

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-837**

**CHEMISTRY REVIEW(S)**

**Chemist NDA Review**  
**Review of Chemistry Manufacturing & Controls**

MAR 24 1999

**NDA #: N 20-837**

**CHEM. REVIEW: # 2**

**REVIEW DATE: March 22, 1999**

<u>SUBMISSION TYPE</u>		<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Correspondence	C	28-MAY-1998	-	31-MAY-1998
Amendment	BC	26-JUN-1998	29-JUN-1998	30-JUN-1998
Amendment	BZ	06-AUG-1998	10-AUG-1998	11-AUG-1998
Amendment	AZ	24-SEP-1998	25-SEP-1998	28-SEP-1998
Amendment	BC	30-SEP-1998	02-OCT-1998	13-OCT-1998
Amendment	BC	08-JAN-1999	11-JAN-1999	13-JAN-1999
Amendment	BC	28-JAN-1999	29-JAN-1999	04-FEB-1999
Amendment	BC	29-JAN-1999	01-FEB-1999	04-FEB-1999
Amendment	BL	18-MAR-1999	19-MAR-1999	19-MAR-1999
Amendment	BC	18-MAR-1999	19-MAR-1999	19-MAR-1999
Amendment	BC	22-MAR-1999	23-MAR-1999	23-MAR-1999
Amendment	BL	23-MAR-1999	24-MAR-1999	24-MAR-1999
Amendment	BL	24-MAR-1999	25-MAR-1999	25-MAR-1999

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:  
Nonproprietary/USAN:  
Code Name:  
Chemical Type/Therapeutic Class:

XOPENEX™ Inhalation Solution  
Levalbuterol hydrochloride  
Not applicable  
3S

**PHARMACOLOGICAL CATEGORY:**

**INDICATION:**

**DOSAGE FORM:**

**STRENGTHS:**

**ROUTE OF ADMINISTRATION:**

**DISPENSED:**

**SPECIAL PRODUCTS:**

Treatment or prevention of [ ] bronchospasm.  
Inhalation solution  
[ ] 0.63 mg, 1.25 mg/3 mL Unit Dose Vials  
(maximum dose/day: 0.63 mg/3mL 3 times a day)  
Oral Inhalation  
Rx  OTC   
Yes  No

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

**Chemical Names:**

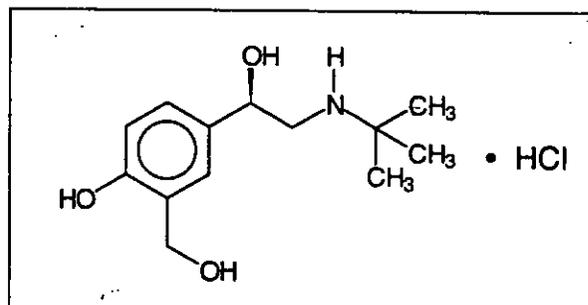
(R)-α-[[1,1-dimethylethyl]amino]methyl]-4-hydroxy-1,3-benzenedimethanol hydrochloride, or

(R)-α-[tert-butylamino]methyl]-4-hydroxy-m-xylene-a,a'-diol hydrochloride

**Molecular Formula:** C<sub>13</sub>H<sub>21</sub>NO<sub>3</sub>•HCl

**Molecular Wt:** 275.78

**CAS Reg. No.:** [50293-90-8]



**Levalbuterol hydrochloride**

**SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF/Type	DMF Holder	Subject	LOA Date	Status	Reference
DMF Type II	[Redacted]	Mfg. of Albuterol sulfate, USP/ Salbutemol sulfate, BP	01-07-1997 09-25-1996	Adequate	Chemist Review (V. Shah, HFD-820), March 25, 1999
DMF Type II		Mfg. of Albuterol sulfate, USP	03-27-1996	Adequate	Chemist Review (V. Shah, HFD-820), March 20, 1999
DMF Type II		Mfg. of racemic Albuterol sulfate (for comparator study)	05-06-1996	Adequate	Chemist Review (S. Brown, HFD-625), Oct. 22, 1997
DMF Type III		Mfg. of [Redacted] 20 Resin for LDPE vials	02-07-1997	Adequate	Chemist Review (V. Shah, HFD-820), March 05, 1998
DMF Type III		Mfg. of foil (to be used for the foil laminate pouch)	02-17-1997	Adequate	Chemist Review (V. Shah, HFD-820), March 25, 1999

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

IND [Redacted] (R)- Albuterol Inhalation Solution

**RELATED DOCUMENTS** (if applicable): None

**CONSULTS:**

CONSULT	Forward Date	Status	Comments
1. Establishment Evaluation (EER)	November 17, 1998	Acceptable March 23, 1999	All other facilities except for [Redacted] were acceptable as of June 19, 1998. [Redacted] facility has been withdrawn as of March 22, 1999. See p 96 for further comments.
2. Microbiology (HFD-160)	February 10, 1998	Acceptable January 29, 1999	See Microbiologist Review #3 dated January 29, 1999. See pp. 75-76, Chemist Rev. #1.
3. Pharmacology	April 09, 1998 March 02, 1999	Complete Acceptable	Albuterol aldehyde is qualified at the proposed specifications. [Redacted] at release and [Redacted] through expiry, in the drug product, respectively. See Pharmacologist Rev. dated March 08, 1999. See p 60 of this review.
4. Biometrics	-	-	Not needed.
5. Methods Validation	-	Pending	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.
6. Labeling & Nomenclature	January 21, 1998	Acceptable March 20, 1998	Xopenex™ (Levalbuterol HCl) Inhalation Solution has been accepted by LNC. See remarks in Section VI, p 88 of this review
7. Environmental Assessment		N/A	Categorical exclusion under CFR §25.15 (d) is claimed. See section IV, p 87 of this review.

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 [redacted] and DMF [redacted] both for the manufacture of precursor [redacted] in the synthesis of the drug substance, levalbuterol hydrochloride, and DMF [redacted] for the [redacted] 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).

/S/ [redacted]

Vibhakar J. Shah, Ph.D. 03/23/99  
Review Chemist, DNDCH (HFD-820)

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 [redacted] 03/24/99

Document: n20837CMCRev2.doc

APPEARS THIS WAY  
ON ORIGINAL

**Chemist NDA Review**  
**Review of Chemistry Manufacturing & Controls**

APR 30 1998

NDA #: N 20-837      CHEM. REVIEW: # 1      REVIEW COMPLETION DATE: April 20, 1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original submission	June 30, 1997	July 01, 1997	July 10, 1997
Amendment (BC)	August 04, 1997	August 06, 1997	
Amendment (BC)	October 21, 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: .  
Nonproprietary/USAN:  
Code Name:  
Chemical Type/Therapeutic Class:

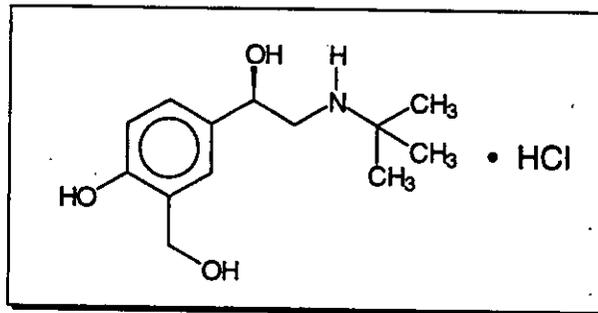
Inhalation Solution (pending)  
Levalbuterol hydrochloride  
Not applicable  
3S

**PHARMACOLOGICAL CATEGORY:**

INDICATION:  
DOSAGE FORM:  
STRENGTHS:  
  
ROUTE OF ADMINISTRATION:  
DISPENSED:  
SPECIAL PRODUCTS:

Treatment or prevention of  bronchospasm  
Inhalation solution  
 0.63 mg, 1.25 mg/3 mL Unit Dose Vials  
(maximum dose/day: 0.63 mg/3mL 3 times a day)  
Oral Inhalation  
Rx   
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)- $\alpha$ -[[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol hydrochloride, or  
(R)- $\alpha$ -[tert-butylamino)methyl]-4-hydroxy-m-xylene-a,a'-diol hydrochloride

Molecular Formula:  $C_{13}H_{21}NO_3 \cdot HCl$

Molecular Wt: 275.78

CAS Reg. No.: [50293-90-8]

**SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF/Type	DMF Holder	Subject	LOA Date	Status	Reference
DMF [redacted] Type II	[redacted]	Mfg. of Albuterol sulfate, USP/ Salbutamol sulfate, BP	01-07-1997 09-25-1996	Inadequate	Chemist Review (V. Shah, HFD-820), March 13, 1998
DMF [redacted] Type II	[redacted]	Mfg. of Albuterol sulfate, USP	03-27-1996	Inadequate	Chemist Review (V. Shah, HFD-820), March 13, 1998
DMF [redacted] Type II	[redacted]	Mfg. of racemic Albuterol sulfate (for comparator study)	05-06-1996	Adequate	Chemist Review (S. Brown, HFD-625), Oct. 22, 1997
DMF [redacted] Type III	[redacted]	Mfg. of [redacted] 20 Resin for LDPE vials	02-07-1997	Adequate	Chemist Review (V. Shah, HFD-820), March 05, 1998
DMF [redacted] Type III	[redacted]	Mfg. of foil (to be used for the foil laminate pouch)	02-17-1997	Inadequate	Chemist Review (V. Shah, HFD-820), March 06, 1998

**B. INDs/NDAs:**

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

IND [redacted] (R)- Albuterol Inhalation Solution

RELATED DOCUMENTS (if applicable): None

**CONSULTS:**

CONSULT	Forward Date	Status	Comments
1. Establishment Evaluation (EER)	September 26, 1997	pending	
2. Microbiology (HFD-160)	February 10, 1998	pending	For the evaluation of [redacted] sterilization process, sterility specification, and sterility validation data for the drug product.
3. Pharmacology	April 09, 1998	pending	For the evaluation of the proposed specifications of albuterol aldehyde [redacted] in the drug substance and [redacted] in the drug product, respectively.
4. Biometrics	-	-	Will be initiated upon receipt of the updated stability data.
5. Methods Validation	-	pending	
6. Labeling & Nomenclature	January 21, 1998 March 20, 1998	Pending	
7. Environmental Assessment		N/A	Categorical exclusion under CFR §25.15 (d) is claimed.

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

Several CMC deficiencies have been found in this NDA 20837 and other supporting documents. These supporting documents include DMF [redacted] and DMF [redacted] both for the manufacture of precursor [redacted] in the synthesis of the drug substance, levalbuterol hydrochloride, and DMF [redacted] for the [redacted]. 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 [redacted] and [redacted] are completely resolved.

[redacted] /S/

Vibhakar L. Shah, Ph.D. 04/28/1998  
Review Chemist, DNDCII (HFD-820)

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

[redacted] /S/

[redacted] /S/  
4/30/98

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

R/D Init by: GPoochikian/

Document: n20837Rev1.doc

APPEARS THIS WAY  
ON ORIGINAL