CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER
20-837/S-010

Trade Name:	Xopenex Inhalation Solution
Generic Name:	levalbuterol hydrochloride
Sponsor:	Sepracor, Inc.
Approval Date:	July 18, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER
20-837/S-010

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER
20-837/S-010

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-837/S-010

Sepracor, Inc.
84 Waterford Drive
Marlborough, MA 01752

Attention: Prabu Nambiar, Ph.D., RAC
Director, Technical Regulatory Affairs

Dear Dr. Nambiar:

Please refer to your supplemental new drug application dated March 29, 2002, received April 1, 2002, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Xopenex (levalbuterol HCl) Inhalation Solution.

We acknowledge receipt of your submissions dated September 4, 2002, December 3, 2002, March 17, July 16, and July 17, 2003.

Your submission of March 17, 2003 constituted a complete response to our August 1, 2002, action letter.

This supplemental new drug application provides for the addition of a new strength (1.25 mg/0.5 mL) of the drug product.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text. Please note that the expiration dating period for this strength (1.25 mg/0.5 mL) of the drug product is 18 months. In addition, we have the following comment.

We remind you of your agreements to revise final printed labels (package insert, foil-pouch label, carton label, etc.) for clarity prior to implementation and to provide representative samples both for the final printed labels and vial samples to the Agency, prior to the launch of the drug product.

The final printed labeling (FPL) must be identical to the submitted labeling (immediate container and carton labels as submitted on March 17, 2003, foil pouch label as submitted on July 16, 2003, and package insert as submitted on July 17, 2003).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-837/S-010." Approval of this submission by FDA is not required before the labeling is used.

In addition, we request that you submit four copies of the introductory promotional materials you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division, the Division of Pulmonary and Allergy Drug Products, one to the Division of Over-the-Counter Drug Products, and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Akilah Green, Regulatory Project Manager, at (301) 827-5580.

Sincerely,

{See appended electronic signature page}

Guirag Poochikian, Ph.D.
Chemistry Team Leader
Division of Pulmonary and Allergy Drug Products, HFD-570
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Guiragos Poochikian
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER
20-837/S-010

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-837/S-010

Sepracor, Inc.
Attention: Prabu Nambiar, Ph.D.
Director, Technical Regulatory Affairs
84 Waterford Drive
Marlborough, MA 01752

Dear Dr. Nambiar:

Please refer to your supplemental new drug application dated March 29, 2002, received April 1, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xopenex (levalbuterol hydrochloride) Inhalation Solution.

We acknowledge receipt of your submissions dated April 12 and June 10, 2002.

This supplemental new drug application provides for the addition of a new strength (1.25 mg/0.5 mL) of the drug product.

We have completed our review of this supplemental application and it is approvable. Before this supplement may be approved, however, you must address the following deficiencies:

1. [redacted]
2.
3.
4.
   a.
   b.
   c.

5. [redacted]

6.

Within 10 days after the date of this letter, you are required to amend this supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all of the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Dr. Craig Ostroff, Regulatory Management Officer, at 301-827-5585.

Sincerely,

{See appended electronic signature page}

Guirag Poochikian, Ph.D.
Chemistry Team Leader
Division of Pulmonary and Allergy Drug Products, HFD-570
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Guiragos Poochikian
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER
20-837/S-010

FINAL PRINTED LABELING

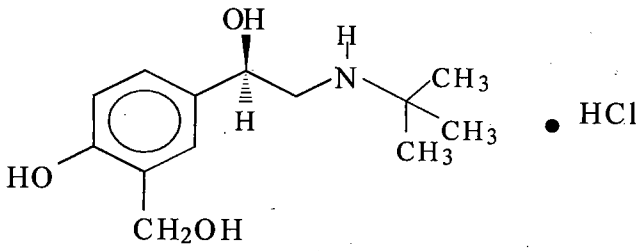
Xopenex® (levalbuterol HCl) Inhalation Solution Concentrate, 1.25 mg*

***Potency expressed as levalbuterol**

PRESCRIBING INFORMATION

DESCRIPTION

Xopenex (levalbuterol HCl) Inhalation Solution is a sterile, clear, colorless, preservative-free solution of the hydrochloride salt of levalbuterol, the (R)-enantiomer of the drug substance racemic albuterol. Levalbuterol HCl is a relatively selective beta$_2$-adrenergic receptor agonist (see **CLINICAL PHARMACOLOGY**). The chemical name for levalbuterol HCl is (R)-α^1-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol hydrochloride, and its established chemical structure is as follows:



The molecular weight of levalbuterol HCl is 275.8, and its empirical formula is $C_{13}H_{21}NO_3$•HCl. It is a white to off-white, crystalline solid, with a melting point of approximately 187°C and solubility of approximately 180 mg/mL in water.

Levalbuterol HCl is the USAN modified name for (R)-albuterol HCl in the United States.

Xopenex (levalbuterol HCl) Inhalation Solution Concentrate supplied in 0.5 mL unit-dose vials should be diluted with sterile normal saline before administration by nebulization. Each 0.5 mL unit-dose vial contains 1.25 mg of levalbuterol (as 1.44 mg of levalbuterol HCl), sodium chloride to adjust tonicity, and hydrochloric acid to adjust the pH to 4.0 (3.3 to 4.5).

CLINICAL PHARMACOLOGY

Activation of beta$_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic-3′, 5′-adenosine monophosphate (cyclic AMP). This increase in cyclic AMP leads to the activation of

protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Levalbuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Levalbuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway.

While it is recognized that $beta_2$-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there is a population of $beta_2$-receptors in the human heart that comprise between 10% and 50% of cardiac beta-adrenergic receptors. The precise function of these receptors has not been established (see **WARNINGS**). However, all beta-adrenergic agonist drugs can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

Preclinical Studies

Results from an *in vitro* study of binding to human beta-adrenergic receptors demonstrated that levalbuterol has approximately 2-fold greater binding affinity than racemic albuterol and approximately 100-fold greater binding affinity than (S)-albuterol. In guinea pig airways, levalbuterol HCl and racemic albuterol decreased the response to spasmogens (e.g., acetylcholine and histamine), whereas (S)-albuterol was ineffective. These results suggest that most of the bronchodilatory effect of racemic albuterol is due to the (R)-enantiomer.

Intravenous studies in rats with racemic albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5.0% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Pharmacokinetics (Adults and Adolescents ≥12 years old)

The inhalation pharmacokinetics of Xopenex Inhalation Solution were investigated in a randomized cross-over study in 30 healthy adults following administration of a single dose of 1.25 mg and a cumulative dose of 5 mg of Xopenex Inhalation Solution and a single dose of 2.5 mg and a cumulative dose of 10 mg of racemic albuterol sulfate inhalation solution by nebulization using a PARI LC Jet™ nebulizer with a Dura-Neb® 2000 compressor.

Following administration of a single 1.25 mg dose of Xopenex Inhalation Solution, exposure to (R)-albuterol (AUC of 3.3 ng•hr/mL) was approximately 2-fold higher than following

administration of a single 2.5 mg dose of racemic albuterol inhalation solution (AUC of 1.7 ng•hr/mL) (see **Table 1**). Following administration of a cumulative 5 mg dose of Xopenex Inhalation Solution (1.25 mg given every 30 minutes for a total of four doses) or a cumulative 10 mg dose of racemic albuterol inhalation solution (2.5 mg given every 30 minutes for a total of four doses), C_{max} and AUC of (R)-albuterol were comparable (see **Table 1**).

Table 1: Mean (SD) Values for Pharmacokinetic Parameters in Healthy Adults

	Single Dose		Cumulative Dose	
	Xopenex 1.25 mg	Racemic albuterol sulfate 2.5 mg	Xopenex 5 mg	Racemic albuterol sulfate 10 mg
C_{max} (ng/mL)				
(R)-albuterol	1.1 (0.45)	0.8 (0.41)**	4.5 (2.20)	4.2 (1.51)**
T_{max} (h)[γ]				
(R)-albuterol	0.2 (0.17, 0.37)	0.2 (0.17, 1.50)	0.2 (–0.18*, 1.25)	0.2 (–0.28*, 1.00)
AUC (ng•h/mL)				
(R)-albuterol	3.3 (1.58)	1.7 (0.99)**	17.4 (8.56)	16.0 (7.12)**
$T_{½}$ (h)				
(R)-albuterol	3.3 (2.48)	1.5 (0.61)	4.0 (1.05)	4.1 (0.97)

γ Median (Min, Max) reported for T_{max}.

* A negative T_{max} indicates C_{max} occurred between first and last nebulizations.

** Values reflect only (R)-albuterol and do not include (S)-albuterol.

Pharmacokinetics (Children 6–11 years old)

The pharmacokinetic parameters of (R)- and (S)-albuterol in children with asthma were obtained using population pharmacokinetic analysis. These data are presented in **Table 2.** For comparison, adult data obtained by conventional pharmacokinetic analysis from a different study also are presented in **Table 2.**

In children, AUC and C_{max} of (R)-albuterol following administration of 0.63 mg Xopenex Inhalation Solution were comparable to those following administration of 1.25 mg racemic albuterol sulfate inhalation solution.

When the same dose of 0.63 mg of Xopenex was given to children and adults, the predicted C_{max} of (R)–albuterol in children was similar to that in adults (0.52 vs. 0.56 ng/mL), while predicted AUC in children (2.55 ng•hr/mL) was about 1.5-fold higher than that in adults (1.65 ng•hr/mL). These data support lower doses for children 6-11 years old compared with the adult doses (see **Dosage and Administration**).

Table 2: (R)-Albuterol Exposure in Adults and Pediatric Subjects (6-11 years)

	Children 6-11 years				Adults ≥12 years	
Treatment	Xopenex 0.31 mg	Xopenex 0.63 mg	Racemic albuterol 1.25mg	Racemic albuterol 2.5 mg	Xopenex 0.63 mg	Xopenex 1.25 mg
$AUC_{0-\infty}$ (ng•hr/mL) [c]	1.36	2.55	2.65	5.02	1.65 [a]	3.3 [b]
C_{max} (ng/mL) [d]	0.303	0.521	0.553	1.08	0.56 [a]	1.1 [b]

[a] The values are predicted by assuming linear pharmacokinetics

[b] The data obtained from Table 1

[c] Area under the plasma concentration curve from time 0 to infinity

[d] Maximum plasma concentration

Pharmacodynamics (Adults and Adolescents ≥12 years old)

In a randomized, double-blind, placebo-controlled, cross-over study, 20 adults with mild-to-moderate asthma received single doses of Xopenex Inhalation Solution (0.31, 0.63, and 1.25 mg) and racemic albuterol sulfate inhalation solution (2.5 mg). All doses of active treatment produced a significantly greater degree of bronchodilation (as measured by percent change from pre-dose mean FEV_1) than placebo, and there were no significant differences between any of the active treatment arms. The bronchodilator responses to 1.25 mg of Xopenex Inhalation Solution and 2.5 mg of racemic albuterol sulfate inhalation solution were clinically comparable over the 6-hour evaluation period, except for a slightly longer duration of action (>15% increase in FEV_1 from baseline) after administration of 1.25 mg of Xopenex Inhalation Solution. Systemic beta-adrenergic adverse effects were observed with all active doses and were generally dose-related for (R)-albuterol. Xopenex Inhalation Solution at a dose of 1.25 mg produced a slightly higher rate of systemic beta-adrenergic adverse effects than the 2.5 mg dose of racemic albuterol sulfate inhalation solution.

In a randomized, double-blind, placebo-controlled, cross-over study, 12 adults with mild-to-moderate asthma were challenged with inhaled methacholine chloride 20 and 180 minutes following administration of a single dose of 2.5 mg of racemic albuterol sulfate, 1.25 mg of Xopenex, 1.25 mg of (S)-albuterol, or placebo using a PARI LC Jet™ nebulizer. Racemic albuterol sulfate, Xopenex, and (S)-albuterol had a protective effect against methacholine-induced bronchoconstriction 20 minutes after administration, although the effect of (S)-albuterol was minimal. At 180 minutes after administration, the bronchoprotective effect of 1.25 mg of Xopenex was comparable to that of 2.5 mg of racemic albuterol sulfate. At 180 minutes after administration, 1.25 mg of (S)-albuterol had no bronchoprotective effect.

In a clinical study in adults with mild-to-moderate asthma, comparable efficacy (as measured by change from baseline FEV_1) and safety (as measured by heart rate, blood pressure, ECG, serum potassium, and tremor) were demonstrated after a cumulative dose of 5 mg of Xopenex Inhalation Solution (four consecutive doses of 1.25 mg administered every

30 minutes) and 10 mg of racemic albuterol sulfate inhalation solution (four consecutive doses of 2.5 mg administered every 30 minutes).

Clinical Trials (Adults and Adolescents ≥12 years old)

The safety and efficacy of Xopenex Inhalation Solution were evaluated in a 4-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in 362 adult and adolescent patients 12 years of age and older, with mild-to-moderate asthma (mean baseline FEV_1 60% of predicted). Approximately half of the patients were also receiving inhaled corticosteroids. Patients were randomized to receive Xopenex 0.63 mg, Xopenex 1.25 mg, racemic albuterol sulfate 1.25 mg, racemic albuterol sulfate 2.5 mg, or placebo three times a day administered via a PARI LC Plus™ nebulizer and a Dura-Neb® portable compressor. Racemic albuterol delivered by a chlorofluorocarbon (CFC) metered dose inhaler (MDI) was used on an as-needed basis as the rescue medication.

Efficacy, as measured by the mean percent change from baseline FEV_1, was demonstrated for all active treatment regimens compared with placebo on day 1 and day 29. On both day 1 (see **Figure 1**) and day 29 (see **Figure 2**), 1.25 mg of Xopenex demonstrated the largest mean percent change from baseline FEV_1 compared with the other active treatments. A dose of 0.63 mg of Xopenex and 2.5 mg of racemic albuterol sulfate produced a clinically comparable mean percent change from baseline FEV_1 on both day 1 and day 29.

Figure 1: **Mean Percent Change from Baseline FEV_1 on Day 1, Adults and Adolescents ≥12 years old**

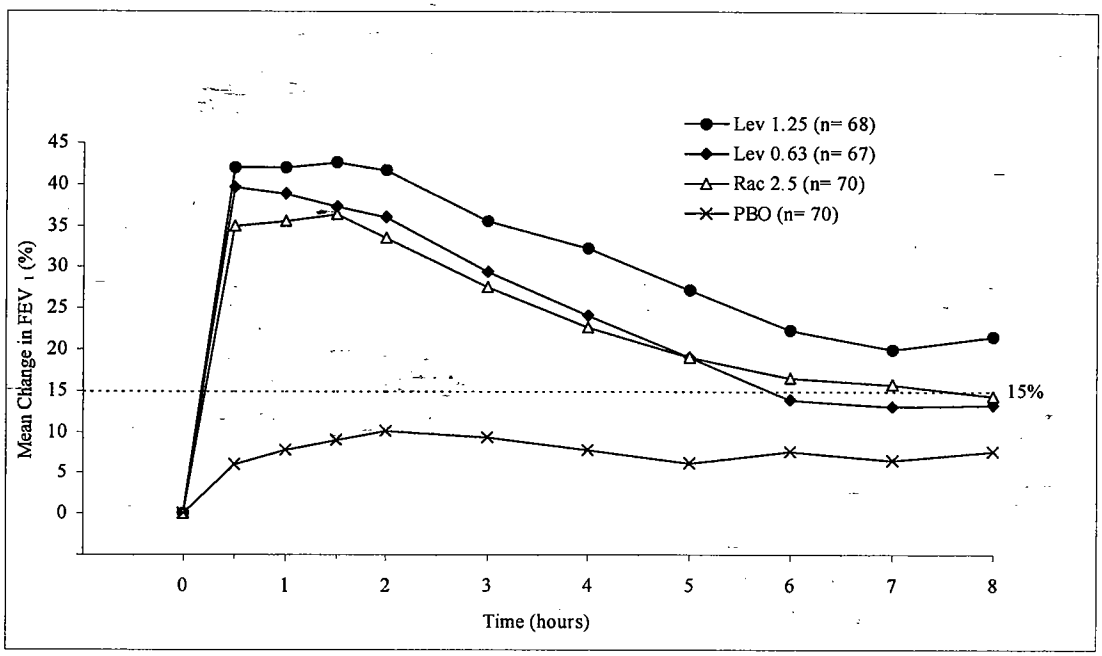
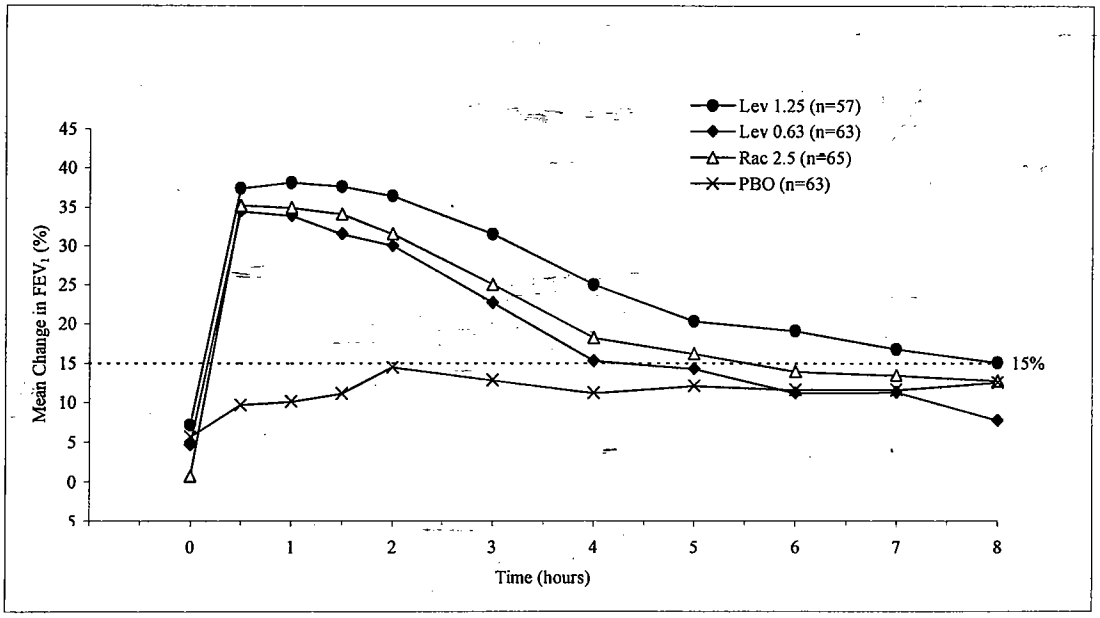


Figure 2: **Mean Percent Change from Baseline FEV_1 on Day 29, Adults and Adolescents ≥12 years old**



The mean time to onset of a 15% increase in FEV_1 over baseline for levalbuterol at doses of 0.63 mg and 1.25 mg was approximately 17 minutes and 10 minutes, respectively, and the mean time to peak effect for both doses was approximately 1.5 hours after 4 weeks of treatment. The mean duration of effect, as measured by a >15% increase from baseline FEV_1, was approximately 5 hours after administration of 0.63 mg of levalbuterol and approximately 6 hours after administration of 1.25 mg of levalbuterol after 4 weeks of treatment. In some patients, the duration of effect was as long as 8 hours.

Clinical Trials (Children 6–11 years old)

A multicenter, randomized, double-blind, placebo- and active-controlled study was conducted in children with mild-to-moderate asthma (mean baseline FEV_1 73% of predicted) (n=316). Following a 1-week placebo run-in, subjects were randomized to Xopenex (0.31 or 0.63 mg), racemic albuterol (1.25 or 2.5 mg), or placebo, which were delivered three times a day for 3 weeks using a PARI LC Plus™ nebulizer and a Dura-Neb® 3000 compressor.

Efficacy, as measured by mean peak percent change from baseline FEV_1, was demonstrated for all active treatment regimens compared with placebo on day 1 and day 21. Time profile FEV_1 curves for day 1 and day 21 are shown in **Figure 3** and **Figure 4,** respectively. The onset of effect (time to a 15% increase in FEV_1 over test-day baseline) and duration of effect (maintenance of a >15% increase in FEV_1 over test-day baseline) of levalbuterol were clinically comparable to those of racemic albuterol.

Figure 3: **Mean Percent Change from Baseline FEV_1 on Day 1, Children 6-11 Years of Age**

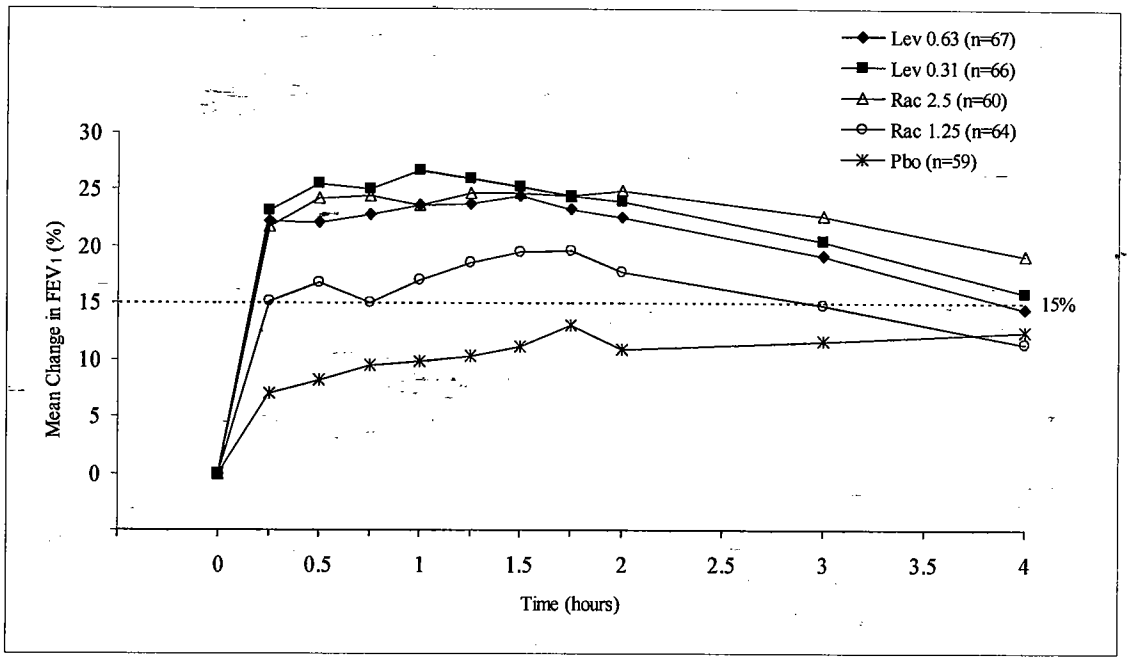
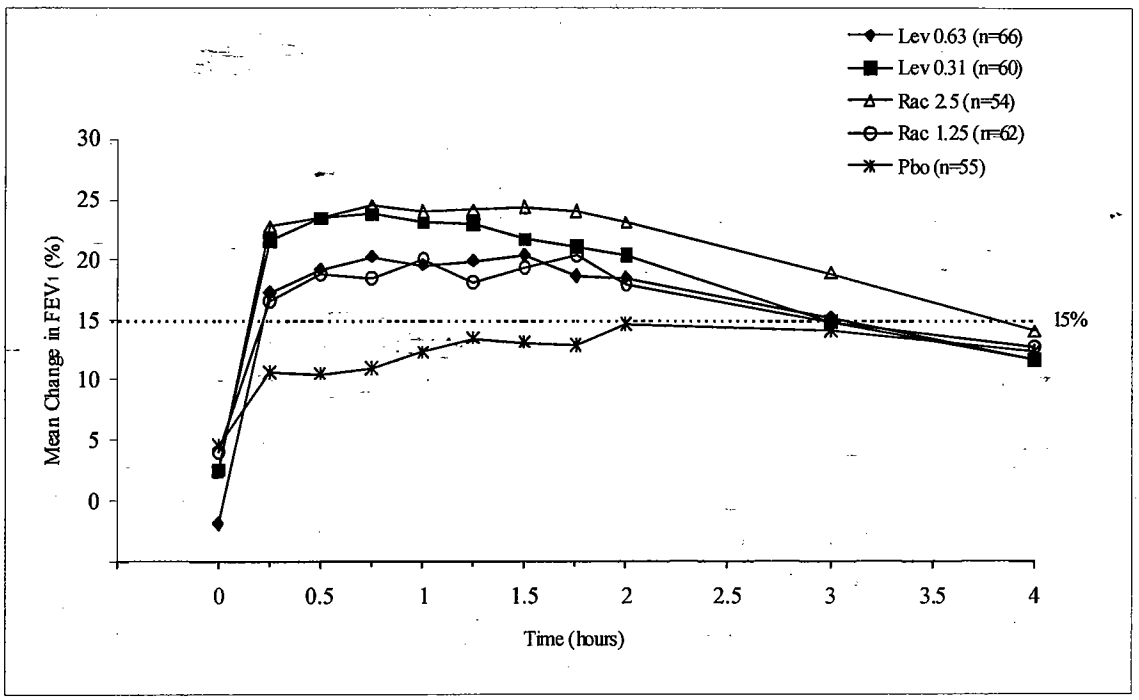


Figure 4: **Mean Percent Change from Baseline FEV_1 on Day 21, Children 6-11 Years of Age**



INDICATIONS AND USAGE

Xopenex (levalbuterol HCl) Inhalation Solution is indicated for the treatment or prevention of bronchospasm in adults, adolescents, and children 6 years of age and older with reversible obstructive airway disease.

CONTRAINDICATIONS

Xopenex (levalbuterol HCl) Inhalation Solution is contraindicated in patients with a history of hypersensitivity to levalbuterol HCl or racemic albuterol.

WARNINGS

1. Paradoxical Bronchospasm: Like other inhaled beta-adrenergic agonists, Xopenex Inhalation Solution can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, Xopenex Inhalation Solution should

be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister or vial.

2. Deterioration of Asthma: Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of Xopenex Inhalation Solution than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

3. Use of Anti-Inflammatory Agents: The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids, to the therapeutic regimen.

4. Cardiovascular Effects: Xopenex Inhalation Solution, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of Xopenex Inhalation Solution at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, Xopenex Inhalation Solution, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5. Do Not Exceed Recommended Dose: Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

6. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of racemic albuterol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving Xopenex Inhalation Solution.

PRECAUTIONS

General

Levalbuterol HCl, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmias; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus;

and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after the use of any beta-adrenergic bronchodilator.

Large doses of intravenous racemic albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other beta-adrenergic agonist medications, levalbuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Information for Patients

See illustrated Patient's Instructions for Use.

The action of Xopenex (levalbuterol HCl) Inhalation Solution may last up to 8 hours. Xopenex Inhalation Solution should not be used more frequently than recommended. Do not increase the dose or frequency of dosing of Xopenex Inhalation Solution without consulting your physician. If you find that treatment with Xopenex Inhalation Solution becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek medical attention immediately. While you are taking Xopenex Inhalation Solution, other inhaled drugs and asthma medications should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, headache, dizziness, and tremor or nervousness. If you are pregnant or nursing, contact your physician about the use of Xopenex Inhalation Solution.

Effective and safe use of Xopenex Inhalation Solution requires consideration of the following information in addition to that provided under Patient's Instructions for Use:

Xopenex Inhalation Solution single-use low-density polyethylene (LDPE) vials should be protected from light and excessive heat. Store in the protective foil pouch between 20°C and 25°C (68°F and 77°F) [see USP Controlled Room Temperature]. Do not use after the expiration date stamped on the container. Open the foil pouch just prior to administration. Once the foil pouch is opened, the contents of the vial should be used immediately. Discard any vial if the solution is not colorless. Xopenex (levalbuterol HCl) Inhalation Solution Concentrate should be diluted with sterile normal saline before administration by nebulization.

The drug compatibility (physical and chemical), efficacy, and safety of Xopenex Inhalation Solution when mixed with other drugs in a nebulizer have not been established.

Drug Interactions

Other short-acting sympathomimetic aerosol bronchodilators or epinephrine should be used with caution with levalbuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

1. Beta-blockers: Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists such as Xopenex (levalbuterol HCl) Inhalation Solution, but may also produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

2. Diuretics: The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non-potassium sparing diuretics.

3. Digoxin: Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of racemic albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving levalbuterol HCl and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and Xopenex Inhalation Solution.

4. Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: Xopenex Inhalation Solution should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of levalbuterol HCl on the vascular system may be potentiated.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No carcinogenesis or impairment of fertility studies have been carried out with levalbuterol HCl alone. However, racemic albuterol sulfate has been evaluated for its carcinogenic potential and ability to impair fertility.

In a 2-year study in Sprague-Dawley rats, racemic albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately 2 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults and children on a mg/m^2 basis). In another

study, this effect was blocked by the coadministration of propranolol, a nonselective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, racemic albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 500 mg/kg (approximately 260 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults and children on a mg/m^2 basis). In a 22-month study in the Golden hamster, racemic albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg (approximately 35 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults and children on a mg/m^2 basis).

Levalbuterol HCl was not mutagenic in the Ames test or the CHO/HPRT Mammalian Forward Gene Mutation Assay. Although levalbuterol HCl has not been tested for clastogenicity, racemic albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay. Reproduction studies in rats using racemic albuterol sulfate demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 55 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis).

Teratogenic Effects — Pregnancy Category C

A reproduction study in New Zealand White rabbits demonstrated that levalbuterol HCl was not teratogenic when administered orally at doses up to 25 mg/kg (approximately 110 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis). However, racemic albuterol sulfate has been shown to be teratogenic in mice and rabbits. A study in CD-1 mice given racemic albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately equal to the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis). The drug did not induce cleft palate formation when administered subcutaneously at a dose of 0.025 mg/kg (less than the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with 2.5 mg/kg of isoproterenol (positive control).

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when racemic albuterol sulfate was administered orally at a dose of 50 mg/kg (approximately 110 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults on a mg/m^2 basis).

A study in which pregnant rats were dosed with radiolabeled racemic albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

There are no adequate and well-controlled studies of Xopenex Inhalation Solution in pregnant women. Because animal reproduction studies are not always predictive of human

response, Xopenex Inhalation Solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During marketing experience of racemic albuterol, various congenital anomalies, including cleft palate and limb defects, have been rarely reported in the offspring of patients being treated with racemic albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between racemic albuterol use and congenital anomalies has not been established.

Use in Labor and Delivery

Because of the potential for beta-adrenergic agonists to interfere with uterine contractility, the use of Xopenex Inhalation Solution for the treatment of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Tocolysis

Levalbuterol HCl has not been approved for the management of preterm labor. The benefit:risk ratio when levalbuterol HCl is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with $beta_2$-agonists, including racemic albuterol.

Nursing Mothers

Plasma levels of levalbuterol after inhalation of therapeutic doses are very low in humans, but it is not known whether levalbuterol is excreted in human milk.

Because of the potential for tumorigenicity shown for racemic albuterol in animal studies and the lack of experience with the use of Xopenex Inhalation Solution by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when Xopenex Inhalation Solution is administered to a nursing woman.

Pediatrics

The safety and efficacy of Xopenex (levalbuterol HCl) Inhalation Solution have been established in pediatric patients 6 years of age and older in one adequate and well-controlled clinical trial (see **CLINICAL PHARMACOLOGY; Pharmacodynamics and Clinical Trials**). Use of Xopenex in children is also supported by evidence from adequate and well-controlled studies of Xopenex in adults, considering that the pathophysiology and the drug's exposure level and effects in pediatric and adult patients are substantially similar. Safety and

effectiveness of Xopenex in pediatric patients below the age of 6 years have not been established.

Geriatrics

Data on the use of Xopenex in patients 65 years of age and older are very limited. A very small number of patients 65 years of age and older were treated with Xopenex Inhalation Solution in a 4-week clinical study (see **CLINICAL PHARMACOLOGY; Clinical Trials**) (n=2 for 0.63 mg and n=3 for 1.25 mg). In these patients, bronchodilation was observed after the first dose on day 1 and after 4 weeks of treatment. There are insufficient data to determine if the safety and efficacy of Xopenex Inhalation Solution are different in patients <65 years of age and patients 65 years of age and older. In general, patients 65 years of age and older should be started at a dose of 0.63 mg of Xopenex Inhalation Solution. If clinically warranted due to insufficient bronchodilator response, the dose of Xopenex Inhalation Solution may be increased in elderly patients as tolerated, in conjunction with frequent clinical and laboratory monitoring, to the maximum recommended daily dose (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS (ADULTS AND ADOLESCENTS ≥12 YEARS OLD)

Adverse events reported in ≥2% of patients receiving Xopenex Inhalation Solution or racemic albuterol and more frequently than in patients receiving placebo in a 4-week, controlled clinical trial are listed in **Table 3**.

Table 3: Adverse Events Reported in a 4-Week, Controlled Clinical Trial in Adults and Adolescents ≥12 years old

Body System Preferred Term	Percent of Patients			
	Placebo (n=75)	Xopenex 1.25 mg (n=73)	Xopenex 0.63 mg (n=72)	Racemic albuterol 2.5 mg (n=74)
Body as a Whole				
Allergic reaction	1.3	0	0	2.7
Flu syndrome	0	1.4	4.2	2.7
Accidental injury	0	2.7	0	0
Pain	1.3	1.4	2.8	2.7
Back pain	0	0	0	2.7
Cardiovascular System				
Tachycardia	0	2.7	2.8	2.7
Migraine	0	2.7	0	0
Digestive System				
Dyspepsia	1.3	2.7	1.4	1.4
Musculoskeletal System				
Leg cramps	1.3	2.7	0	1.4
Central Nervous System				
Dizziness	1.3	2.7	1.4	0
Hypertonia	0	0	0	2.7
Nervousness	0	9.6	2.8	8.1
Tremor	0	6.8	0	2.7
Anxiety	0	2.7	0	0
Respiratory System				
Cough increased	2.7	4.1	1.4	2.7
Infection viral	9.3	12.3	6.9	12.2
Rhinitis	2.7	2.7	11.1	6.8
Sinusitis	2.7	1.4	4.2	2.7
Turbinate edema	0	1.4	2.8	0

The incidence of certain systemic beta-adrenergic adverse effects (e.g., tremor, nervousness) was slightly less in the Xopenex 0.63 mg group compared with the other active treatment groups. The clinical significance of these small differences is unknown.

Changes in heart rate 15 minutes after drug administration and in plasma glucose and potassium 1 hour after drug administration on day 1 and day 29 were clinically comparable in the Xopenex 1.25 mg and racemic albuterol 2.5 mg groups (see **Table 4**). Changes in

heart rate and plasma glucose were slightly less in the Xopenex 0.63 mg group compared with the other active treatment groups (see **Table 4**). The clinical significance of these small differences is unknown. After 4 weeks, effects on heart rate, plasma glucose, and plasma potassium were generally diminished compared with day 1 in all active treatment groups.

Table 4: Mean Changes from Baseline Heart Rate at 15 Minutes and Glucose and Potassium at 1 Hour after First Dose (Day 1) in Adults and Adolescents ≥12 years old

	Mean Changes (day 1)		
Treatment	Heart Rate (bpm)	Glucose (mg/dL)	Potassium (mEq/L)
Xopenex 0.63 mg, n=72	2.4	4.6	–0.2
Xopenex 1.25 mg, n=73	6.9	10.3	–0.3
Racemic albuterol 2.5 mg, n=74	5.7	8.2	–0.3
Placebo, n=75	–2.8	–0.2	–0.2

No other clinically relevant laboratory abnormalities related to administration of Xopenex Inhalation Solution were observed in this study.

In the clinical trials, a slightly greater number of serious adverse events, discontinuations due to adverse events, and clinically significant ECG changes were reported in patients who received Xopenex 1.25 mg compared with the other active treatment groups.

The following adverse events, considered potentially related to Xopenex, occurred in less than 2% of the 292 subjects who received Xopenex and more frequently than in patients who received placebo in any clinical trial:

Body as a Whole:	chills, pain, chest pain
Cardiovascular System:	ECG abnormal, ECG change, hypertension, hypotension, syncope
Digestive System:	diarrhea, dry mouth, dry throat, dyspepsia, gastroenteritis, nausea
Hemic and Lymphatic System:	lymphadenopathy
Musculoskeletal System:	leg cramps, myalgia
Nervous System:	anxiety, hypesthesia of the hand, insomnia, paresthesia, tremor
Special Senses:	eye itch

The following events, considered potentially related to Xopenex, occurred in less than 2% of the treated subjects but at a frequency less than in patients who received placebo: asthma exacerbation, cough increased, wheezing, sweating, and vomiting.

ADVERSE REACTIONS (CHILDREN 6-11 YEARS OLD)

Adverse events reported in ≥2% of patients in any treatment group and more frequently than in patients receiving placebo in a 3-week, controlled clinical trial are listed in **Table 5.**

Table 5: Most Frequently Reported Adverse Events (≥2% in Any Treatment Group) and Those Reported More Frequently Than in Placebo during the Double-Blind Period (ITT Population, 6-11 Years Old)

	Percent of Patients				
Body System Preferred Term	Placebo (n=59)	Xopenex 0.31 mg (n=66)	Xopenex 0.63 mg (n=67)	Racemic albuterol 1.25 mg (n=64)	Racemic albuterol 2.5 mg (n=60)
Body as a Whole					
Abdominal pain	3.4	0	1.5	3.1	6.7
Accidental injury	3.4	6.1	4.5	3.1	5.0
Asthenia	0	3.0	3.0	1.6	1.7
Fever	5.1	9.1	3.0	1.6	6.7
Headache	8.5	7.6	11.9	9.4	3.3
Pain	3.4	3.0	1.5	4.7	6.7
Viral Infection	5.1	7.6	9.0	4.7	8.3
Digestive System					
Diarrhea	0	1.5	6.0	1.6	0
Hemic and Lymphatic					
Lymphadenopathy	0	3.0	0	1.6	0
Musculoskeletal System					
Myalgia	0	0	1.5	1.6	3.3
Respiratory System					
Asthma	5.1	9.1	9.0	6.3	10.0
Pharyngitis	6.8	3.0	10.4	0	6.7
Rhinitis	1.7	6.1	10.4	3.1	5.0
Skin and Appendages					
Eczema	0	0	0	0	3.3
Rash	0	0	7.5	1.6	0
Urticaria	0	0	3.0	0	0
Special Senses					
Otitis Media	1.7	0	0	0	3.3

Note: Subjects may have more than one adverse event per body system and preferred term.

Changes in heart rate, plasma glucose, and serum potassium are shown in **Table 6.** The clinical significance of these small differences is unknown.

Table 6: Mean Changes from Baseline Heart Rate at 30 Minutes and Glucose and Potassium at 1 Hour after First Dose (Day 1) and Last Dose (Day 21) in Children 6-11 years old

	Mean Changes (Day 1)		
Treatment	Heart Rate (bpm)	Glucose (mg/dL)	Potassium (mEq/L)
Xopenex 0.31 mg, n=66	0.8	4.9	–0.31
Xopenex 0.63 mg, n=67	6.7	5.2	–0.36
Racemic albuterol 1.25 mg, n=64	6.4	8.0	–0.27
Racemic albuterol 2.5 mg, n=60	10.9	10.8	–0.56
Placebo, n=59	–1.8	0.6	–0.05
	Mean Changes (Day 21)		
Treatment	Heart Rate (bpm)	Glucose (mg/dL)	Potassium (mEq/L)
Xopenex 0.31 mg, n= 60	0	2.6	–0.32
Xopenex 0.63 mg, n=66	3.8	5.8	–0.34
Racemic albuterol 1.25 mg, n= 62	5.8	1.7	–0.18
Racemic albuterol 2.5 mg, n= 54	5.7	11.8	–0.26
Placebo, n= 55	–1.7	1.1	–0.04

OVERDOSAGE

The expected symptoms with overdosage are those of excessive beta-adrenergic receptor stimulation and/or occurrence or exaggeration of any of the symptoms listed under **ADVERSE REACTIONS,** e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min., arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and sleeplessness. Hypokalemia also may occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with the abuse of Xopenex Inhalation Solution. Treatment consists of discontinuation of Xopenex Inhalation Solution together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of Xopenex Inhalation Solution.

The intravenous median lethal dose of levalbuterol HCl in mice is approximately 66 mg/kg (approximately 70 times the maximum recommended daily inhalation dose of levalbuterol HCl for adults and children on a mg/m^2 basis). The inhalation median lethal dose has not been determined in animals.

DOSAGE AND ADMINISTRATION

Children 6–11 years old: The recommended dosage of Xopenex (levalbuterol HCl) Inhalation Solution for patients 6–11 years old is 0.31 mg administered three times a day, by nebulization. Routine dosing should not exceed 0.63 mg three times a day.

Adults and Adolescents ≥12 years old: The recommended starting dosage of Xopenex (levalbuterol HCl) Inhalation Solution for patients 12 years of age and older is 0.63 mg administered three times a day, every 6 to 8 hours, by nebulization.

Patients 12 years of age and older with more severe asthma or patients who do not respond adequately to a dose of 0.63 mg of Xopenex Inhalation Solution may benefit from a dosage of 1.25 mg three times a day.

Patients receiving the highest dose of Xopenex Inhalation Solution should be monitored closely for adverse systemic effects, and the risks of such effects should be balanced against the potential for improved efficacy.

The use of Xopenex Inhalation Solution can be continued as medically indicated to control recurring bouts of bronchospasm. During this time, most patients gain optimal benefit from regular use of the inhalation solution.

If a previously effective dosage regimen fails to provide the expected relief, medical advice should be sought immediately, since this is often a sign of seriously worsening asthma that would require reassessment of therapy.

The drug compatibility (physical and chemical), efficacy, and safety of Xopenex Inhalation Solution when mixed with other drugs in a nebulizer have not been established.

The safety and efficacy of Xopenex Inhalation Solution have been established in clinical trials when administered using the PARI LC Jet™ and PARI LC Plus™ nebulizers, and the PARI Master® Dura-Neb® 2000 and Dura-Neb® 3000 compressors. The safety and efficacy of Xopenex Inhalation Solution when administered using other nebulizer systems have not been established.

HOW SUPPLIED

Xopenex (levalbuterol HCl) Inhalation Solution Concentrate *(foil pouch label color red)* is supplied in 0.5 mL unit-dose, low-density polyethylene (LDPE) vials, and is a clear, colorless, sterile, preservative-free, aqueous solution. Each vial contains 1.25 mg of levalbuterol (as 1.44 mg of levalbuterol HCl) and is available in cartons of 30 (NDC 63402-515-30) individually pouched vials.

Xopenex (levalbuterol HCl) Inhalation Solution is also available in 3 mL vials in three different strengths of levalbuterol: 0.31 mg (NDC 63402-511-24), 0.63 mg (NDC 63402-512-24), and 1.25 mg (NDC 63402-513-24).

CAUTION

Federal law (U.S.) prohibits dispensing without prescription.

Store Xopenex (levalbuterol HCl) Inhalation Solution Concentrate in the protective foil pouch at 20-25°C (68-77°F) [see USP Controlled Room Temperature]. Protect from light and excessive heat. Open the foil pouch just prior to administration. Once the foil pouch is opened, the contents of the vial should be used immediately. Discard any vial if the solution is not colorless. Xopenex (levalbuterol HCl) Inhalation Solution Concentrate should be diluted with sterile normal saline before administration by nebulization.

Manufactured for:
Sepracor Inc.
Marlborough, MA 01752 USA
by Cardinal Health, Woodstock, IL 60098 USA
For customer service, call 1-888-394-7377.
To report adverse events, call 1-877-737-7226.
For medical information, call 1-800-739-0565.

April 2004
400438

PHARMACIST — DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

Patient's Instructions for Use

Xopenex® (levalbuterol HCl) Inhalation Solution Concentrate; 1.25 mg*; 0.5 mL Unit-Dose Vials

***Potency expressed as levalbuterol**

Read complete instructions carefully before using.

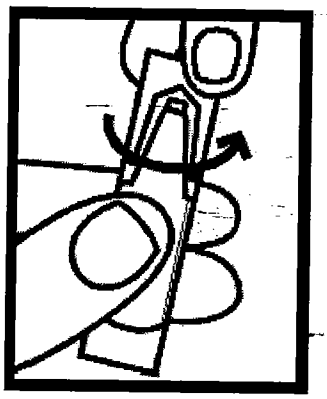


Figure 1

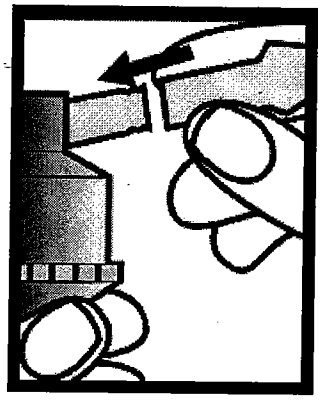


Figure 2

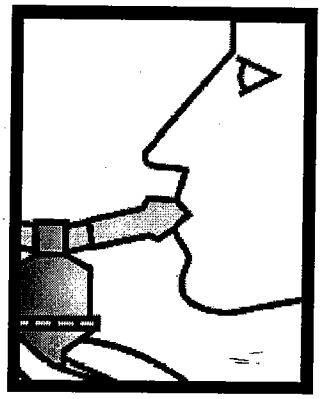


Figure 3

For the 0.5 mL Concentrate only:

1. Open the foil pouch by tearing on the serrated edge along the seam of the pouch. Remove the unit-dose vial for immediate use.
2. Carefully twist open the top of the unit-dose vial (**Figure 1**) and squeeze the entire contents into the nebulizer reservoir.
3. Add 2.5 mL (or the amount as directed by your physician) of sterile normal saline solution. Gently swirl the nebulizer to mix the contents.
4. Connect the nebulizer reservoir to the mouthpiece or face mask (**Figure 2**).
5. Connect the nebulizer to the compressor.
6. Sit in a comfortable, upright position. Place the mouthpiece in your mouth (**Figure 3**) (or put on the face mask) and turn on the compressor.
7. Breathe as calmly, deeply, and evenly as possible until no more mist is formed in the nebulizer reservoir (about 5 to 15 minutes). At this point, the treatment is finished.
8. Clean the nebulizer (see manufacturer's instructions).

Note: Xopenex (levalbuterol HCl) Inhalation Solution should be used in a nebulizer only under the direction of a physician. More frequent administration or higher doses are not recommended without first discussing with your doctor. This solution should not be injected or administered orally. Protect from light and excessive heat. Store in the protective foil pouch at 20-25°C (68-77°F) [see USP Controlled Room Temperature]. Open the foil pouch just prior to administration. Once the foil pouch is opened, the contents of the vial should be used immediately. Discard any vial if the solution is not colorless. Xopenex (levalbuterol HCl) Inhalation Solution Concentrate should be diluted with sterile normal saline before administration by nebulization.

The safety and effectiveness of Xopenex Inhalation Solution have not been determined when one or more drugs are mixed with it in a nebulizer. Check with your doctor before mixing any medications in your nebulizer.

Manufactured for:
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April 2004
400438

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER
20-837/S-010

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION #:NDA	20,837	APPLICATION TYPE:	Supplement 010
SPONSOR:	Sepracor	PRODUCT/PROPRIETARY NAME:	Xopenex
		USAN Established Name:	Levalbuterol
CATEGORY OF DRUG:	bronchodilator	ROUTE OF ADMINISTRATION:	Inhalation solution
MEDICAL REVIEWER:	Nicklas	REVIEW DATE:	9 July 2002

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
29 March 2002 and 10 June 2002	1 April 2002 and 11 June 2002	Informational supplement	See overview below

Overview of Application/Review: On 29 March 2002, the sponsor submitted a prior approval supplement for a more concentrated formulation of Xopenex Inhalation Solution (1.25 mg/0.5 ml compared to the approved product, 1.25 mg/3 ml), which was to be diluted with 2.5 ml of normal saline prior to administration. An in-house meeting was held on 10 April 2002 to discuss this new concentration of Xopenex Inhalation Solution in a LDPE unit dose vial which was 6 times more concentrated than the currently approved drug product. The sponsor stated that the new concentration offered advantages over the marketed product, which were: 1) assurance of accurate dosing; 2) avoidance of potential leachables and extractables from dropper components; 3) unit-dose sterility; and 4) elimination of preservatives required for multiple use vials. It was the consensus at this in-house meeting that the proposed concentration of 1.25 mg/0.5 ml was unacceptable, because: 1) it would lead to confusion and possibly incorrect dosing; 2) there was potential for contamination; and 3) less drug was likely to be delivered to the patient, compared to the 3 ml drug product, since the residual amount of drug left in the vial at the time of mixing would be greater because of the higher concentration. The latter is a safety issue in patients who rely on the drug product to reverse potentially life-threatening bronchospasm. These concerns were conveyed to the sponsor by the Division on 7 May 2002, with a request for information on the rationale for the development of and the intended marketing plans for this drug product.

The sponsor in the submission of 10 June 2002 has responded to this request from the Division and proposes a conference call with the Division to discuss this rationale. The rationale given by the sponsor includes: 1) there is an approved generic racemic albuterol concentration in a 0.5 ml LDPE vial; 2) marketing efforts will be directed at hospitals and institutions, where there is a market for unit dose products and in a setting where accurate dose administration will be more likely, especially since the sponsor will be developing distinct packaging for this drug product; 3) there is a decreased risk of contamination; 4) there will be more precise dose delivery; and 5) there will be increased educational initiatives developed by the sponsor for this drug product. An in-house meeting was held on 8 July 2002 and the sponsor's response was discussed. From a clinical standpoint, the Division continues to feel that there are significant potential risks associated with the use of this concentrated formulation of Xopenex Inhalation Solution, and therefore this drug product is non-approvable.

The Division contacted the Office of Generic Drugs in regard to their approval of Nephron's ANDA 75,664 for albuterol vials designed for single use, an action that appeared to be discordant with the position the Division is taking in regard to the more concentrated form of Xopenex, which is also designed for single use. OGD pointed out that both the multidose bottle and single use vial of generic albuterol require dilution with saline prior to use and that both products are the same strength. Therefore, there is a significant difference between the situation that OGD faced in approving ANDA 75,664 and the situation in regard to the proposed Xopenex drug product, in that the approved Xopenex product is single use and does not require dilution with saline, while the proposed higher concentration Xopenex does require dilution with saline, and is also more concentrated.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Richard Nicklas
7/9/02 12:19:41 PM
MEDICAL OFFICER

Badrul Chowdhury
7/9/02 04:22:51 PM
MEDICAL OFFICER
I concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
20-837/S-010

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW - 1	1. ORGANIZATION CDER/ORM/ODEII/DPDP/HFD-570 CDER/OPS/ONDC/DNDCII/HFD-820	2. NDA Number: N 20837

3. NAME AND ADDRESS OF APPLICANT (*City and State*)

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

4. AF NUMBER

5. SUPPLEMENT(S)

SCS-010* March 29, 2002
SCS-10(BZ)* June 10, 2002

* Subject of this Review

6. NAME OF DRUG(S)	7. NONPROPRIETARY NAME
Xopenex® Inhalation Solution	Levalbuterol hydrochloride

8. SUPPLEMENT PROVIDES FOR:

Marketing of a new strength of the drug product, containing 1.25 mg levalbuterol hydrochloride in 0.5 mL and labeling it as Xopenex ®(levalbuterol hydrochloride) Inhalation Solution Concentrate, 1.25 mg/0.5 mL"

9. AMENDMENT(S), REPORT(S), ETC.

Letter Assign

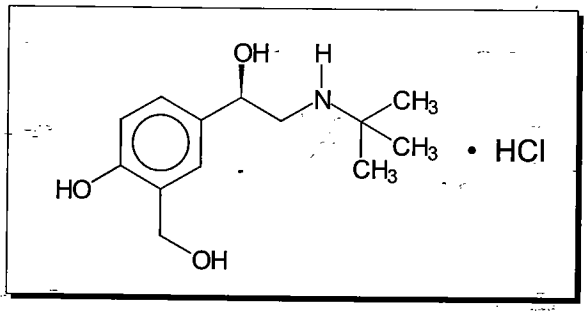
10. PHARMACOLOGICAL CATEGORY/INDICATION	11. HOW DISPENSED	13. RELATED IND/NDA/DMF
Treatment or prevention of acute bronchospasm	Rx ☒ OTC ☐ 12. SPECIAL DRUG PRODUCT Yes ☐ No ☒	

14. DOSAGE FORM(s)/Dose	15. POTENCY	17. RECORDS AND REPORTS
Sterile Inhalation Solution 1.25 mg/3mL 3 times a day	0.31 mg, 0.63 mg, 1.25 mg per 3 mL Unit Dose Vials; 1.25 mg per 0.5mL/UDV	CURRENT Yes _____No REVIEWED Yes _____No

16. CHEMICAL NAME AND STRUCTURE:

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

Molecular Formula: $C_{13}H_{21}NO_3 \cdot HCl$
Molecular Wt: 275.78
CAS Reg. No.: [50293-90-8]



Levalbuterol Hydrochloride

18. COMMENTS: See attached review notes.

19. CONCLUSIONS AND RECOMMENDATIONS:

- From CMC viewpoint this supplement is **approvable**. The draft comment listed on page 23 of this review should be communicated to the applicant in an appropriate action letter by the CSO.

File: C:\C-5053847(E)\CMCReviews\NDAs\N20837\N20837scs010\n20837scs010CR1.doc (Total pages = 27)	F/T by: *V. Shah,* R/D Init. By: *G. Poochikian,*
20. REVIEWER'S NAME *Vibhakar J. Shah, Ph.D.* / **SIGNATURE**	**DATE OF COMPLETION** July 26, 2002

DISTRIBUTION	Orig. NDA 20837	Review Chemist: *V. Shah*	CSO: C. Ostroff	
CC:	HFD-570 Div File	Chemistry TL: *G. Poochikian*		

25 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable

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/s/

Vibhakar J. Shah
7/30/02 02:44:15 PM
CHEMIST

From CMC perspective this supplement is approvable. Comments listed on page 22 of this review should be communicated to the applicant in an appropriate action letter by the CSO.

Guiragos Poochikian
7/30/02 02:50:44 PM
CHEMIST

CHEMIST'S REVIEW - 2	1. ORGANIZATION CDER/ORM/ODEII/DPDP/HFD-570 CDER/OPS/ONDC/DNDCII/HFD-820	2. NDA Number: N 20837

3. NAME AND ADDRESS OF APPLICANT (*City and State*)

Sepracor Inc.
84, Waterford Drive
Marlborough, MA 01752 - 7010
Tel: (508) 481 -6700 Fax: (508) 481-7683

4. AF NUMBER

5. SUPPLEMENT(S)

SCS-010 March 29, 2002

6. NAME OF DRUG(S)

Xopenex® Inhalation Solution

7. NONPROPRIETARY NAME

Levalbuterol hydrochloride

8. SUPPLEMENT PROVIDES FOR:

Marketing of a new strength of the drug product, containing 1.25 mg levalbuterol hydrochloride in 0.5 mL and labeling it as Xopenex ®(levalbuterol hydrochloride) Inhalation Solution Concentrate, 1.25 mg/0.5 mL"

9. AMENDMENT(S), REPORT(S), ETC.

SCS-010 (BC)*	July 17, 2003
SCS-010 (BC)*	July 16, 2003
SCS-010 (AC)*	March 17, 2003
SCS-010(BC)*	December 03, 2002
SCS-010(MR)*	September 04, 2002
SCS-010 (BZ)	June 10, 2002

* Subject of this Review

10. PHARMACOLOGICAL CATEGORY/INDICATION

Treatment or prevention of acute bronchospasm

11. HOW DISPENSED

Rx ☒ **OTC** ☐

12. SPECIAL DRUG PRODUCT

Yes ☐ **No** ☒

13. RELATED IND/NDA/DMF

14. DOSAGE FORM(s)/Dose

Sterile Inhalation Solution
1.25 mg/3mL 3 times a day

15. POTENCY

0.31 mg, 0.63 mg, 1.25 mg per 3 mL Unit Dose Vials; 1.25 mg per 0.5mL/UDV

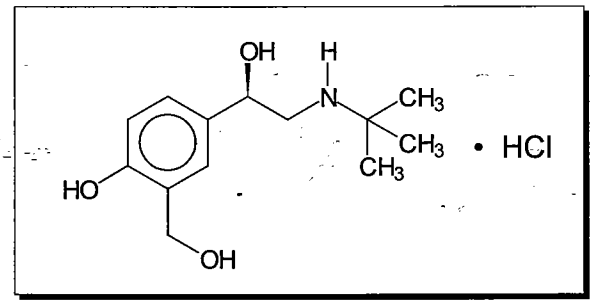
17. RECORDS AND REPORTS

CURRENT Yes ___ No_____
REVIEWED Yes ___ No_____

16. CHEMICAL NAME AND STRUCTURE:

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

Molecular Formula: $C_{13}H_{21}NO_3 \cdot HCl$
Molecular Wt: 275.78
CAS Reg. No.: [50293-90-8]



Levalbuterol Hydrochloride

18. COMMENTS: See attached review notes.

19. CONCLUSIONS AND RECOMMENDATIONS:

- From CMC viewpoint this supplement may be **approved**. The agreements listed on page 16 should be communicated to the applicant in an appropriate action letter by the CSO.

File: C:\C-5053847(E)\CMCReviews\NDAs\N20837\N20837scs010\n20837scs010CR2.doc (Total pages = 17)	**F/T by**: *V. Shah,* **R/D Init. By**: *G. Poochikian,*
20. REVIEWER'S NAME *Vibhakar J. Shah, Ph.D.* / **SIGNATURE**	**DATE OF COMPLETION** July 17, 2003

DISTRIBUTION	Orig. **NDA 20837**	**Review Chemist**: *V. Shah*	**CSO**: A. Green	
CC:	HFD-570 Div File	**Chemistry TL**: *G. Poochikian*		

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/s/

Vibhakar J. Shah
7/17/03 06:04:03 PM
CHEMIST

From CMC perspective this supplement may be approved. The agreements listed on page 15 of this review should be communicated to the applicant in an appropriate action letter by the CSO.

Guiragos Poochikian
7/17/03 06:07:09 PM
CHEMIST

CHEMIST'S REVIEW – 2 Addendum	1. ORGANIZATION CDER/ORM/ODEII/DPDP/HFD-570 CDER/OPS/ONDC/DNDCII/HFD-820	2. NDA Number: N 20837

3. NAME AND ADDRESS OF APPLICANT (*City and State*)

Sepracor Inc.
84, Waterford Drive
Marlborough, MA 01752 - 7010
Tel: (508) 481 -6700 Fax: (508) 481-7683

4. AF NUMBER

5. SUPPLEMENT(S)
SCS-010 March 29, 2002

6. NAME OF DRUG(S)
Xopenex® Inhalation Solution

7. NONPROPRIETARY NAME
Levalbuterol hydrochloride

8. SUPPLEMENT PROVIDES FOR:
Marketing of a new strength of the drug product, containing 1.25 mg levalbuterol hydrochloride in 0.5 mL and labeling it as Xopenex ®(levalbuterol hydrochloride) Inhalation Solution Concentrate, 1.25 mg/0.5 mL"

9. AMENDMENT(S), REPORT(S), ETC.

SCS-010 (BC)*	July 17, 2003
SCS-010 (BC)*	July 16, 2003
SCS-010 (AC)*	March 17, 2003
SCS-010(BC)*	December 03, 2002
SCS-010(MR)*	September 04, 2002
SCS-010 (BZ)	June 10, 2002

* Subject of this Review

10. PHARMACOLOGICAL CATEGORY/INDICATION
Treatment or prevention of acute bronchospasm

11. HOW DISPENSED
Rx ☒ **OTC** ☐

12. SPECIAL DRUG PRODUCT
Yes ☐ **No** ☒

13. RELATED IND/NDA/DMF

14. DOSAGE FORM(s)/Dose
Sterile Inhalation Solution
1.25 mg/3mL 3 times a day

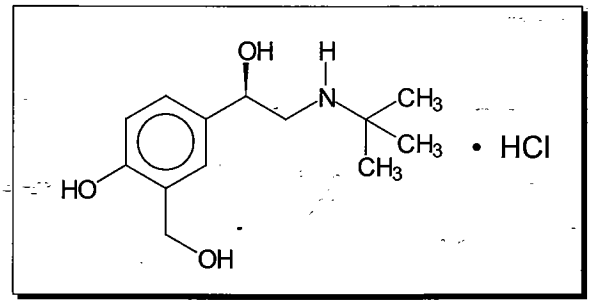
15. POTENCY
0.31 mg, 0.63 mg, 1.25 mg per 3 mL Unit Dose Vials; 1.25 mg per 0.5mL/UDV

17. RECORDS AND REPORTS
CURRENT Yes ___ No_____
REVIEWED Yes ___ No_____

16. CHEMICAL NAME AND STRUCTURE:

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

Molecular Formula: $C_{13}H_{21}NO_3 \cdot HCl$
Molecular Wt: 275.78
CAS Reg. No.: [50293-90-8]



Levalbuterol Hydrochloride

18. COMMENTS: See attached review notes.

19. CONCLUSIONS AND RECOMMENDATIONS:

- From CMC viewpoint this supplement may be **approved**. The agreements listed on page 16 of Chemistry Review-2 (dated July 17, 2003) should be communicated to the applicant in an appropriate action letter by the CSO.
- Xopenex ®(levalbuterol hydrochloride) Inhalation Solution Concentrate, 1.25 mg/0.5 mL is granted 18 month of expiration dating period when stored at USP Controlled Room Temperature (25° ± 2°C/60% ± 5% RH).

File: C:\C-5053847(E)\CMCReviews\NDAs\N20837\N20837scs010\n20837scs010CR2Addendum.doc (Total pages = 2)	**F/T by:** *V. Shah,* **R/D Init. By:** *G. Poochikian,*

20. REVIEWER'S NAME	SIGNATURE	DATE OF COMPLETION
Vibhakar J. Shah, Ph.D.		July 18, 2003

DISTRIBUTION	Orig. NDA 20837	Review Chemist: *V. Shah*	CSO: A. Green	
CC:	HFD-570 Div File	Chemistry TL: *G. Poochikian*		

3 page(s) of draft labeling has been removed from this portion of the review.

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/s/

Vibhakar J. Shah
7/18/03 11:37:05 AM
CHEMIST

Addendum to Chemist Review-2 (07/17/2003) to include a revised copy of individual foil pouch label. Chemist Review-2 recommendation, that is supplement may be approved, remains unchanged. Appropriate action letter needs to be issued to the applicant.

Guiragos Poochikian
7/18/03 12:34:26 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER
20-837/S-010

CORRESPONDENCE AND ADMINISTRATIVE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-837\S-010

Sepracor Inc.
84 Waterford Drive
Marlborough, MA 01752-7010

Attention: Prabu Nambiar, Ph.D, RAC
Senior Director, Technical Regulatory Affairs

Dear Dr. Salem:

We acknowledge receipt of your August 9, 2004, submission containing final printed labeling in response to our July 18, 2003, letter approving your supplemental new drug application for Xopenex (levalbuterol HCL) Inhalation Solution.

We have reviewed the labeling that you submitted in accordance with our July 18, 2003, letter and we find it acceptable.

If you have any questions, call Akilah Green, Regulatory Project Manager, at 301-827-5585.

Sincerely,

{See appended electronic signature page}

Badrul Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
10/5/04 04:23:11 PM

Project Manager Labeling Review

NDA 20-837/S-010 Xopenex (levalbuterol HCL) Inhalation Solution

SPONSOR: Sepracor

SUBMISSION DATED: August 9, 2004 RECEIVED: August 10, 2004

This submission contains final printed labeling as requested in our approval letter dated July 18, 2003. This supplemental application provided for the addition of a new strength (1.25mg/0.5mL) of Xopenex (levalbuterol HCL) Inhalation Solution.

I compared the labeling dated August 9, 2004, to the labeling approved July 18, 2003, [immediate container and carton labels submitted March 17, 2003, foil pouch label submitted July 16, 2003, and package insert submitted July 17, 2003]. The final printed labeling is identical to the approved labeling with minor editorial revisions with the following exceptions:

1. The word "Concentrate" was added under the drug strength on the foil pouch, and on the carton and container, which is consistent with our suggestions for the package insert.
2. The manufacturer's name changed from "Automated Liquid Packaging" to "Cardinal Health" in the package insert.
3. "1-877-SEPRACOR" was changed to "For customer service, call 1-888-394-7377" in the package insert.

The labeling changes were discussed with the chemist, Vibhakar Shah and he agreed with the revisions. The labeling should be acknowledged and retained.

Akilah Green
Regulatory Project Manager
Division of Pulmonary and Allergy Drug Products

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/s/

Akilah Green
10/5/04 03:12:49 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-837/S-010

Sepracor, Inc.
84 Waterford Drive
Marlborough, MA 01752

Attention: Prabu Nambiar, Ph.D.
Director, Technical Regulatory Affairs

Dear Dr. Nambiar:

We acknowledge receipt on March 18, 2003, of your March 17, 2003, resubmission to your supplemental new drug application for Xopenex (levalbuterol HCl) Inhalation Solution, 1.25 mg/0.5 mL.

We consider this a complete response to our August 1, 2002, action letter. Therefore, the user fee goal date is July 18, 2003.

If you have any questions, call Dr. Craig Ostroff, Regulatory Management Officer, at 301-827-5585.

Sincerely,

{See appended electronic signature page}

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Craig Ostroff
4/1/03 03:46:49 PM
Signed for Sandy Barnes

Your submission dated, March 17, 2003 to NDA 20837, S-010, is currently under review and we have the following request(s):

The following comments pertain to Xopenex ®(levalbuterol hydrochloride) Inhalation Solution Concentrate 1.25 mg/0.5 mL.

- Include *sterility* (USP <71>) testing at appropriate testing intervals in the post-approval stability protocol for the drug product, stored at [redacted] C/ [redacted] RH storage condition.

- As requested earlier, provide dimension specifications for the foil pouch (e.g., length, width, thickness and depth etc.) that wraps the unit dose vial.

- Add the phrase, " [redacted] on foil pouch label, just above the phrase " Dilute Before Use".

- Replace the statements, [redacted] Discard any vial if the solution is not colorless" and other similar statements in the labeling [e.g., Package insert (Line 268-270), Caution (Line 537-540), Patient's Instructions for use (Line 601-604)] with "Open the foil pouch just prior to the administration. Once the foil pouch is opened, the content of the vial should be used immediately. Discard any vial if the solution is not colorless".

- Commit to provide representative samples of Final Print Labels (Foil-pouch label, carton label etc.) and vial samples to the Agency, prior to the launch of the drug product.

If there are any questions, please contact Ms. Akilah Green, Project Manager, or the review chemist, Vibhakar Shah at 301-827-1050.

3 page(s) has been removed because it contains pre-decisional opinions, judgments, or recommendations within inter-agency or intra-agency communications, including drafts (Exemption 5) that is not disclosable.

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/s/

Craig Ostroff
7/9/02 03:44:18 PM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 6, 2002

NDA: N 20-837/SCS-10
Xopenex (levalbuterol HCl) Inhalation Solution, 1.25/0.5 mL

SPONSOR: Sepracor

TYPE OF MEETING: Teleconference Meeting; IMTS 9410

ATTENDEES:

Division of Pulmonary & Allergy Drug Products (DPADP, HFD-570), except as noted

Craig Ostroff, Pharm.D.	Project Manager
Guirag Poochikian, Ph.D.	Chemistry Team Leader
Vibhakar Shah, Ph.D.	Chemistry Reviewer

Sepracor, Inc.:

Prabu Nambiar, Ph.D.	Director, Technical Regulatory Affairs
William McVicar	Executive Program Director
Walt Pikorski	Vice President, Outsourcing and Logistics
James Wachholz	Executive Director, Regulatory Affairs
Tom Wilson	Director, Quality Control

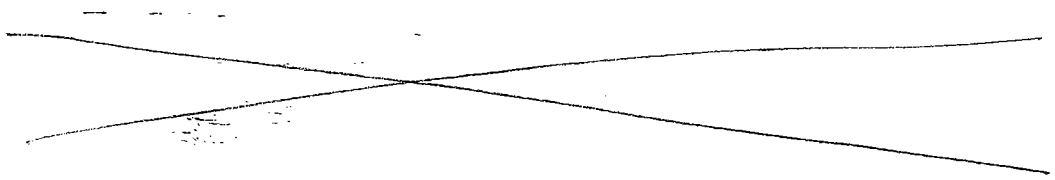
BACKGROUND

Sepracor (applicant) submitted NDA 20-837/SCS-010 for Xopenex Inhalation Solution concentrate on March 29, 2002. An Approvable (AE) letter was issued for SCS-010 by the Agency on August 1, 2002. The applicant submitted a meeting request dated September 4, 2002, to discuss a revised design for the unit-dose vial.

MEETING DISCUSSION

[Comments stated by the Division are in a normal font and those of the sponsor are in *italics*]

The Division stated that it is particularly important that each unit-dose-vial (UDV) of the proposed concentrated product [that require dilution per labeling for administration] be packaged in an individual overwrap pouch. Packaging of a UDV in an individual overwrap pouch will allow for the proposed concentrated product to be readily distinguishable from currently marketed three strengths of this product (0.31 mg, 0.63 mg, 1.25 mg all in 3 mL). The individual overwrapping of a UDV provides for increased patient safety, addresses the out-of-pouch extension of shelf-life issue and would be in line with the policy and precedent that has already been set here at the Center with the approval of Nephron's albuterol concentrate (1.25mg/0.5mL) product. Consequently, for similar drug products, we need to be uniform and consistent in our review across the Center.



The applicant stated that they recognize there are clinical concerns that need to be addressed with any form of concentrated drug product and therefore an individual pouch design for a UDV could be a logical resolution to such an issue.

The Division noted that the Center has received complaints concerning patient confusion with legibility for the products packaged in LDPE containers. It is important to take appropriate precautions to ensure that adequate labeling is developed to warn the patient about the concentrated status of this product.

The applicant asked if the labeling on the vial could be adequately changed so that they could forgo the single-pouch design?

The Division responded that given the approval of Nephron's product (which is packaged into individual UDV pouches), along with the potential for confusion with legibility issues and hence the potential for mix-up of drug products packaged similarly, it is unlikely that the Center will reverse this precedent. The Center expects that similar-type products may have to be packaged in an individual UDV pouching as indicated in the draft guidance on LDPE packaging, entitled: "Guidance for Industry – Inhalation Drug Products Packaged in Semipermeable container Closure Systems."

The applicant indicated that they might have technical and financial issues in making the individual pouch process feasible. What does the Division think if they remove the long tab?

The Division responded that we would have to consider the applicant's entire proposal as a whole (label, overwrap labeling, vial, etc.) and then discuss the proposal internally within the division and across the Center before providing the applicant definitive guidance.

The applicant asked if the Division would provide on-going comments (e.g. dimensional drawings of the unit dose vials, etc.) on partial proposals until a final proposal is prepared.

Any partial submissions for Division comment, prior to submission of the applicant's entire proposal, will be reviewed as allowable resources dictate.

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/s/

Craig Ostroff
12/6/02 10:45:43 AM

DIVISION DIRECTOR'S MEMORANDUM

Date: July 31, 2002

To: NDA 20-837/SCS-010, SCS-10 (BM) (BL)

From: Badrul A. Chowdhury, MD, PhD
Acting Director, Division of Pulmonary and Allergy Drug Products

Product: Xopenex (levalbuterol) Inhalation Solution Concentrate, 1.25 mg/0.5 mL

Applicant: Sepracor, Inc., Marlborough, Massachusetts

Introduction

Sepracor submitted a prior approval supplement to NDA 20-837 for a more concentrated formulation of Xopenex Inhalation Solution containing 1.25 mg in 0.5 ml compared to the approved product of 1.25 mg in 3 ml. There are CMC issues and clinical implications surrounding this application, which is briefly summarized below.

Chemistry and Manufacturing

Xopenex is currently approved for marketing in three dosage strengths, 1.25 mg in 3 mL, 0.63 mg in 3 mL, and 0.31 mg in 3 mL. All are packaged in sealed low-density polyethylene unit dose vials and secondarily overwrapped in sealed foil pouches that are _____ They are all ready-for-use unit dose vials. The applicant is proposing to market a new dosage form of Xopenex, which is a concentrated formulation containing 1.25 mg of levalbuterol in 0.5 ml. This will require dilution with 2.5 ml of normal saline prior to administration to patients. There are CMC issues with expiration dating, out-of-pouch storage period, and packaging configuration, for which the application is recommended an Approvable action. These are detailed in Dr. Shah's review dated July 26, 2002.

Clinical and Regulatory

The proposed new dosage form of Xopenex does not appear to provide any advantage from a clinical perspective over the already approved dosage form. Rather the new dosage form may create potential problems with the required added step of dilution with normal saline in the nebulizer chamber, and the potential confusion in the marketplace with the availability of two dosage forms of the same medication. Dr. Nicklas discusses these concerns in his review of the application dated July 8, 2002. These issues were also discussed in internal meetings and communicated with the applicant. The applicant provided some rationale supporting the new dosage form in their response dated June 10, 2002. The rationale appears to be primarily business and economic in nature.

Sepracor also refers to the approval of ANDA 75-664, a generic racemic albuterol concentrate by Nephron. The Office of Generic drug has allowed Nephron to market generic racemic albuterol concentrate in 0.5 ml single dose LDPE vial. Sepracor's approach is similar to Nephron's approach, and Sepracor rightfully argues that they should be allowed to compete in the albuterol concentrate marketplace, which is primarily in the hospital inpatient or physician's office setting. This issue was discussed with the Office of Generic Drugs and with the Office of Drug Evaluation II. Although, I do not see Sepracor's application to market a levalbuterol concentrate an improvement over the current dosage form, however, from a regulatory standpoint there is no mechanism to prevent Sepracor from marketing this new concentrate dosage form, particularly because there is a similar dosage form, Nephron's racemic albuterol single dose concentrate, that is already approved for marketing. Therefore, once the CMC issues are resolved, this application should be approved.

APPEARS THIS WAY
ON ORIGINAL

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/s/

Badrul Chowdhury
7/31/02 04:05:37 PM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 15, 2003

To: Prabu Nambiar, Ph.D.	**From:** Vibhakar Shah, Ph.D.
Company: Sepracor Inc.	Division of Pulmonary and Allergy Drug Products
Fax number: (508) 357-7491	**Fax number:** 301-827-1271
Phone number:	**Phone number:** 301-827-1050
Subject: NDA 20837/SCS-010 (AC) dated March 17, 2003	
Total no. of pages including cover:	2

Comments:

Document to be mailed: YES ☒ NO

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