEPA	Proposed Trade name, (b) (4) is unacceptable. Newly proposed trade name, (b) (4) is under evaluation.	July-26-2012	Forest Ford
EA	Categorical Exclusion granted		
Microbiology	Not Applicable		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

Chemistry Review for NDA 203496

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA 203496 for [redacted] (b) (4) (treprostinil) Extended Release Tablets (0.125, 0.25, [redacted] (b) (4) 1 and 2.5 mg) is approvable from CMC perspective pending resolution to deficiencies communicated to the sponsor (August-27-2012) at the end of this review. Recommended shelf life is 36 months for 0.125, [redacted] (b) (4) and 1 mg strength drug product tablets and 30 months for 0.25 and 2.5 mg strength tablets. Additionally, the Office of Compliance has not provided a final recommendation as to the acceptability of manufacturing and testing facilities for this NDA.

Note: [redacted] (b) (4) (Treprostinil diethanolamine) Sustained Release Tablets is the proposed name for the new dosage form for this active in the original NDA. The tradename [redacted] (b) (4) was considered unacceptable by DMEPA and the new tradename [redacted] (b) (4) is under evaluation by DMEPA. Based on quality review, the trade name will include (treprostinil) Extended Release Tablets as the recommended established name. Additionally, Treprostinil Diolamine is the United States Adopted Name (USAN) for Treprostinil Diethanolamine. These names may have been interchangeably used in this review and not intended to cause confusion.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None applicable .

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The proposed drug product [redacted] (b) (4) consists of the active Treprostinil , a tricyclic benzindene analogue of prostacyclin as a diethanolamine salt which is a new chemical entity (NCE) developed to treat Pulmonary Arterial Hypertension (PAH). Remodulin (treprostinil) Injection and Tyvaso (treprostinil) Inhalation Solution are currently marketed by the sponsor, United Therapeutics, for the same indication of PAH. This drug product is an alternate and new oral dosage form developed as a sustained release formulation designed to deliver the active over 12 hr period at zero-order kinetics employing , "EnSoTrol® Osmotic Technology platform". This technology entails coating of drug product tablet cores with a semi-permeable membrane agent and a single aperture is laser-drilled on one side of the tablet through which the drug is released upon administration. The drug product is a round biconvex tablet consisting of 0.125, 0.25, [redacted] (b) (4), 1 and 2.5 mg of active treprostinil (acid form) with strength identifying [redacted] (b) (4), green, white, yellow and pink [redacted] (b) (4)

coating respectively. The tablets are also printed on one side with, "UT" and the corresponding strength in black. The formulation consists of the pharmaceutical excipients, xylitol, maltodextrin, sodium lauryl sulfate, magnesium stearate, cellulose acetate, and triethyl citrate [redacted] (b) (4) The drug product is intended to be marketed as 100 count tablets packaged in 40 cc HDPE opaque white plastic bottle and a [redacted] (b) (4) [redacted] (b) (4) closure with induction seal liner. Each bottle also contains [redacted] (b) (4) desiccant pouch and [redacted] (b) (4) coil.

Treprostinil sustained release tablet formulation was developed [redacted] (b) (4) Batch analysis data for several batches (>65) manufactured through out development were provided and included three batches of each strength as registration batches. The stability of 33 batches of Treprostinil sustained release tablets manufactured at pilot and commercial scale and packaged in HDPE containers. (b) (4) [redacted] stored at long term (25°C/60%RH), intermediate (30°C/75%RH) and accelerated (40°C/75%RH) storage conditions were evaluated for appearance, assay, impurities, dissolution and [redacted] (b) (4) for stability per ICH guideline. Stability data obtained were statistically assessed by pooling of batches (including registration batches up to 18 months) and linear regression analysis was employed for estimation of expiration dating and proposed shelf-life [redacted] (b) (4) The sponsor submitted evaluation of stability data (up to 24 months) for registration batches in terms of revised acceptance criteria for dissolution in response to information request (IR) letter in support of the proposed [redacted] (b) (4) shelf-life. However, based on evaluation of the stability data, a 30 month shelf-life is recommended for 0.25 and 2.5 mg strength tablets. The drug product is recommended to be stored at 25 °C (77 °F) with excursions permitted to 15-30 °C (59-86 °F) (USP Controlled Room Temperature).

Drug Substance:

Treprostinil Diethanolamine (UT-15C) is a white to cream-colored solid and consists of five chiral centers with a well-defined single enantiomer associated with each chiral center. The chemical structure of Treprostinil Diethanolamine was determined to be 2-hydroxy-*N*-(2-hydroxyethyl)ethanaminium 2-({(1*R*,2*R*,3a*S*,9a*S*)-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*]naphthalen-5-yl}oxy)acetate. Treprostinil diethanolamine has an aqueous solubility of 453 mg/mL in water. UT-15C is manufactured by United Therapeutics at Silver Spring , MD facility from [redacted] (b) (4) the starting material and the process was qualified by way of its use in manufacturing of two approved drug products namely, Remodulin and Tyvaso. The manufacturing process for the starting material , acquired from two different vendors, was adequately described in the application and appropriately referenced to respective DMFs through Letters of authorization. The final drug substance is obtained in relatively more stable [redacted] (b) (4) [redacted] While the sponsor agreed to revise the specification for the drug substance to include quantitation of diethanol amine content, details of an appropriate analytical method intended for this purpose and supporting data are pending. The stability of the drug substance is adequately evaluated and proposed retest dating of [redacted] (b) (4) for the drug substance lots is considered acceptable.

B. Description of How the Drug Product is Intended to be Used

[redacted] (b) (4) drug product is intended to be marketed as 100 count tablets packaged in 40 cc HDPE opaque white plastic bottle and a [redacted] (b) (4) closure with induction seal liner. Each bottle also contains [redacted] (b) (4) desiccant pouch and [redacted] (b) (4) coil. The recommended storage conditions for the drug product are:

"Store at 25 °C (77 °F) with excursions permitted to 15-30 °C (59-86 °F) (USP Controlled Room Temperature)."

C. Basis for Approvability or Not-Approval Recommendation

The recommendation for approvability of this NDA 203496 for [redacted] (b) (4) (treprostinil) Extended Release Tablets of 0.125, 0.25, [redacted] (b) (4), 1 and 2.5 mg strengths is based on the evaluation of quality information submitted in the original application and the supporting documents with the recommended changes to the dissolution acceptance criteria and the proposed specification. However, prior to the approval of this NDA, the sponsor has to provide satisfactory information to resolve the deficiencies identified at the end of this review. In addition, the overall recommendation of acceptability of manufacturing and testing facilities from the Office of Compliance is pending.

III. Administrative

A. Reviewer's Signature

Reference ID: 3181252

B. Endorsement Block

Chemist Name/Date: Shastri Bhamidipati, Ph.D.
Chemistry Team Leader Name/Date: Kasturi Srinivasachar, Ph.D.
Project Manager Name/Date:

C. CC Block

Original NDA 203496
DNP (HFD-110)/NDA Division File
DNP(HFD-110)/CSO/D. Brum
ONDQA/DNDQAI/Chemist/S. Bhamidipati
ONDQA/DNDQAI /Lead/K.Srinivasachar
ONDQA/DNDQAI RPM/T. Bouie
ONDQA/DNDQAI /Branch Chief/R. Sood

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/s/

SHASTRI P BHAMIDIPATI
08/28/2012

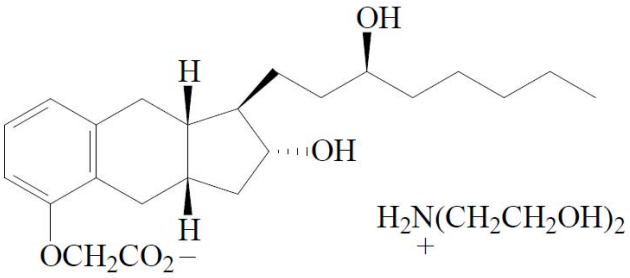
RAMESH K SOOD
08/28/2012

Initial Quality Assessment

Branch I

Pre-Marketing Assessment Division I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	203-496
Applicant:	United Therapeutics Corp
Letter Date	Dec 24, 2011
Stamp Date	Dec 27, 2011
PDUFA Date	Oct 27, 2012
Tradename:	(b) (4) (proposed)
Established Name:	Treprostinil diethanolamine
Dosage Form:	Sustained release tablets
Route of Administration:	Oral
Indication:	Pulmonary Arterial Hypertension
Assessed by:	Akm Khairuzzaman, Ph.D.
ONDQA Fileability:	Yes



treprostinil diethanolamine

Reference ID: 3073883

Summary

This is an e-CTD 505(b)(1) NDA for a sustained release tablets (osmotic pump system) containing treprostinil diethanolamine (UT-15C), a chemically stable tricyclic analog of prostacyclin (PGI2) for the treatment of Pulmonary Arterial Hypertension (PAH). Treprostinil diethanolamine is a salt, the base of which is also manufactured by the same applicant for the approved drug products namely: Remodulin (treprostinil) Injection and Tyvaso (treprostinil) Inhalation Solution. Both these drug products are also manufactured by the same applicant, United Therapeutics Inc. Therefore, under this NDA, the applicant has referenced to NDA-22-387 for the same active moiety, but also provided detailed information on the drug substance. An orphan drug designation was granted for this drug on June 17, 2010. There was no CMC specific pre-NDA meeting and related IND is 71537.

Drug Substance

The active ingredient (drug substance) is a diethanolamine salt of an existing approved drug, treprostinil manufactured by the same applicant. The manufacturing process of the active pharmaceutical ingredient, treprostinil diethanolamine was thus developed by this applicant in conjunction with the advancement of the manufacturing process for treprostinil based on their prior knowledge. The chemical name of the drug substance is *[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1Hbenz[f]inden-5-yl]oxy]acetic acid•2,2'-iminodiethanol (1:1).*

The compound is a well characterized small molecule with molecular formula $C_{23}H_{34}O_5 \bullet C_4H_{11}NO_2$ and molecular weight 495.66 (salt). It is highly water soluble (453 mg/ml in water) with a pKa value of 3.35. It exists as a white to cream colored (b) (4) solid. The applicant has reported the existence of two polymorphs namely (b) (4) (b) (4) Therefore, there should not be significant solubility differences between these two different forms, which would not contribute to any bioavailability differences. The applicant is claiming this drug as a BCS class I compound based on their extensive solubility and Caco-2 permeability experiment.

The drug substance is manufactured in Silver Spring, Maryland (b) (4) The manufacturing process begins with (b) (4) the drug substance approved in Remodulin (treprostinil) Injection and Tyvaso (treprostinil) Inhalation Solution. The applicant has provided (b) (4) . Additionally, applicant has

Reference ID: 3073883

provided (b) (4) The proposed specification of the drug substance is given in the following table.

Table 1. Regulatory proposed specification of the drug substance

Attribute	Acceptance Criteria
Appearance	A white to cream-colored solid
Identification (IR)	(b) (4)
Identification (diethanolamine)	
Identification (HPLC)	
Residue on Ignition	
Water	
Melting Range	
Specific Rotation	
Heavy Metals	
Organic Volatile Impurities	
Assay	
Impurities	

In total 17 lots of drug substance have been tested after storage under long-term conditions for up to 48 months and accelerated storage conditions up to six months. The details of these data are subject to review. There is no DMF reference for the drug substance and all information pertaining to its manufacture, control, batch analysis and stability are provided in the NDA.

Drug Product

The proposed drug product (b) (4) is a sustained release tablet formulation in (b) (4) different strengths namely: 0.125, 0.25, (b) (4) 1 and 2.5 mg as treprostinil base. They are round biconvex tablets which are (b) (4), green, white, yellow, and pink, respectively. The sustained release mechanism is built on an established technology called "EnSoTrol® Osmotic Technology platform" in which tablets are coated with a semi-permeable membrane with a single laser-drilled aperture through the membrane. The semi permeable membrane allows water to diffuse into the tablets dissolving the drug and osmotic agents resulting in an increased pressure within the core of the tablets known as "osmotic pressure". This pressure is the driving force for the drug to come out of the tablet core through the laser drilled aperture at a kinetic rate of zero order or pseudo zero-

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PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

NDA Number: 203496 **Applicant:** United Therapeutics Corp. **Stamp Date:** 27 Dec 2011
Established/Proper Name: (b) (4) / treprostinil diethanolamine Sustained Release Tablets
NDA Type: 3,4

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		Standard eCTD format.
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		Categorical exclusion is requested.
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Has stability data and analysis been provided to support the requested expiration date?	X		Based on the statistical analysis, the applicant has claimed (b) (4) shelf life (b) (4) months for bottles
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		There was no CMC specific Pre-NDA meeting
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		Several oral formulations were evaluated prior to the selection of a 12-hour SR tablet formulation for final development. Information on all formulations used for clinical studies are provided in 2.7.1.
14	Is there a Methods Validation package?	X		Analytical method validation is provided in 3.2.P.5.3
15	Is a separate microbiological section included?		X	Solid oral dosage form.
16	Have all DMF references been identified?	X		Packaging DMFs see Sec. 1.4.4

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IS THE CMC SECTION OF THE APPLICATION FILEABLE? Yes
If the NDA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant. **NA**

Akm Khairuzzaman, Ph.D.	Jan 19, 2012
Product Quality Reviewer, DPA 1, ONDQA	Date

Ramesh Sood	Jan 19, 2012
Branch Chief, DPA 1, ONDQA	Date

Reference ID: 3073883

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/s/

AKM KHAIRUZZAMAN
01/19/2012

RAMESH K SOOD
01/19/2012