TRADENAME
(Arformoterol Tartrate)
Inhalation Solution
NDA 21-912

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

Applicant: Sepracor, Inc.
84 Waterford 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.

EER Status: Acceptable 29-JUL-2006

Consults: EA: Categorical exclusion granted under 21 CFR 25.31(b) for arformoterol
DMETS: Pending, proposed tradename: Brovana
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-[[1(R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-, (2R,3R)-2,3-dihydroxybutanedioate (1:1 salt).

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

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 $\square$ at room temperature when

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 overwrapped in $\square$ foil pouches.
regulatory methods have been validated.

Arformaterol Tartrate Inhalation Solution packaged in 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.

Adequate stability data were provided to support the proposed expiration dating period of 18 months for drug product packaged in 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).

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

/s/

________________________
Blair Fraser
9/29/2006 05:44:19 AM
CHEMIST
NDA 21-912

(also presented as Brovana)

(Arformoterol Tartrate)
Inhalation Solution

Sepracor Inc.

Chien-Hua Niu, Ph.D.
ONDQA/DPMA-I
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  III. LABELING & PACKAGE INSERT
  IV. Claim Of Categorical Exclusion
  V. List Of Deficiencies To Be Communicated
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:

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7. NAME & ADDRESS OF APPLICANT:

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

8. DRUG PRODUCT NAME/CODE/TYPEx:

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<sub>2</sub>-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:

   ![Structural Formula Image]

   Molecular Formula: \( \text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_4 \cdot \text{C}_4\text{H}_6\text{O}_6 \) (1:1 salt)
   Molecular Weight: 495.5 g/mol
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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7 – Other (explain under "Comments")

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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 beta2-adrenergic receptor agonist. Compared to racemic formoterol, arformoterol showed greater affinity for both beta adrenergic receptor subtypes and also greater selectivity for the beta2-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]formamide (2R,3R)-2,3-dihydroxybutanedioate. The chemical structure and molecular formula for arformoterol tartrate are shown below:

![Chemical structure of arformoterol tartrate](image)

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
REVIEW NOTE

The structure of arformoterol was elucidated by a variety 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.

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 14 days at room temperature when stored.

**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.

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

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<th>Function</th>
<th>Amount/Unit</th>
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<td>Active</td>
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<td>USP</td>
<td>Buffer Component</td>
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<td>Sodium Citrate, (\star)</td>
<td>USP</td>
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<td><strong>Total</strong></td>
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\(^a\): 0.6967 gm of Arformoterol free base = 1.0 gm Arformoterol Tartrate
\(^b\): The amount in the table is the theoretical for the batch

Arformoterol Tartrate Inhalation Solution is filled in LDPE vials which are then over wrapped in pouches.

The proposed regulatory methods have been validated.
The results from leachables study indicated

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 a 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,

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

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 . 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°C/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).

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-1
Chemistry Branch Chief Name/Date: Blair Fraser, Ph.D. /ONDQA/DPMA-1

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
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/s/

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

Sepracor Inc.

Chien-Hua Niu, Ph.D.
ONDQA/DPMA-I
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Chemistry Assessment .............................................................. 11

   I. DRUG SUBSTANCE
   II. DRUG PRODUCT
   III. LABELING & PACKAGE INSERT
   IV. Claim Of Categorical Exclusion
   V. List Of Deficiencies To Be Communicated


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:

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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:

   ![Structural Formula Image]

   Molecular Formula: C$_{19}$H$_{24}$N$_{2}$O$_{4}$ • C$_{4}$H$_{6}$O$_{6}$ (1:1 salt)
   Molecular Weight: 495.5 g/mol
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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The Chemistry Review for NDA 21-912

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A. Recommendation and Conclusion on Approvability
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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)

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![Chemical Structure of Arformoterol Tartrate](image)

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
The structure of arformoterol was elucidated by a variety of analytical and spectrophotometric techniques, including elemental analysis, UV and IR spectroscopy, NMR (\(^1^H\) and \(^1^C\)) spectroscopy, mass spectrometry, and X-ray crystallography. Arformoterol tartrate is a white to off-white solid. 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 2 years at room temperature when stored.

**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.

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

<table>
<thead>
<tr>
<th>Component</th>
<th>Quality Standard</th>
<th>Function</th>
<th>Amount/Unit</th>
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</thead>
<tbody>
<tr>
<td>Arformoterol Tartrate</td>
<td>USP</td>
<td>Active</td>
<td></td>
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<tr>
<td>Citric Acid, /</td>
<td>USP</td>
<td>Buffer Component</td>
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<td>Sodium Citrate,</td>
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<td>Buffer Component</td>
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<tr>
<td>Sodium Chloride</td>
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</tr>
</tbody>
</table>

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

Arformoterol Tartrate Inhalation Solution is filled in LDPE vials which are then over wrapped in foil pouches.

The proposed regulatory methods have been validated.
The results from leachables study indicated

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

Arformoterol Tartrate Inhalation Solution packaged in

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,

Based on stability data from samples packaged in

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).
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 Sepracor Canada Limited at Windsor, Nova Scotia, Canada. (4) All these batches were produced with the drug substance manufactured by Sepracor Canada Limited at Windsor, Nova Scotia, Canada. (5) 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°C/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).

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
Page(s) Withheld

Trade Secret / Confidential

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/s/

Chien-Hua Niu
8/23/2006 07:57:48 AM
CHEMIST

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
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    C. CC Block ....................................................................................................................... 10

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I. **DRUG SUBSTANCE**

II. **DRUG PRODUCT**

III. **LABELING & PACKAGE INSERT**

IV. Claim Of Categorical Exclusion

V. List Of Deficiencies To Be Communicated
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:

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<thead>
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<th>Submission Type</th>
<th>Document Date</th>
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<tbody>
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<td>Original</td>
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<td>Amendment</td>
<td>18-APR-2006</td>
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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 beta₂-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:

   ![Structural Formula Image]

   Molecular Formula: \( \text{C}_{19}\text{H}_{24}\text{N}_{2}\text{O}_{4} \cdot \text{C}_{4}\text{H}_{6}\text{O}_{6} \) (1:1 salt)

   Molecular Weight: 495.5 g/mol
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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<th>TYPE</th>
<th>HOLDER</th>
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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:

<table>
<thead>
<tr>
<th>DOCUMENT</th>
<th>APPLICATION NUMBER</th>
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<tr>
<td>IND</td>
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Appears This Way On Original
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<th>DATE</th>
<th>REVIEWER</th>
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<tr>
<td>Biometrics</td>
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<td>EES</td>
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<td>Office of Compliance</td>
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<td>Pharm/Tox</td>
<td>Pending</td>
<td></td>
<td>Timothy Robison</td>
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<tr>
<td>Biopharm</td>
<td>Pending</td>
<td></td>
<td>Shinja Rhea Kim</td>
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<tr>
<td>LNC</td>
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<td>Methods Validation</td>
<td>The method validation package will be sent to and validated by the FDA laboratories</td>
<td></td>
<td>Chien-Hua Niu</td>
</tr>
<tr>
<td>DMETS</td>
<td>Revision of the labels and labeling</td>
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<tr>
<td>EA</td>
<td>Categorical exclusion</td>
<td></td>
<td>Chien-Hua Niu</td>
</tr>
</tbody>
</table>

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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$_2$-adrergeric 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]foramidine (2R,3R)-2,3-dihydroxybutanedioate. The chemical structure and molecular formula for arformoterol tartrate are shown below:

![Chemical Structure of Arformoterol Tartrate]

Arformoterol tartrate is not a new molecular entity manufactured by Sepracor Canada Ltd. The API has two chiral centers with stereochemical configuration of RR. The manufacturing process for arformoterol tartrate...
The structure of arformoterol was elucidated by a variety of analytical and spectrophotometric techniques, including elemental analysis, UV and IR spectroscopy, NMR (1H and 13C) spectroscopy, mass spectrometry, and X-ray crystallography. Arformoterol tartrate is a white to off-white solid.

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 2 years at room temperature when stored.

**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.

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<td>Buffer Component</td>
<td></td>
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<td>USP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
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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

Arformoterol Tartrate Inhalation Solution is filled in LDPE vials which are then over wrapped in foil pouches.

The proposed regulatory methods have been validated.
The results from leachables study indicated □

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

Arformoterol Tartrate Inhalation Solution packaged in □ □ □ 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 □

Based on stability data from samples packaged in □ 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).

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

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 \[\text{b(4)}\] 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°C/40% RH for 2.8 months.

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-1
Chemistry Branch Chief Name/Date: Blair Fraser, Ph.D. /ONDQA/DPMA-1

C. CC Block

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

b(4) Trade Secret / Confidential

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

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