

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-387**

**CHEMISTRY REVIEW(S)**

### CMC BRANCH CHIEF MEMORANDUM

**To:** NDA 22-387  
**From:** Ramesh Sood, Ph.D., Branch Chief, ONDQA  
**Date:** 28-Jul-2009  
**Drug:** Tyvaso (treprostinil) inhalation solution  
**Route of administration:** Oral Inhalation  
**Strength:** 0.6 mg/mL  
**Subject:** "Approval" recommendation for NDA 22-387

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Treprostinil for inhalation (Tyvaso™) is being developed as an alternative to the subcutaneously and intravenously delivered treprostinil solution (Remodulin Injection, NDA 21-272, approved 22-May-2002). Treprostinil is the free acid of a synthetic tricyclic benzindene analogue of prostacyclin. The proposed indication is for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with New York Heart Association (NYHA) Class III symptoms. b(4)

Several pending CMC issues were identified in my previous memo. The company has addressed these issues to the reviewer's satisfaction. The issues related to the drug substance have been resolved.

The facilities related to the manufacturing of the drug product and described in the NDA have been recommended for approval by the Office of Compliance. Categorical exclusion from an environmental assessment requested by the applicant is acceptable.

An acceptable recommendation is made by the microbiology reviewer.

**Recommended action:** The application is recommended for "APPROVAL" from CMC perspective.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22387	ORIG 1	UNITED THERAPEUTICS CORP	TREPROSTINIL FOR INHALATION

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/s/

RAMESH K SOOD  
07/28/2009



**NDA 22-387**

**Tyvaso (treprostinil)  
Inhalation Solution**

**United Therapeutics Corporation**

**Monica D. Cooper, Ph.D.  
ONDQA Pre-Marketing Assessment  
Division I/Branch I**

**Reviewed for the Division of Cardiovascular  
and Renal Products, HFD-110**



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1. NDA 22-387
2. REVIEW #: 2
3. REVIEW DATE: 22-Jul-2009
4. REVIEWER: Monica D. Cooper, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	27-Jun-2008
Amendment (N000 BC)	03-Jul-2008
Amendment (N000 BC)	14-Aug-2008
Amendment (N000 BC)	29-Oct-2008
Amendment (N000 BZ)	25-Feb-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (N000 BZ)	12-Mar-2009 (Revised Carton and Container Labels)
Amendment (N000 BC)	03-Apr-2009 (In-Use Stability Study)
Amendment (N000 BL)	02-Jul-2009 (Revised Carton and Container Labels)
Amendment (N000 BL)	09-Jul-2009 (Revised Carton and Container Labels)
Amendment (N000)	22-Jul-2009 (Revised Carton and Container Labels)



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name	United Therapeutics Corporation
Address	One Park Drive, Suite 400 Research Triangle Park, NC 27709
Representative	Dean Bunce, Sr. VP Regulatory Affairs
Telephone	919-485-8350 ext. 1218
FAX Number	919-313-1298

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name	Tyvaso
Non-Proprietary Name (USAN)	treprostinil
Code Names	UT-15
Chemistry Type	5, 3
Submission Priority	S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Prostacyclin analog for pulmonary arterial hypertension

11. DOSAGE FORM: Sterile Solution

12. STRENGTH/POTENCY: 0.6 mg/mL

13. ROUTE OF ADMINISTRATION: Inhalation

14. Rx/OTC DISPENSED:  Rx  OTC

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

SPOTS product – Form Completed

Not a SPOTS product



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

#### 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

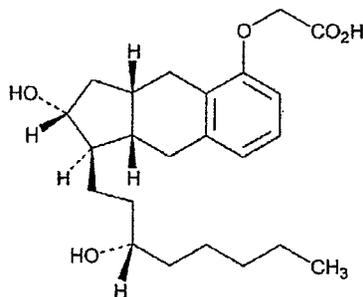
Chemical Names: (1) Acetic acid, [[(1*R*,2*R*,3*aS*,9*aS*)-2,3,3*a*,4,9,9*a*-hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-1*H*-benz[*f*]inden-5-yl]oxy]-

(2) [(1*R*,2*R*,3*aS*,9*aS*)-2-Hydroxy-1-((3*S*)-3-hydroxyoctyl)-2,3,3*a*,4,9,9*a*-hexahydro-1*H*-cyclopent[*b*]naphthalen-5-yl]oxy]acetate

US Adopted Name (USAN): treprostinil

Laboratory Codes: UT-15  
LRX-15  
15AU81

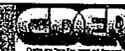
Structural Formula:



Chemical Formula:  $C_{23}H_{34}O_5$   
Molecular Weight: 390.51  
CAS Number: 81846-19-7



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED
—	III	—	b(4)	3	Adequate	24-Apr-2008 (G. Lunn)

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type I 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")

<sup>2</sup> 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	70,362	Treprostinil for Inhalation
NDA	21-272	Remodulin Injection
NDA Supplement	21-272/SCM-010 (approved 01-May-2009)	New DS (treprostinil) Manufacturing Site and Synthetic Process



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

#### 18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	01-Dec-2008	S. Ferguson
LNC	N/A	----	----
Methods Validation	Not Necessary	----	----
OSE-DMEPA	Tradename: Tyvaso Acceptable	01-Jul-2009	J. Park
EA	Categorical Exclusion: Acceptable	23-Mar-2009	M. Cooper (CMC Review #1)
Microbiology	Acceptable	24-Mar-2009	J. Metcalfe



# The Chemistry Review for NDA 22-387

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This new drug application (22-387) is recommended for **APPROVAL** from the perspective of chemistry, manufacturing, and controls.

An information request letter was sent to the applicant on 13-Jan-2009 outlining the CMC information needed to complete this application. An Amendment dated 25-Feb-2009 included a partial response to the issues. The final issue regarding in-use stability of the drug product in the Optineb nebulizer was addressed in the Amendment dated 03-Apr-2009. All CMC issues have now been adequately resolved.

All drug substance information was referenced to NDA 21-272 for Remodulin Injection. A supplement for the new treprostinil drug substance manufacturing facility and synthetic process (NDA 21-272/SCM-010) was approved on 01-May-2009 (see reviews by L. Rocca dated 14-Apr-2009 and T. Bowie dated 01-May-2009).

The adequacy of the Optineb nebulizer is being evaluated by CDRH. A summary of the device issues and the company's responses to deficiencies were provided separately (see consult reviews by Sugato De and Ron Kaye).

The Office of Microbiology (J. Metcalfe) evaluated the sterility assurance of the drug product and found it acceptable (see microbiology review dated 24-Mar-2009).

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

There are no Phase 4 commitments.

### II. Summary of Chemistry Assessments

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

Treprostinil for inhalation (Tyvaso™) was developed as an alternative to the subcutaneously and intravenously delivered treprostinil solution (Remodulin Injection, NDA 21-272, approved 22-May-2002). Treprostinil is the free acid of a synthetic tricyclic benzindene analogue of prostacyclin. The proposed indication is for the treatment of pulmonary arterial



## CHEMISTRY REVIEW



### Executive Summary Section

hypertension (WHO Group I) in patients with New York Heart Association (NYHA) Class III — symptoms. b(4)

#### Drug Substance

Treprostinil is a chemically-synthesized small molecule with 5 stereocenters, manufactured as a single enantiomer. It is a white to cream-colored powder, which is practically insoluble in water. All of the drug substance information was referenced to the approved NDA 21-272 for Remodulin Injection. For the convenience of the reviewer, the applicant provided the drug substance specification table and batch data for 5 recent lots. The current retest date for treprostinil drug substance is — when stored at 2 – 8°C. b(4)

#### Drug Product

The drug product is an aqueous solution of treprostinil (0.6 mg/mL) formulated with sodium chloride, sodium citrate, sodium hydroxide, and hydrochloric acid in water for injection. The excipients are compendial and have been used in previously approved inhalation solutions. The formulation is identical to the currently marketed Remodulin Injection (NDA 21-272), except for the absence — in the current formulation (Tyvaso). b(4)

Since treprostinil drug substance is practically insoluble in water, the treprostinil sodium salt was developed for use in the aqueous drug product formulation. It was noted that the treprostinil sodium salt is extremely difficult to handle since the solid is deliquescent. Thus, a manufacturing procedure was designed to form the sodium salt of treprostinil — during the manufacture of the drug product. A slight molar excess of sodium hydroxide was added to the formulation to ensure that all of the treprostinil was converted to the sodium salt. Forced degradation studies of treprostinil showed it to be more stable under basic conditions; therefore, formulation as the sodium salt provided a stability advantage as well.

Tyvaso is — packaged into — ampoules with nominal fill volumes of 2.9 mL and a pH of 6.0 – 7.2. The filled ampoules are further packaged into 4 ampoules per pouch. b(4)

The product showed good stability when stored under long-term conditions (25°C/40% RH) out to 36 months and under accelerated conditions (40°C/20% RH) for 6 months. However, the drug product is photosensitive and should be carefully labeled as such. There is support for a 36-month shelf-life for the drug product when stored at controlled room temperature in LDPE ampoules inside foil pouches (i.e. protected from light). This is consistent with the applicant's proposed expiration date and storage conditions. In-use stability studies determined that the drug product is stable for use in the Optineb nebulizer for a maximum of 24 hours.

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

Tyvaso (treprostinil) Inhalation Solution, 0.6 mg/mL, is intended for oral inhalation using the Optineb-ir, an ultrasonic, pulsed-delivery nebulizer. The Optineb-ir, manufactured by



## CHEMISTRY REVIEW



### Executive Summary Section

Nebutec Medicinal Products, is intended for single patient use in the administration of treprostinil for inhalation. The drug product solution is packaged in 2.9 mL ampoules, supplied as 4 ampoules within a foil pouch. One ampoule (2.9 mL) of treprostinil for inhalation should be transferred to the nebulizer for use each day. The solution remaining in the nebulizer after 1 day should be discarded. Since the drug is photosensitive, unused ampoules should be stored in the foil pouch until use.

Tyvaso is dosed in 4 separate inhalation sessions per day, during waking hours. The inhalation sessions should be at least 4 hours apart. Therapy should begin with 3 breaths of Tyvaso per inhalation session (each breath delivers approximately 5 – 6 mcg of treprostinil), given 4 times daily. Dosage should be increased to 6 breaths per inhalation session (4 times daily), and subsequently increased to the target maintenance dose of 9 breaths per inhalation session given 4 times daily, as tolerated. The maximum dose used in clinical studies was 12 breaths (i.e., 72 mcg of treprostinil) per inhalation session.

#### C. Basis for Approvability or Not-Approval Recommendation

This new drug application (22-387) is recommended for **APPROVAL** from the perspective of chemistry, manufacturing, and controls. All deficiencies have been adequately resolved.

### III. Administrative

#### A. Reviewer's Signature

/s/ M.D. Cooper, Ph.D.

#### B. Endorsement Block

Chemistry Reviewer:	Monica D. Cooper, Ph.D.
Pharmaceutical Assessment Lead:	Kasturi Srinivasachar, Ph.D.
Branch Chief:	Ramesh Sood, Ph.D.
Project Manager:	Dan Brum, Pharm.D.

#### C. CC Block

Orig. NDA 22-387  
HFD-110/Division File

18 Page(s) Withheld

X Trade Secret / Confidential (b4)

\_\_\_\_\_ Draft Labeling (b4)

\_\_\_\_\_ Draft Labeling (b5)

\_\_\_\_\_ Deliberative Process (b5)

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/s/

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Monica Cooper  
7/22/2009 04:36:00 PM  
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Ramesh Sood  
7/23/2009 10:10:19 AM  
CHEMIST

## CMC BRANCH CHIEF MEMORANDUM

**To:** NDA 22-387  
**From:** Ramesh Sood, Ph.D., Branch Chief, ONDQA  
**Date:** 17-Apr-2009  
**Drug:** Tyvaso (treprostinil) inhalation solution  
**Route of administration:** Oral Inhalation  
**Strength:** 0.6 mg/mL  
**Subject:** "Complete Response" recommendation for NDA 22-387

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**Introduction:** Treprostinil for inhalation (Tyvaso™) is being developed as an alternative to the subcutaneously and intravenously delivered treprostinil solution (Remodulin Injection, NDA 21-272, approved 22-May-2002). Treprostinil is the free acid of a synthetic tricyclic benzindene analogue of prostacyclin. The proposed indication is for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with New York Heart Association (NYHA) Class III symptoms. b(4)

**Drug Substance:** Treprostinil is a chemically-synthesized small molecule with 5 stereocenters, manufactured as a single enantiomer. It is a white to cream-colored powder, which is practically insoluble in water. The chemistry, manufacturing and controls information (CMC) for the drug substance was referenced to the approved NDA 21-272 for Remodulin Injection. The NDA submission included the drug substance specification table and batch data for 5 recent lots. The current retest date for treprostinil drug substance is \_\_\_\_\_ when stored at 2 – 8°C. A supplement for a new treprostinil drug substance manufacturing facility and synthetic process is currently pending (NDA 21-272/SCM-010). The previous treprostinil drug substance manufacturing site \_\_\_\_\_ was closed in 2006. So at the time of writing this memorandum there is no approved drug substance source for this NDA. The approval of this NDA is contingent upon the approval of the currently pending supplemental application (NDA 21-272/SCM-010).

**Drug product:** Tyvaso (treprostinil) Inhalation Solution, 0.6 mg/mL, is intended for oral inhalation using the Optineb-ir, an ultrasonic, pulsed-delivery nebulizer. The Optineb-ir, manufactured by Nebutech Medicinal Products, is intended for single patient use in the administration of treprostinil for inhalation. The drug product is an aqueous solution of treprostinil (0.6 mg/mL) formulated with sodium chloride, sodium citrate, sodium hydroxide, and hydrochloric acid in water for injection. The excipients are compendial and have been used in previously approved inhalation solutions. The formulation is identical to the currently marketed Remodulin Injection (NDA 21-272), except for the absence of \_\_\_\_\_ b(4)  
\_\_\_\_\_ in the current formulation (Tyvaso).

Since treprostinil drug substance is practically insoluble in water, the treprostinil sodium salt was developed for use in the aqueous drug product formulation. It was noted that the treprostinil sodium salt is extremely difficult to handle since the solid is deliquescent. To facilitate handling of sodium salt of treprostinil, it is being generated \_\_\_\_\_ during the manufacture of the drug product. \_\_\_\_\_ sodium hydroxide is added to the formulation to ensure that all b(4)

of the treprostinil was converted to the sodium salt. The compounded solution is packaged into ampoules with nominal fill volumes of 2.9 mL and a pH of 6.0 – 7.2. The filled ampoules are further packaged into 4 ampoules per pouch. The quality of the drug product is ensured through appropriate in-process controls and acceptable final specification that include test and acceptance criteria for appearance, identification (HPLC/UPLC and IR), assay (HPLC/UPLC), related substances (HPLC), pH, particulate matter (<USP 788>), osmolality, fill weight, weight loss and sterility.

b(4)

The drug product solution is packaged in 2.9 mL ampoules, supplied as 4 ampoules within a foil pouch. One ampoule (2.9 mL) of treprostinil for inhalation should be transferred to the nebulizer for use each day. The solution remaining in the nebulizer after 1 day should be discarded. Since the drug is photosensitive, unused ampoules should be stored in the foil pouch until use.

The requested 36-month expiration period is being assigned to this product when stored at controlled room temperature in LDPE ampoules inside foil pouches (i.e. protected from light). An in-use stability study of the drug product in the proposed Optineb nebulizer has not been completed and is currently pending.

The facilities related to the manufacturing of the drug product and described in the NDA have been recommended for approval by the Office of Compliance. Categorical exclusion from an environmental assessment requested by the applicant is acceptable.

An acceptable recommendation is made by the microbiology reviewer.

**Pending Issues:** The drug product cannot be recommended for approval from CMC perspective in its current form because of the following pending issues.

1. The approval of the new drug substance source/manufacturing is pending as per NDA 21-272/SCM-010.
2. Evaluation of the Optineb nebulizer was consulted to CDRH. CDRH recommendation is pending at this point. Information requests were sent to the applicant on 03-Mar-2009 and 06-Apr-2009 that included several device issues related to the usability of the device. The applicant has not responded to these requests.
3. Some additional labeling related issues will be resolved later during the labeling negotiations.

**Recommended action:** The application cannot be recommended for approval in its current form from CMC perspective.

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/s/

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Ramesh Sood  
4/27/2009 10:15:46 AM  
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**NDA 22-387**

**Tyvaso (treprostinil)  
Inhalation Solution**

**United Therapeutics Corporation**

**Monica D. Cooper, Ph.D.  
ONDQA Pre-Marketing Assessment  
Division I/Branch I**

**Reviewed for the Division of Cardiovascular  
and Renal Products, HFD-110**

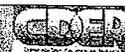


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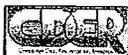
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1. NDA 22-387
2. REVIEW #: 1
3. REVIEW DATE: 23-Mar-2009
4. REVIEWER: Monica D. Cooper, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	27-Jun-2008
Amendment (N000 BC)	03-Jul-2008
Amendment (N000 BC)	14-Aug-2008
Amendment (N000 BC)	29-Oct-2008
Amendment (N000 BZ)	25-Feb-2009

7. NAME & ADDRESS OF APPLICANT:

Name	United Therapeutics Corporation
Address	One Park Drive, Suite 400 Research Triangle Park, NC 27709
Representative	Dean Bunce, Sr. VP Regulatory Affairs
Telephone	919-485-8350 ext. 1218
FAX Number	919-313-1298

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name	Tyvaso
Non-Proprietary Name (USAN)	treprostinil
Code Names	UT-15
Chemistry Type	5, 3
Submission Priority	S



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY: Prostacyclin analog for pulmonary arterial hypertension
11. DOSAGE FORM: Sterile Solution
12. STRENGTH/POTENCY: 0.6 mg/mL
13. ROUTE OF ADMINISTRATION: Inhalation
14. Rx/OTC DISPENSED:  Rx  OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

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

Chemical Names: (1) Acetic acid, [[(1*R*,2*R*,3*aS*,9*aS*)-2,3,3*a*,4,9,9*a*-hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-1*H*-benz[*f*]inden-5-yl]oxy]-  
(2) [(1*R*,2*R*,3*aS*,9*aS*)-2-Hydroxy-1-((3*S*)-3-hydroxyoctyl)-2,3,3*a*,4,9,9*a*-hexahydro-1*H*-cyclopent[*b*]naphthalen-5-yl]oxy]acetate

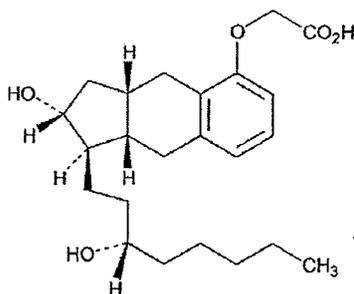
US Adopted Name (USAN): treprostinil  
Laboratory Codes: UT-15, LRX-15, 15AU81



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet



Chemical Formula: C<sub>23</sub>H<sub>34</sub>O<sub>5</sub>  
Molecular Weight: 390.51  
CAS Number: 81846-19-7

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED
—	III	—	b(4)	3	Adequate	24-Apr-2008 (G. Lunn)

<sup>1</sup> 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")

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



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	70,362	Treprostinil for Inhalation
NDA	21-272	Remodulin Injection
NDA Supplement	21-272/SCM-010 (currently pending)	New DS (treprostinil) Manufacturing Site and Synthetic Process

### 18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	01-Dec-2008	S. Ferguson
LNC	N/A	----	----
Methods Validation	Not Necessary	----	----
OSE-DMEPA	Tradename: Tyvaso Acceptable	19-Feb-2009	J. Park
EA	Categorical Exclusion: Acceptable	See Review Date Above	M. Cooper
Microbiology	Pending		J. Metcalfe



# The Chemistry Review for NDA 22-387

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This new drug application (22-387) cannot be recommended for approval from the perspective of chemistry, manufacturing, and controls due to several pending issues noted below.

1) All drug substance information is referenced to NDA 21-272 (Remodulin Injection). A supplement for a new treprostinil drug substance manufacturing facility and synthetic process is currently pending (NDA 21-272/SCM-010). The previous treprostinil drug substance manufacturing site \_\_\_\_\_ was closed in 2006. Given that no other drug substance manufacturer is provided in this submission, the current NDA cannot be approved until the supplemental NDA 21-272/SCM-010 is approved. **b(4)**

2) An information request letter was sent to the applicant on 13-Jan-2009 outlining the CMC information needed to complete this application. The Amendment dated 25-Feb-2009 included a partial response to these issues. An in-use stability study of the drug product in the proposed Optineb nebulizer has not been completed and submitted for our review.

3) Evaluation of the Optineb nebulizer was consulted to CDRH. CDRH has not provided a recommendation at this time. However, an information request was sent to the applicant on 03-Mar-2009 that included several device issues. These issues are currently pending.

4) The Office of Microbiology has not provided a recommendation on the sterility assurance of the drug product.

Since this application is not complete, labeling issues have not been sent to the applicant. Recommended revisions to the labels are noted at the end of this review.

The Office of Compliance has given an acceptable recommendation for the manufacturing and testing facilities (see Establishment Evaluation Summary at the end of this review).

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

There are no Phase 4 commitments.



## CHEMISTRY REVIEW



### Executive Summary Section

## II. Summary of Chemistry Assessments

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

Treprostinil for inhalation (Tyvaso™) was developed as an alternative to the subcutaneously and intravenously delivered treprostinil solution (Remodulin Injection, NDA 21-272, approved 22-May-2002). Treprostinil is the free acid of a synthetic tricyclic benzindene analogue of prostacyclin. The proposed indication is for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with New York Heart Association (NYHA) Class III — symptoms. **b(4)**

#### Drug Substance

Treprostinil is a chemically-synthesized small molecule with 5 stereocenters, manufactured as a single enantiomer. It is a white to cream-colored powder, which is practically insoluble in water. All of the drug substance information was referenced to the approved NDA 21-272 for Remodulin Injection. For the convenience of the reviewer, the applicant provided the drug substance specification table and batch data for 5 recent lots. The current retest date for treprostinil drug substance is ——— when stored at 2 – 8°C. **b(4)**

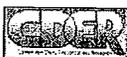
#### Drug Product

The drug product is an aqueous solution of treprostinil (0.6 mg/mL) formulated with sodium chloride, sodium citrate, sodium hydroxide, and hydrochloric acid in water for injection. The excipients are compendial and have been used in previously approved inhalation solutions. The formulation is identical to the currently marketed Remodulin Injection (NDA 21-272), except for the absence ( ——— ) in the current formulation (Tyvaso). **b(4)**

Since treprostinil drug substance is practically insoluble in water, the treprostinil sodium salt was developed for use in the aqueous drug product formulation. It was noted that the treprostinil sodium salt is extremely difficult to handle since the solid is deliquescent. Thus, a manufacturing procedure was designed to form the sodium salt of treprostinil — during the manufacture of the drug product. A slight molar excess of sodium hydroxide was added to the formulation to ensure that all of the treprostinil was converted to the sodium salt. Forced degradation studies of treprostinil showed it to be more stable under basic conditions; therefore, formulation as the sodium salt provided a stability advantage as well.

Tyvaso is ——— packaged into ——— ampoules with nominal fill volumes of 2.9 mL and a pH of 6.0 – 7.2. The filled ampoules are further packaged into 4 ampoules per pouch. **b(4)**

The product showed good stability when stored under long-term conditions (25°C/40% RH) out to 36 months and under accelerated conditions (40°C/20% RH) for 6 months. However, the drug product is photosensitive and should be carefully labeled as such. There is support for a 36-month shelf-life for the drug product when stored at controlled room temperature in LDPE ampoules inside foil pouches (i.e. protected from light). This is consistent with the applicant's proposed expiration date and storage conditions. An in-use stability study of the



## CHEMISTRY REVIEW



### Executive Summary Section

drug product in the proposed Optineb nebulizer has not been completed and is currently pending.

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

Tyvaso (treprostinil) Inhalation Solution, 0.6 mg/mL, is intended for oral inhalation using the Optineb-ir, an ultrasonic, pulsed-delivery nebulizer. The Optineb-ir, manufactured by Nebutech Medicinal Products, is intended for single patient use in the administration of treprostinil for inhalation. The drug product solution is packaged in 2.9 mL ampoules, supplied as 4 ampoules within a foil pouch. One ampoule (2.9 mL) of treprostinil for inhalation should be transferred to the nebulizer for use each day. The solution remaining in the nebulizer after 1 day should be discarded. Since the drug is photosensitive, unused ampoules should be stored in the foil pouch until use.

Tyvaso is dosed in 4 separate inhalation sessions per day, during waking hours. The inhalation sessions should be at least 4 hours apart. Therapy should begin with 3 breaths of Tyvaso per inhalation session (each breath delivers approximately 5 – 6 mcg of treprostinil), given 4 times daily. Dosage should be increased to 6 breaths per inhalation session (4 times daily), and subsequently increased to the target maintenance dose of 9 breaths per inhalation session given 4 times daily, as tolerated. The maximum dose used in clinical studies was 12 breaths (i.e., 72 mcg of treprostinil) per inhalation session.

#### **C. Basis for Approvability or Not-Approval Recommendation**

This new drug application (22-387) cannot be recommended for approval from the perspective of chemistry, manufacturing, and controls due to several pending issues that were noted in Section I.A. above.

### **III. Administrative**

#### **A. Reviewer's Signature**

/s/ M.D. Cooper, Ph.D.

#### **B. Endorsement Block**

Chemistry Reviewer:

Monica D. Cooper, Ph.D.

Pharmaceutical Assessment Lead:

Kasturi Srinivasachar, Ph.D.

Branch Chief:

Ramesh Sood, Ph.D.

Project Manager:

Dan Brum, Pharm.D.



## CHEMISTRY REVIEW



### Executive Summary Section

#### **C. CC Block**

Orig. NDA 22-387  
HFD-110/Division File

83 Page(s) Withheld

8 Trade Secret / Confidential (b4)

\_\_\_\_\_ Draft Labeling (b4)

\_\_\_\_\_ Draft Labeling (b5)

\_\_\_\_\_ Deliberative Process (b5)

Initial Quality Assessment  
Branch I

<b>OND Division:</b>	Division of Cardiovascular and Renal Products
<b>NDA:</b>	22-387
<b>Applicant:</b>	United Therapeutics Corporation
<b>Letter Date:</b>	27 June 2008
<b>Stamp Date:</b>	27 June 2008
<b>PDUFA Date:</b>	27 Apr. 2009
<b>Tradename:</b>	Tyvaso
<b>Established Name:</b>	Treprostinil sodium
<b>Dosage Form:</b>	Sterile solution, 0.6 mg/mL
<b>Route of Administration:</b>	Inhalation
<b>Indication:</b>	Pulmonary arterial hypertension
<b>Assessed by:</b>	Kasturi Srinivasachar
<b>ONDQA Fileability:</b>	Yes

**Summary**

This is an e-CTD submission for inhaled treprostinil. The drug product is very similar to the approved injection formulation, Remodulin, for the same indication. The only differences are the absence of \_\_\_\_\_ and the strength. Clinical trials were conducted under IND 70,362. There have been no CMC specific meetings with the Applicant but an interdisciplinary meeting (Type C/Guidance) with CMC issues for discussion was held on Nov. 1, 2006. The Applicant stated that a simplified \_\_\_\_\_ drug substance had been submitted as a supplement to NDA 21-272 and that in 2007 the manufacture would be transferred \_\_\_\_\_ to Silver Spring, MD. The NDA for treprostinil for inhalation would be filed with data from the NEBU-TEC OPTINEB ultrasonic nebulizer

b(4)

There was agreement that a 10 day study of the chemical stability and microbiological properties of treprostinil in the nebulizer would be adequate to support in-use labeling provisions. A pre-NDA multidisciplinary meeting was held on May 16, 2008 and specifications for drug substance and drug product were discussed. The Applicant was requested to follow the recommendations in the FDA guidance "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products" for leachables. In connection with the testing for extractables from various components of the nebulizer in contact with the drug product, they were asked to submit the results of USP Biological Reactivity Tests (<87> and <88>).

**Drug Substance**

Treprostinil is the free acid of a synthetic tricyclic benzindene analogue of prostacycline. This is the same drug substance as in Remodulin and all CMC information is referred to NDA 21-272. As agreed to at the pre-NDA meeting, the current specifications and batch analysis data for drug substance batches used in the manufacture of Tyvaso are provided. There has been a site change for the manufacture of treprostinil \_\_\_\_\_ to the United Therapeutics, Silver Spring, MD, facility. It is stated that the \_\_\_\_\_ site ceased operations in 2006 and all future manufacture will take place in Silver Spring, MD. Data have been provided for 3 batches from

b(4)

\_\_\_\_\_ and 2 from Silver Spring, MD. The Specification Table 1 in the QOS is missing a page containing tests for assay, related substances and bioburden. The correct complete table is in Module 3. b(4)

### Drug Product

The drug product formulation is very similar to that of Remodulin with the same excipients except \_\_\_\_\_ which is not used. Remodulin is supplied in various concentrations whereas Tyvaso will be marketed only as a 0.6 mg/mL solution. The container closure system is a \_\_\_\_\_ LDPE ampoule with an integrated twist-off cap. \_\_\_\_\_ is used to manufacture the sterile solution and a batch size \_\_\_\_\_ is proposed for commercial lots. The fill volume was lowered to 2.9 mL for the commercial batches from \_\_\_\_\_ used in clinical/registration batches. The product specifications are the same as for Remodulin except for the absence of specific \_\_\_\_\_ tests and the addition of tests for fill weight and osmolality. Stability studies have been conducted on 5 batches – 2 full scale \_\_\_\_\_ and 3 at 1/5 full scale \_\_\_\_\_. The 5 bulk lots of ampoules were packaged into two different final configurations: 1) foil pouches with adhesive label and 2) pre-printed foil pouches. Three lots of each packaging configuration were placed into the stability program. Ampoules in pouches with an adhesive label represent the proposed commercial packaging. 36 months' long term data are available for the 3 pilot scale batches and 9 and 6 months' data are provided for the full scale batches. A 36 month expiration date is proposed. b(4)

### Device

Trepostinil for inhalation is delivered to the patient using an ultrasonic nebulizer. This device, the Optineb-ir, is intended for single patient use and operates ultrasonically by energizing a piezoelectric transducer at 2.4 MHz. This action collimates distilled water stored in the water reservoir energizing liquid medicine stored in the medicine cup creating an aerosol. The Optineb's software controls the aerosolization process to occur during expiration and then responds by providing visual and audible signals to the patient to inhale the vapor. A series of check valves allows the aerosol to develop without airflow and to direct the particle range restricted aerosol to the patient's mouth during inspiration. The Optineb performs this operation for three consecutive cycles accurately dispensing the prescribed dosage at a predetermined particle size.

### Critical Review Issues

#### Drug substance

- A PA supplement has recently been submitted for the new manufacturing facility in Silver Spring, MD. The outcome of the review of this supplement should be noted since it will impact this NDA as well.

#### Drug Product

- Is the absence of tests for specific \_\_\_\_\_ in the specification acceptable?
- Is the limit of NMT \_\_\_\_\_ for total impurities justified considering the stability results over 36 months?
- Has the Applicant evaluated the drug product for compounds that leach from \_\_\_\_\_ components of the container closure and any inks, paper or adhesives from the labels or packaging in their stability studies, as recommended at the pre-NDA meeting? b(4)

- Has the Applicant complied with the request to perform USP Biological Reacivity Tests, <87> and <88> , for extractables from device components in contact with the drug product?
- Has the commitment for stability testing of the first three marketed batches been submitted? Two full scale batches are already in the stability program – is this sufficient?
- Have data been submitted to support the labeling statement that ampoules removed from the foil pouch should be used within 7 days.

**Device**

- Is the nebulizer well characterized in terms of dose emitted and aerodynamic particle/droplet size distribution?
- Are the in-use studies adequate to support administration of the drug for a day in the nebulizer?

**Labeling**

The established name should be ‘treprostinil’ and not ‘treprostinil sodium’ to match the dosage form strength.

**Comments and Recommendations**

The application is fileable. Manufacturing, testing and packaging facilities have been entered into EES and the reviewer should verify the accuracy and completeness of the entries. Microbiology and CDRH (for the nebulizer) consults have been requested. A single CMC reviewer, preferably one with some experience in inhalation products, is recommended for this application.

Kasturi Srinivasachar  
Pharmaceutical Assessment Lead  
Ramesh Sood, Ph.D.  
Branch Chief

July 23, 2008  
Date  
July 23, 2008  
Date

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

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Kasturi Srinivasachar  
7/23/2008 11:30:22 AM  
CHEMIST

Ramesh Sood  
7/23/2008 01:39:15 PM  
CHEMIST