# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-912**

# CHEMISTRY REVIEW(S)

**TRADENAME**
**(Arformoterol Tartrate)**
**Inhalation Solution**
**NDA 21-912**

**Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls**

**Applicant:** Sepracor, Inc.
84Waterford Drive
Marlborough, MA 01752

**Indication:** long term maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

**Presentation:** Unit dose inhalation solution, formulated as an isotonic, sterile, aqueous solution, consisting of 15 micrograms of Arformoterol ( 22 micrograms as Arformoterol Tartrate) in a citrate-buffered saline solution (pH 5.0) in 2 mL LDPE vial, sealed with twist-off cap, and over-wrapped in [ ] foil pouch. b(4)

**EER Status:** **Acceptable** 29-JUL-2006

**Consults:**
**EA:** Categorical exclusion granted under 21 CFR 25.31(b) for arfomoterol
**DMETS:** **Pending,** proposed tradename: [ ] Brovana b(4)
**Microbiology:** **Approval,** 7-JUL-2006
**Methods Validation:** Method validation package is provided. Samples will be requested for method validation study to be conducted by FDA laboratories.
**Pharm/Tox:** **Complete,** 3-AUG-2006
**BioPharm:** **Complete,** 4-AUG-2006
**Biometrics:** **Complete,** 24-MAY-2006

**Original Submission:** 8-DEC-2005

**Post-Approval Agreements:**

The firm agrees to include testing for leachables in the post-approval stability protocol and stability commitment

The firm agrees to submit the validation report for Method 00976 to the Agency upon completion and prior to commercialization of the product.

The firm agrees to conduct further extractable studies of the foil and submit the data to FDA.

**Drug Substance:**

Arformoterol is a selective long-term $\beta_2$-adrenergic receptor agonist. Compared to racemic formoterol, chiral arformoterol showed greater affinity for both $\beta$ adrenergic receptor subtypes and also greater selectivity for the $\beta_2$-receptor. Arformoterol tartrate is designated chemically as formamide, N-[2-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl] phenyl]-, (2R,3R)-2,3-dihydroxybutanedioate (1:1 salt).

[ b(4) ]

The structure of arformoterol was elucidated using several analytical and spectrophotometric techniques, including elemental analysis, UV and IR spectroscopy, NMR ($^1H$ and $^{13}C$) spectroscopy, mass spectrometry, and X-ray crystallography.

[ b(4) ] The proposed regulatory methods have been validated. The impurities and degradation products have been investigated. Reference standard for API has been developed and characterized.

Arformoterol tartrate is stable for up to [ ] at room temperature when [ ] b(4)

**Conclusion:** Drug substance is acceptable.

**Drug Product:**

Arformoterol tartrate inhalation solution is formulated as an isotonic, preservative-free, sterile, aqueous solution consisting of 15 micrograms arformoterol tartrate in a citrate-buffered saline solution (pH 5.0). All excipients are USP/NF grade. The solution is filled into LDPE vials which are then over-wrapped in [ ] foil pouches.

[ ] b(4)

[redacted] The proposed regulatory methods have been validated. b(4)

Arformaterol Tartrate Inhalation Solution packaged in [redacted] the single vial pouch configuration shows no significant changes in terms of appearance, color of solution, weight loss, delivered volume, particulate matter or sterility at any of the storage conditions studied. b(4)

Adequate stability data were provided to support the proposed expiration dating period of 18 months for drug product packaged in [redacted] single vial pouch configurations. These data also support the proposed six-week out of pouch in-use storage period at room temperature (20° - 25°C). b(4)

**Conclusion:** Drug product is satisfactory.

**Additional Items:**

All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

A method validation package, describing the test methods and validation procedures, including information supporting the reference standard, is provided. Samples of the drug substance and drug product will be requested for the method validation study to be conducted in the FDA laboratories.

Pending approval of the tradename, the package insert, container labels, and carton labels are acceptable.

**Overall Conclusion:**

From a CMC perspective, the application is recommended for approval.

Blair A. Fraser, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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/s/

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Blair Fraser
9/29/2006 05:44:19 AM
CHEMIST

# NDA 21-912

[ ] b(4)

(also presented as Brovana)

# (Arformoterol Tartrate) Inhalation Solution

# Sepracor Inc.


# Chien-Hua Niu, Ph.D.
# ONDQA/DPMA-I

# Table of Contents

# Chemistry Review Data Sheet

1. NDA 21-912

2. REVIEW #: 1

3. REVIEW DATE: August 1, 2006

4. REVIEWER: Chien-Hua Niu, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

| Submission Type | Document Date |
|---|---|
| Original | 08-DEC-2005 |
| Amendment | 03-JAN-2006 |
| Amendment | 31-MAR-2006 |
| Amendment | 18-APR-2006 |
| Amendment | 12-JUL-2006 |
| Amendment | 21-JUL-2006 |

7. NAME & ADDRESS OF APPLICANT:

**Name:** Sepracor Inc.
**Address:** 84 Waterford Drive
Marlborough, MA 01752

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Brovana
b) on-Proprietary Name (USAN): Arformoterol tartrate
c) Code Name/# (ONDC only): 200815-49-2 (CAS registry number)
d) Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority: **1 S**

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: A long acting beta$_2$-adrenergic receptor agonist

11. DOSAGE FORM: Inhalation Solution

12. STRENGTH/POTENCY: 15 mcg/2 mL

13. ROUTE OF ADMINISTRATION: Oral Inhalation

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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

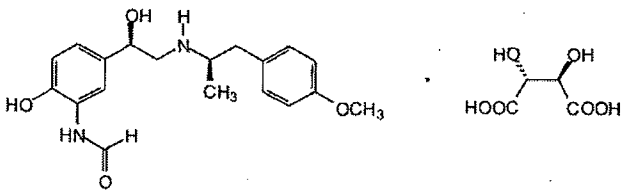
_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

Chemical Name: Arformoterol tartrate

Structural Formula:




Molecular Formula: $C_{19}H_{24}N_2O_4 \cdot C_4H_6O_6$ (1:1 salt)
Molecular Weight: 495.5 g/mol

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| [redacted] | II | [redacted] | [redacted] | 1 | Adequate | 09-April -03 | Review by Chien-Hua Niu for NDA #21912 |
| [redacted] | III | | [redacted] | 3 | Adequate | 19-March-01 | Reviewed by Vibhakar Shah for NDA #20-949 |
| [redacted] | III | | [redacted] | 3 | Adequate | 04-February-02 | Reviewed by Shin-Hou Liu for ANDA #75437 |

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 | 55,302 | Arformoterol used for the treatment of bronchoconstriction |

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## 18. STATUS:

**ONDQA:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | Complete | 05/24/06 | Ji Yang Guo |
| EES | Acceptable | 06/29/06 | Office of Compliance |
| Pharm/Tox | Complete | 08/03/06 | Timothy Robison |
| Biopharm | Complete | 08/04/06 | Shinja Rhea Kim |
| LNC | N/A | | |
| Methods Validation | The method validation package will be sent to and validated by the FDA laboratories | | Chien-Hua Niu |
| DMETS | Revision of the labels and labeling | 08/02/06 | Michelle Safarik |
| EA | Categorical exclusion | | Chien-Hua Niu |

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On Original

**REVIEW NOTE**

# The Chemistry Review for NDA 21-912

## *The Executive Summary*

## I. Recommendations

**A. Recommendation and Conclusion on Approvability**
The application can be approved from chemistry point of view.

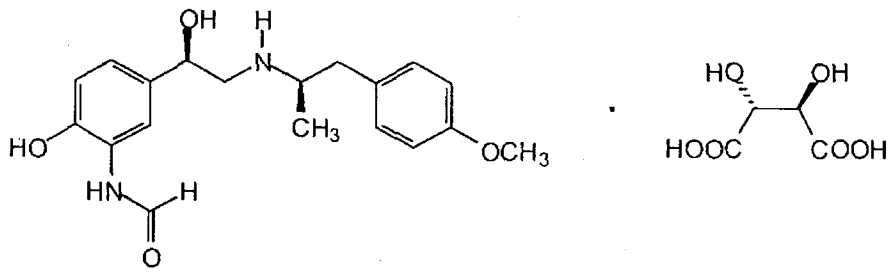
**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:** None

## II. Summary of Chemistry Assessments

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

Arformoterol is a selective long-term beta$_2$-adreergic receptor agonist. Compared to racemic formoterol, arformoterol showed greater affinity for both beta adrenergic receptor subtypes and also greater selectivity for the beta$_2$-receptor. The pharmacologic effects of arformoterol are at least in part attributable to stimulation of intracellular adenyl cyclase. Increased intracellular cyclic AMP levels cause relaxation of bronchial smooth muscle contractions and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

**DRUG SUBSTANCE:** Arformoterol tartrate is designated chemically as (-)-N-[2-hydroxy-5-[(1R)-1-hydroxy-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]foramide (2R,3R)-2,3-dihydroxybutanedioate. The chemical structure and molecular formula for arformoterol tartrate are shown below:




Arformoterol tartrate is not a new molecular entity manufactured by Sepracor Canada Ltd. The API has two chiral centers with sterochemical configuration of RR. The manufacturing process for arformoterol tartrate [redacted] b(4)

## REVIEW NOTE

The structure of arformoterol was elucidated by a varity of analytical and spectrophotometric techniques, including elemental analysis, UV and IR spectroscopy, NMR ($^{1}H$ and $^{13}C$) spectroscopy, mass spectrometry, and X-ray crystallography. Arformoterol tartrate is a white to off-white solid, [redacted] b(4)

[redacted] b(4)

[redacted] The proposed regulatory methods have been validated. The impurities and degradation products have been investigated. Reference standard for API has been developed and characterized. b(4)

Based on data from ICH stability studies on 6 lots, arformoterol tartrate is stable for up to [redacted] at room temperature when stored [redacted] b(4)

**DRUG PRODUCT:** The proposed drug product is manufactured by [redacted] Arformoterol tartrate inhalation solution is formulated as isotonic, preservative-free, sterile aqueous solution consisting of arformoterol tartrate in a citrate-buffer saline solution (pH 5.0). All excipients are USP/NF grade. The manufacturing process and in-process controls are described in detail. b(4)

The composition and components of the inhalation solution (15 µg/2 mL) are listed below:

| Component | Quality Standard | Function | Amount/Unit |
|---|---|---|---|
| Arformoterol Tartrate[a] | [redacted] | Active | [redacted] |
| Citric Acid, [redacted] | USP | Buffer Component | |
| Sodium Citrate, [redacted] | USP | Buffer Component | |
| Sodium Chloride | USP | [redacted] | |
| [redacted] | [redacted] | [redacted] | |
| Total | | | |

[a]: 0.6967 gm of Arformoterol free base = 1.0 gm Arformoterol Tartrate
[b]: The amount in the table is the theoretical for the batch

b(4)

Arformoterol Tartrate Inhalation Solution is filled in LDPE vials which are then over wrapped in [redacted] pouches. b(4)

[redacted] The proposed regulatory methods have been validated. b(4)

## REVIEW NOTE

The results from leachables study indicated [redacted]

[redacted]

b(4)

Stability tests performed include appearance, color of solution, weight loss, pH, delivered volume, assay for API, impurities, isomeric purity, particular matter, and sterility.

Arformaterol Tartrate Inhalation Solution packaged in [redacted] single vial pouch configuration shows no significant changes in terms of appearance, color of solution, weight loss, delivered volume, particulate matter or sterility at any of the storage conditions studied. However, the rate of impurity formation, [redacted]

b(4)

[redacted]

Based on stability data from samples packaged in [redacted] single vial pouch configuration stored at refrigerated conditions, an expiration dating period of 18 months is recommended for Arformoterol Tartrate Inhalation Solution. These data also support the proposed six-week in-use storage period at room temperature (20° - 25°C).

b(4)

The sponsor has cited a regulation [21 CFR 25.31(b)] to claim a categorical exclusion from filling an environmental assessment.

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

Brovana Inhalation Solution is indicated for long term maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The firm indicates that the recommended dosage of Brovana Inhalation Solution is 15 mcg administered twice a day (morning and evening) by nebulization.

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

The recommendation that this application is can be **approved** from a CMC viewpoint is based on the following: (1) The general procedures for the synthesis of arformoterol tartrate are outlined in the NDA. (2) Chemical structures of major impurities and degradation products are illustrated. (3) Seven primary stability batches for 15 mcg/2 mL solution have been manufactured by [redacted]. All these batches were produced with the drug substance manufactured by Sepracor Canada Limited at Windsor, Nova Scotia, Canada. (4) Stability data indicate that no significant changes were observed in terms of appearance, color of solution, weight loss, delivered volume, assay, impurity, isomeric purity, particulate matter and sterility when stored at 5°C for a period of 18 months and cycled to 25°/40% RH for 2.8 months. and (5) CGMP inspection of the manufacturing sites for the drug substance, the drug product as well as testing and packaging sites have been completed and found to be acceptable by the Office of Compliance (see the attached).

b(4)

**Pending Issue: A number of chemistry non-approvability requests for information on the structural characterization of enantiomeric isomers and spectroscopic spectra are being made after completion of the CMC review of the 7/12/06 amendment**

## III. Administrative

**A. Reviewer's Signature**

**B. Endorsement Block**

Chemist Name/Date: Chien-Hua Niu, Ph.D./ONDQA/DPMA-I
Chemistry Branch Chief Name/Date: Blair Fraser, Ph.D. /ONDQA/DPMA-I

**C. CC Block**

Dr. Blair Fraser/Dr. Prasad Peri
Project Manager Name/Date: Ladan Jafarir, OND/HFD-570

# 6 Page(s) Withheld

b(4) Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Chemistry-* 1

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/s/
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Chien-Hua Niu
9/20/2006 04:05:24 PM
CHEMIST

Blair Fraser
9/21/2006 06:00:20 AM
CHEMIST

# NDA 21-912

[ ]

(also presented as Brovana)

# (Arformoterol Tartrate) Inhalation Solution

b(4)

# Sepracor Inc.

Chien-Hua Niu, Ph.D.
ONDQA/DPMA-I

# Table of Contents

# Chemistry Review Data Sheet

1. NDA 21-912

2. REVIEW #: 3

3. REVIEW DATE: September 20, 2006

4. REVIEWER: Chien-Hua Niu, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

| Submission Type | Document Date |
|---|---|
| Original | 08-DEC-2005 |
| Amendment | 03-JAN-2006 |
| Amendment | 31-MAR-2006 |
| Amendment | 18-APR-2006 |
| Amendment | 12-JUL-2006 |
| Amendment | 21-JUL-2006 |
| Amendment | 12-SEP-2006 |

7. NAME & ADDRESS OF APPLICANT:

**Name:** Sepracor Inc.
**Address:** 84 Waterford Drive
Marlborough, MA 01752

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Brovana
b) on-Proprietary Name (USAN): Arformoterol tartrate
c) Code Name/# (ONDC only): 200815-49-2 (CAS registry number)
d) Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority: **1 S**

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: A long acting beta$_2$-adrenergic receptor agonist

11. DOSAGE FORM: Inhalation Solution

12. STRENGTH/POTENCY: 15 mcg/2 mL

13. ROUTE OF ADMINISTRATION: Oral Inhalation

14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

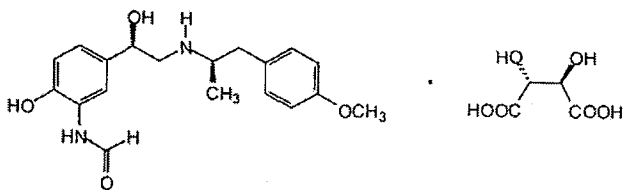
_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

Chemical Name: Arformoterol tartrate

Structural Formula:




Molecular Formula: $C_{19}H_{24}N_2O_4 \cdot C_4H_6O_6$ (1:1 salt)
Molecular Weight: 495.5 g/mol

Chemistry Review Data Sheet

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| [redacted] | II | [redacted] | [redacted] | 1 | Adequate | 09-April -03 | Review by Chien-Hua Niu for NDA #21912 |
| [redacted] | III | | [redacted] | 3 | Adequate | 19-March-01 | Reviewed by Vibhakar Shah for NDA #20-949 |
| [redacted] | III | | [redacted] | 3 | Adequate | 04-February-02 | Reviewed by Shin-Hou Liu for ANDA #75437 |

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
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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 | 55,302 | Arformoterol used for the treatment of bronchoconstriction |

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## 18. STATUS:

**ONDQA:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | Complete | 05/24/06 | Ji Yang Guo |
| EES | Acceptable | 06/29/06 | Office of Compliance |
| Pharm/Tox | Complete | 08/03/06 | Timothy Robison |
| Biopharm | Complete | 08/04/06 | Shinja Rhea Kim |
| LNC | N/A | | |
| Methods Validation | The method validation package will be sent to and validated by the FDA laboratories | | Chien-Hua Niu |
| DMETS | Revision of the labels and labeling | 08/02/06 | Michelle Safarik |
| EA | Categorical exclusion | | Chien-Hua Niu |

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On Original

REVIEW NOTE

# The Chemistry Review for NDA 21-912

## *The Executive Summary*

## I. Recommendations

**A. Recommendation and Conclusion on Approvability**
The application can be approved from chemistry point of view.

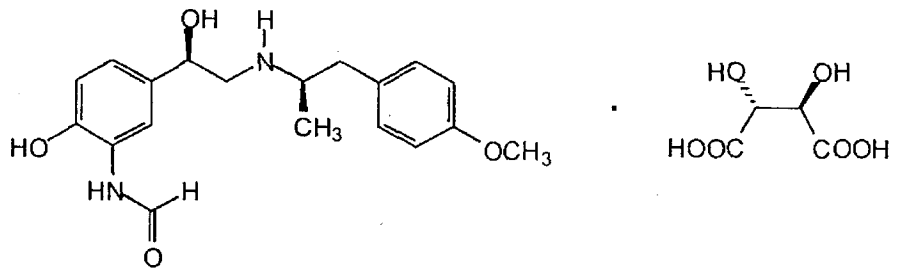
**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:** None

## II. Summary of Chemistry Assessments

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

Arformoterol is a selective long-term beta$_2$-adreergic receptor agonist. Compared to racemic formoterol, arformoterol showed greater affinity for both beta adrenergic receptor subtypes and also greater selectivity for the beta$_2$-receptor. The pharmacologic effects of arformoterol are at least in part attributable to stimulation of intracellular adenyl cyclase. Increased intracellular cyclic AMP levels cause relaxation of bronchial smooth muscle contractions and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

**DRUG SUBSTANCE:** Arformoterol tartrate is designated chemically as (-)-N-[2-hydroxy-5-[(1R)-1-hydroxy-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]foramide (2R,3R)-2,3-dihydroxybutanedioate. The chemical structure and molecular formula for arformoterol tartrate are shown below:




Arformoterol tartrate is not a new molecular entity manufactured by Sepracor Canada Ltd. The API has two chiral centers with sterochemical configuration of RR. The manufacturing process for arformoterol tartrate C

b(4)

C

C

J

J

J

## REVIEW NOTE

The structure of arformoterol was elucidated by a varity of analytical and spectrophotometric techniques, including elemental analysis, UV and IR spectroscopy, NMR ($^{1}H$ and $^{13}C$) spectroscopy, mass spectrometry, and X-ray crystallography. Arformoterol tartrate is a white to off-white solid, [redacted] b(4)

[redacted] b(4)

[redacted] b(4)

[redacted] The proposed regulatory methods have been validated. The impurities and degradation products have been investigated. Reference standard for API has been developed and characterized.

Based on data from ICH stability studies on 6 lots, arformoterol tartrate is stable for up to [redacted] at room temperature when stored [redacted] b(4)

**DRUG PRODUCT:** The proposed drug product is manufactured by [redacted] Arformoterol tartrate inhalation solution is formulated as isotonic, preservative-free, sterile aqueous solution consisting of arformoterol tartrate in a citrate-buffer saline solution (pH 5.0). All excipients are USP/NF grade. The manufacturing process and in-process controls are described in detail. b(4)

The composition and components of the inhalation solution (15 µg/2 mL) are listed below:

| Component | Quality Standard | Function | Amount/Unit |
|---|---|---|---|
| Arformoterol Tartrate[a] | [redacted] | Active | [redacted] |
| Citric Acid, / [redacted] | USP | Buffer Component | |
| Sodium Citrate, [redacted] | USP | Buffer Component | |
| Sodium Chloride | USP | [redacted] | |
| [redacted] | | | |
| Total | | | |

[a]: 0.6967 gm of Arformoterol free base = 1.0 gm Arformoterol Tartrate
[b]: The amount in the table is the theoretical for the batch

b(4)

Arformoterol Tartrate Inhalation Solution is filled in LDPE vials which are then over wrapped in [redacted] foil pouches. b(4)

[redacted] The proposed regulatory methods have been validated. b(4)

## REVIEW NOTE

The results from leachables study indicated [redacted]

b(4)

b(4)

Stability tests performed include appearance, color of solution, weight loss, pH, delivered volume, assay for API, impurities, isomeric purity, particular matter, sterility, and leachables.

Arformaterol Tartrate Inhalation Solution packaged in [redacted] single vial pouch configuration shows no significant changes in terms of appearance, color of solution, weight loss, delivered volume, particulate matter or sterility at any of the storage conditions studied. However, the rate of impurity formation, [redacted]

b(4)

Based on stability data from samples packaged in [redacted] single vial pouch configuration stored at refrigerated conditions, an expiration dating period of 18 months is recommended for Arformoterol Tartrate Inhalation Solution. These data also support the proposed six-week in-use storage period at room temperature (20° - 25°C).

b(4)

## REVIEW NOTE

The sponsor has cited a regulation [21 CFR 25.31(b)] to claim a categorical exclusion from filling an environmental assessment.

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

Brovana Inhalation Solution is indicated for long term maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The firm indicates that the recommended dosage of Brovana Inhalation Solution is 15 mcg administered twice a day (morning and evening) by nebulization.

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

The recommendation that this application is can be **approved** from a CMC viewpoint is based on the following: (1) The general procedures for the synthesis of arformoterol tartrate are outlined in the NDA. (2) Chemical structures of major impurities and degradation products are illustrated. (3) Seven primary stability batches for 15 mcg/2 mL solution have been manufactured by [redacted]. All these batches were produced with the drug substance manufactured by Sepracor Canada Limited at Windsor, Nova Scotia, Canada. (4) Stability data indicate that no significant changes were observed in terms of appearance, color of solution, weight loss, delivered volume, assay, impurity, isomeric purity, particulate matter and sterility when stored at 5°C for a period of 18 months and cycled to 25°/40% RH for 2.8 months. and (5) CGMP inspection of the manufacturing sites for the drug substance, the drug product as well as testing and packaging sites have been completed and found to be acceptable by the Office of Compliance (see the attached).

b(4)

## III. Administrative

### A. Reviewer's Signature

### B. Endorsement Block

Chemist Name/Date: Chien-Hua Niu, Ph.D./ONDQA/DPMA-I
Chemistry Branch Chief Name/Date: Blair Fraser, Ph.D. /ONDQA/DPMA-I

### C. CC Block

Dr. Blair Fraser/Dr. Prasad Peri
Project Manager Name/Date: Ladan Jafarir, OND/HFD-570

19 Page(s) Withheld

b(4) Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Chemistry-* 2

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/s/

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Chien-Hua Niu
8/23/2006 07:57:48 AM
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Blair Fraser
8/23/2006 08:12:34 AM
CHEMIST

# NDA 21-912

# Brovana
# (Arformoterol Tartrate)
# Inhalation Solution

# Sepracor Inc.

Chien-Hua Niu, Ph.D.
ONDQA/DPMA-I

# Table of Contents

# Chemistry Review Data Sheet

1. NDA 21-912

2. REVIEW #: 1

3. REVIEW DATE: January 30, 2006

4. REVIEWER: Chien-Hua Niu, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

| **Submission Type** | **Document Date** |
|---|---|
| Original | 08-DEC-2005 |
| Amendment | 03-JAN-2006 |
| Amendment | 31-MAR-2006 |
| Amendment | 18-APR-2006 |

7. NAME & ADDRESS OF APPLICANT:

**Name:** Sepracor Inc.
**Address:** 84 Waterford Drive
Marlborough, MA 01752

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Brovana
b) on-Proprietary Name (USAN): Arformoterol tartrate
c) Code Name/# (ONDC only): 200815-49-2 (CAS registry number)
d) Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority: **1 S**

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: A long acting beta$_2$-adrenergic receptor agonist

11. DOSAGE FORM: Inhalation Solution

12. STRENGTH/POTENCY: 15 mcg/2 mL

13. ROUTE OF ADMINISTRATION: Oral Inhalation

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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

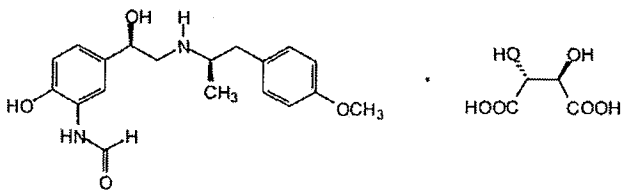
_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

Chemical Name: Arformoterol tartrate

Structural Formula:




Molecular Formula: $C_{19}H_{24}N_2O_4 \cdot C_4H_6O_6$ (1:1 salt)
Molecular Weight: 495.5 g/mol

Chemistry Review Data Sheet

## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| [redacted] | II | [redacted] | [redacted] | 1 | Adequate | 09-April -03 | Review by Chien-Hua Niu for NDA #21912 |
| [redacted] | III | | [redacted] | 3 | Adequate | 19-March-01 | Reviewed by Vibhakar Shah for NDA #20-949 |
| [redacted] | III | | [redacted] | 3 | Adequate | 04-February-02 | Reviewed by Shin-Hou Liu for ANDA #75437 |

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 | 55,302 | Arformoterol used for the treatment of bronchoconstriction |

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On Original

## 18. STATUS:

**ONDQA:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Biometrics | Complete | 5/24/06 | Ji Yang Guo |
| EES | Pending | | Office of Compliance |
| Pharm/Tox | Pending | | Timothy Robison |
| Biopharm | Pending | | Shinja Rhea Kim |
| LNC | N/A | | |
| Methods Validation | The method validation package will be sent to and validated by the FDA laboratories | | Chien-Hua Niu |
| DMETS | Revision of the labels and labeling | | |
| EA | Categorical exclusion | | Chien-Hua Niu |

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On Original

**REVIEW NOTE**

# The Chemistry Review for NDA 21-912

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

The application can be approved from chemistry point of view.

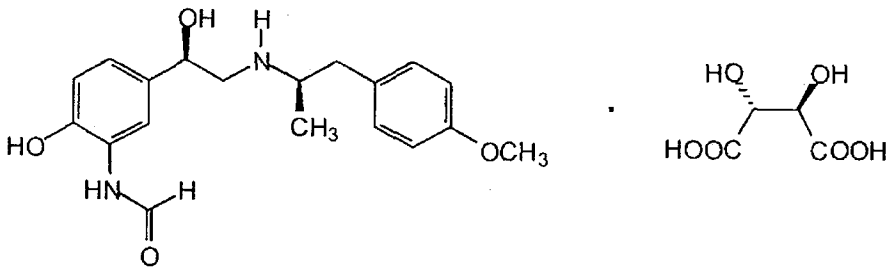
### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: None

## II. Summary of Chemistry Assessments

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

Arformoterol is a selective long-term beta$_2$-adreergic receptor agonist. Compared to racemic formoterol, arformoterol showed greater affinity for both beta adrenergic receptor subtypes and also greater selectivity for the beta$_2$-receptor. The pharmacologic effects of arformoterol are at least in part attributable to stimulation of intracellular adenyl cyclase. Increased intracellular cyclic AMP levels cause relaxation of bronchial smooth muscle contractions and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

**DRUG SUBSTANCE:** Arformoterol tartrate is designated chemically as (-)-N-[2-hydroxy-5-[(1R)-1-hydroxy-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]foramide (2R,3R)-2,3-dihydroxybutanedioate. The chemical structure and molecular formula for arformoterol tartrate are shown below:




Arformoterol tartrate is not a new molecular entity manufactured by Sepracor Canada Ltd. The API has two chiral centers with sterochemical configuration of RR. The manufacturing process for arformoterol tartrate [redacted] b(4)

## REVIEW NOTE

The structure of arformoterol was elucidated by a varity of analytical and spectrophotometric techniques, including elemental analysis, UV and IR spectroscopy, NMR ($^{1}H$ and $^{13}C$) spectroscopy, mass spectrometry, and X-ray crystallography. Arformoterol tartrate is a white to off-white solid, [ ] b(4)

[ ]

[ ] b(4)

[ ]

[ ] The proposed regulatory methods have been validated. The impurities and degradation products have been investigated. Reference standard for API has been developed and characterized. b(4)

Based on data from ICH stability studies on 6 lots, arformoterol tartrate is stable for up to [ ] at room temperature when stored [ ] b(4)

**DRUG PRODUCT:** The proposed drug product is manufactured by [ ] Arformoterol tartrate inhalation solution is formulated as isotonic, preservative-free, sterile aqueous solution consisting of arformoterol tartrate in a citrate-buffer saline solution (pH 5.0). All excipients are USP/NF grade. The manufacturing process and in-process controls are described in detail. b(4)

The composition and components of the inhalation solution (15 µg/2 mL) are listed below:

| Component | Quality Standard | Function | Amount/Unit |
|---|---|---|---|
| Arformoterol Tartrate[a] | [ ] | Active | [ ] |
| Citric Acid, [ ] | USP | Buffer Component | |
| Sodium Citrate, [ ] | USP | Buffer Component | |
| Sodium Chloride | USP | [ ] | |
| [ ] | [ ] | [ ] | |
| Total | | | |

[a]: 0.6967 gm of Arformoterol free base = 1.0 gm Arformoterol Tartrate
[b]: The amount in the table is the theoretical for the batch

b(4)

Arformoterol Tartrate Inhalation Solution is filled in LDPE vials which are then over wrapped in [ ] foil pouches. b(4)

[ ]

[ ] The proposed regulatory methods have been validated.

b(4)

## REVIEW NOTE

The results from leachables study indicated [redacted]

b(4)

Stability tests performed include appearance, color of solution, weight loss, pH, delivered volume, assay for API, impurities, isomeric purity, particular matter, and sterility.

Arformaterol Tartrate Inhalation Solution packaged in [redacted] single vial pouch configuration shows no significant changes in terms of appearance, color of solution, weight loss, delivered volume, particulate matter or sterility at any of the storage conditions studied. However, the rate of impurity formation, [redacted]

b(4)

Based on stability data from samples packaged in [redacted] single vial pouch configuration stored at refrigerated conditions, an expiration dating period of 18 months is recommended for Arformoterol Tartrate Inhalation Solution. These data also support the proposed six-week in-use storage period at room temperature (20° - 25°C).

b(4)

The sponsor has cited a regulation [21 CFR 25.31(b)] to claim a categorical exclusion from filling an environmental assessment.

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

Brovana Inhalation Solution is indicated for long term maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The firm indicates that the recommended dosage of Brovana Inhalation Solution is 15 mcg administered twice a day (morning and evening) by nebulization.

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

The recommendation that this application is can be **approved** from a CMC viewpoint is based on the following: (1) The general procedures for the synthesis of arformoterol tartrate are outlined in the NDA. However, a number of chemistry non-approvability requests for information on the synthesis, specifications, and reference standard are being made. (2) Chemical structures of major impurities and degradation products are illustrated. (3) Seven primary stability batches for 15 mcg/2 mL solution have been manufactured by ⊂ ⊐ All these batches were produced with the drug substance manufactured by Sepracor Canada Limited at Windsor, Nova Scotia, Canada. and (4) Stability data indicate that no significant changes were observed in terms of appearance, color of solution, weight loss, delivered volume, assay, impurity, isomeric purity, particulate matter and sterility when stored at 5°C for a period of 18 months and cycled to 25°/40% RH for 2.8 months. b(4)

**Pending Issue:** CGMP inspection of the manufacturing sites for the drug substance, the drug product as well as testing and packaging sites have not been completed by the Office of Compliance.

## III. Administrative

### A. Reviewer's Signature

### B. Endorsement Block

Chemist Name/Date: Chien-Hua Niu, Ph.D./ONDQA/DPMA-I
Chemistry Branch Chief Name/Date: Blair Fraser, Ph.D. /ONDQA/DPMA-I

### C. CC Block

Dr. Chi-wan Chen/ Dr. Blair Fraser
Project Manager Name/Date: Ladan Jafarir, OND/HFD-570

# 17 Page(s) Withheld

b(4) Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Chemistry-* 3

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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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Chien-Hua Niu
6/15/2006 02:53:27 PM
CHEMIST

Blair Fraser
6/15/2006 03:30:53 PM
CHEMIST