CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-837

CHEMISTRY REVIEW(S)
**Chemist NDA Review**

**Review of Chemistry Manufacturing & Controls**

**NDA #: N 20-837**

**CHEM. REVIEW: # 2**

**REVIEW DATE:** March 22, 1999

<table>
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<th>DOCUMENT DATE</th>
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<td>31-MAY-1998</td>
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<td>06-AUG-1998</td>
<td>11-AUG-1998</td>
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<td>08-JAN-1999</td>
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<td>BL</td>
<td>24-MAR-1999</td>
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All the above amendments are subjects of this review.

**NAME & ADDRESS OF APPLICANT:**

Sepracor Inc.  
111, Locke Drive  
Marlborough, MA 01752  
Tel: (508) 481-6700  Fax: (508) 481-7683

**DRUG PRODUCT NAME:**

- **Proprietary:** XOPENEX™ Inhalation Solution
- **Nonproprietary/USAN:** Levalbuterol hydrochloride
- **Code Name:** Not applicable
- **Chemical Type/Therapeutic Class:** 3S

**PHARMACOLOGICAL CATEGORY:**

- **INDICATION:** Treatment or prevention of bronchospasm
- **DOSEAGE FORM:** Inhalation solution
- **STRENGTHS:** 0.63 mg, 1.25 mg/3 mL Unit Dose Vials (maximum dose/day: 0.63 mg/3 mL 3 times a day)
- **ROUTE OF ADMINISTRATION:** Oral Inhalation
- **DISPENSED:** Yes
- **SPECIAL PRODUCTS:** OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Chemical Names:
- (R)-α-[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol hydrochloride, or
- (R)-α-[tert-butylamino]methyl]-4-hydroxy-m-xylene-a,a'-diol hydrochloride

Molecular Formula: C_{13}H_{21}NO_{3}·HCl
Molecular Wt: 275.78
CAS Reg. No.: [50293-90-8]

![Chemical Structure Diagram](attachment:chemical_structure.png)
SUPPORTING DOCUMENTS:

A. DMFs:

<table>
<thead>
<tr>
<th>DMF/Type</th>
<th>DMF Holder</th>
<th>Subject</th>
<th>LOA Date</th>
<th>Status</th>
<th>Reference</th>
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<tr>
<td>DMF Type II</td>
<td></td>
<td>Mfg. of Albuterol sulfate, USP/Salbutamol sulfate, BP</td>
<td>01-07-1997</td>
<td>Adequate</td>
<td>Chemist Review (V. Shah, HFD-820), March 25, 1999</td>
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<tr>
<td>DMF Type II</td>
<td></td>
<td>Mfg. of Albuterol sulfate, USP</td>
<td>03-27-1996</td>
<td>Adequate</td>
<td>Chemist Review (V. Shah, HFD-820), March 20, 1999</td>
</tr>
<tr>
<td>DMF Type II</td>
<td></td>
<td>Mfg. of racemic Albuterol sulfate (for comparator study)</td>
<td>05-06-1996</td>
<td>Adequate</td>
<td>Chemist Review (S. Brown, HFD-625), Oct. 22, 1997</td>
</tr>
<tr>
<td>DMF Type III</td>
<td></td>
<td>Mfg. of Resin for LDPE vials</td>
<td>02-07-1997</td>
<td>Adequate</td>
<td>Chemist Review (V. Shah, HFD-820), March 05, 1998</td>
</tr>
<tr>
<td>DMF Type III</td>
<td></td>
<td>Mfg. of foil (to be used for the foil laminate pouch)</td>
<td>02-17-1997</td>
<td>Adequate</td>
<td>Chemist Review (V. Shah, HFD-820), March 25, 1999</td>
</tr>
</tbody>
</table>

B. INDs/NDAs: The following IND has been specified by the applicant in support of this application.

IND (R)-Albuterol Inhalation Solution

RELATED DOCUMENTS (if applicable): None

CONSULTS:

<table>
<thead>
<tr>
<th>CONSULT</th>
<th>Forward Date</th>
<th>Status</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>1. Establishment Evaluation (EER)</td>
<td>November 17, 1998</td>
<td>Acceptable March 23, 1999</td>
<td>All other facilities except for were acceptable as of June 19, 1998. Facility has been withdrawn as of March 22, 1999. See p 96 for further comments.</td>
</tr>
<tr>
<td>3. Pharmacology</td>
<td>April 09, 1998</td>
<td>Complete Acceptable</td>
<td>Albuterol aldehyde is qualified at the proposed specifications. Through expiry, in the drug product, respectively. See Pharmacologist Rev. dated March 08, 1999. See p 60 of this review.</td>
</tr>
<tr>
<td>4. Biometrics</td>
<td>-</td>
<td>-</td>
<td>Not needed.</td>
</tr>
<tr>
<td>5. Methods Validation</td>
<td>-</td>
<td>Pending</td>
<td>Applicant has been asked to submit methods validation package in triplicate as soon as possible on receipt of the action letter. See remarks in Section V, p 87 of this review.</td>
</tr>
<tr>
<td>6. Labeling &amp; Nomenclature</td>
<td>January 21, 1998</td>
<td>Acceptable March 20, 1998</td>
<td>Xopenex™ (Levalbuterol HCl) Inhalation Solution has been accepted by LNC. See remarks in Section VI, p 88 of this review.</td>
</tr>
<tr>
<td>7. Environmental Assessment</td>
<td>N/A</td>
<td></td>
<td>Categorical exclusion under CFR 25.15 (d) is claimed. See section IV, p 87 of this review.</td>
</tr>
</tbody>
</table>
REMARKS/COMMENTS:

- Test methods used for the drug substance and the drug product should be forwarded to the FDA Laboratories, on receipt of methods validation package in triplicate from the applicant.

CONCLUSIONS & RECOMMENDATIONS:

From CMC perspective, the applicant has addressed all the deficiencies of AE letter dated July 01, 1998. The CMC comments raised in conjunction with the supporting documents, DMF and DMF, both for the manufacture of precursor in the synthesis of the drug substance, levalbuterol hydrochloride, and DMF for the have also been adequately resolved.

Consequently, from CMC perspective, the NDA 20837 for Xopenex™ (levalbuterol hydrochloride) Inhalation solution, submitted by Sepracor, Inc. may be approved.

Several Phase IV commitments which are made by the applicant and few other comments should be forwarded to the applicant (p 122 of this review).

cc:
Org. NDA 20837
HFD-570/Division File
HFD-570/Chemist/VShah
HFD-570/CSO/PJani
HFD-570/TL/GPoochikian

R/D Init by: GPoochikian

Document: n20837CMCRv2.doc
Chemist NDA Review
Review of Chemistry Manufacturing & Controls

NDA #: N 20-837

CHEM. REVIEW: # 1

SUBMISSION TYPE
Original submission
Amendment (BC)

DOCUMENT DATE
June 30, 1997
August 04, 1997

REVIEW COMPLETION DATE: April 20, 1998

CDER DATE
July 01, 1997
August 06, 1997

ASSIGNED DATE
July 10, 1997
October 22, 1997

NAME & ADDRESS OF APPLICANT:
Applicant:
Sepracor Inc.,
111, Locke Drive
Marlborough, MA 01752
Tel: (508) 481 -6700 Fax: (508) 481-7683

DRUG PRODUCT NAME:
Proprietary: Inhalation Solution (pending)
Nonproprietary/USAN: Levalbuterol hydrochloride
Code Name: Not applicable
Chemical Type/Therapeutic Class: 3S

PHARMACOLOGICAL CATEGORY:
INDICATION: Treatment or prevention of bronchospasm
DOSAGE FORM: Inhalation solution
STRENGTHS: 0.63 mg, 1.25 mg/3 mL Unit Dose Vials (maximum dose/day: 0.63 mg/3mL 3 times a day)

ROUTE OF ADMINISTRATION:
Oral Inhalation

DISPENSED:
Rx ☒

SPECIAL PRODUCTS:
Yes ☐ No ☒

(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

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

Levalbuterol hydrochloride
(R)-α-[(1,1-dimethylethyl)amino[methyl]-4-hydroxy-1,3-benzenedimethanol hydrochloride, or (R)-α-[tert-butilamino)methyl]-4-hydroxy-m-xylene-a,a’-diol hydrochloride

Molecular Formula: C₁₅H₂₃NO₃·HCl
Molecular Wt: 275.78
CAS Reg. No.: [50293-90-8]
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<tbody>
<tr>
<td>DMR Type II</td>
<td></td>
<td>Mfg. of Albuterol sulfate, USP</td>
<td>03-27-1996</td>
<td>Inadequate</td>
<td>Chemist Review (V. Shah, HFD-820), March 13, 1998</td>
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<td>DMR Type II</td>
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<td>Mfg. of racemic Albuterol sulfate (for comparator study)</td>
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<td>Adequate</td>
<td>Chemist Review (S. Brown, HFD-625), Oct. 22, 1997</td>
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<td>DMR Type III</td>
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<td>Mfg. of 20 Resin for LDPE vials</td>
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<td>Adequate</td>
<td>Chemist Review (V. Shah, HFD-820), March 05, 1998</td>
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<tr>
<td>DMR Type III</td>
<td></td>
<td>Mfg. of foil (to be used for the foil laminate pouch)</td>
<td>02-17-1997</td>
<td>Inadequate</td>
<td>Chemist Review (V. Shah, HFD-820), March 06, 1998</td>
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B. INDs/NDAs:

The following IND has been specified by the applicant in support of this application.

IND (R)-Albuterol Inhalation Solution

RELATED DOCUMENTS (if applicable): None

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<th>Status</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Establishment Evaluation (EER)</td>
<td>September 26, 1997</td>
<td>pending</td>
<td>For the evaluation of sterilization process, sterility specification, and sterility validation data for the drug product.</td>
</tr>
<tr>
<td>2. Microbiology (HFD-160)</td>
<td>February 10, 1998</td>
<td>pending</td>
<td>For the evaluation of the proposed specifications of albuterol aldehyde in the drug substance and in the drug product, respectively.</td>
</tr>
<tr>
<td>3. Pharmacology</td>
<td>April 09, 1998</td>
<td>pending</td>
<td>Will be initiated upon receipt of the updated stability data.</td>
</tr>
<tr>
<td>4. Biometrics</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>5. Methods Validation</td>
<td>-</td>
<td>pending</td>
<td></td>
</tr>
<tr>
<td>7. Environmental Assessment</td>
<td>March 20, 1998</td>
<td>N/A</td>
<td>Categorical exclusion under CFR §25.15 (d) is claimed.</td>
</tr>
</tbody>
</table>
REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

Several CMC deficiencies have been found in this NDA 20837 and other supporting documents. These supporting documents include DMF... and DMF... both for the manufacture of precursor... in the synthesis of the drug substance, levalbuterol hydrochloride, and DMF... for the... The DMF holders have been notified of the CMC comments respective to each DMF. Consequently the NDA 20837 for levalbuterol hydrochloride Inhalation solution, submitted by Sepracor, Inc. can not be approved until the CMC issues contained in the draft letter and also in the CMC reviews of the supporting DMFs... and... are completely resolved.

cc:
Org. NDA 20837
HFD-570/Division File
HFD-570/Chemist/V Shah
HFD-570/CSO/PJani
HFD-570/TL/GPoochikian

R/D Init by: GPoochikian/ 4/30/98

Note that all significant issues were discussed with Dr. Pooshikian by Dr. Shah.

APPEARS THIS WAY ON ORIGINAL