DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR 26 1999

TRANSMITTED VIA FACSIMILE

Mr. James Allen Wachholz
Senior Director, Regulatory Affairs
Sepracor Inc.
111 Locke Drive
Marlborough, MA 01752

RE: NDA# 20-837
Xopenex (levalbuterol HCl) Inhalation Solution
MACMIS ID# 7771

Dear Mr. Wachholz:

As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a press release issued by Sepracor Inc. (Sepracor) on March 26, 1999, through PRNewswire, for its newly approved prescription drug product, Xopenex (levalbuterol HCl) Inhalation Solution. We have determined that the press release makes unsubstantiated and misleading promotional claims that are inconsistent with the approved product labeling, overstate the safety and efficacy of Xopenex, or otherwise lack fair balance. Therefore, the press release violates the Federal Food, Drug, and Cosmetic Act and its implementing regulations.

Misleading Tone of Press Release Suggests Superior Safety

The overall tone of the press release misleadingly suggests that Xopenex (at either dosage strength of 0.63 mg or 1.25 mg) is a significantly safer albuterol inhalation product over standard racemic drugs that contain a 50:50 mixture of mirror-image isomers, because of its single-isomer molecular structure. However, these statements or suggestions are not adequately substantiated or fairly balanced with important contextual information. In addition, given the reference to approval of the two dosage strengths, and the need for some patients to use the higher Xopenex dosage (1.25 mg for those patients with more severe asthma or who do not respond to the 0.63 mg dosage strength), the safety and efficacy profile of the two Xopenex dosage strengths are not adequately distinguished among the various promotional claims.

Paragraph 1:

- Incomplete Indication Statement: "Xopenex…for the treatment and prevention of bronchospasm."

The indication statement is misleading because it is incomplete by not limiting the patient population (i.e., in adults and adolescents 12 years and older, with reversible obstructive airway disease, such as asthma). In addition, this introductory discussion lacks important context to explain that bronchodilator therapy is a rescue asthma therapy for bronchospasm.

- "In Sepracor's clinical trials, Xopenex demonstrated excellent safety and efficacy and a duration of action that lasted up to 8 hours."

The claim "excellent safety and efficacy" is misleading because it minimizes the seriousness of the cardiovascular-related side effects and it lacks fair balance to identify these side effects in a reasonably prominent and comparable manner to these benefit claims. Furthermore, although the first sentence refers to approval of two dosage strengths of Xopenex, there is no fair balance distinguishing the greater adverse events profile associated with the higher dosage of Xopenex 1.25 mg, that is intended for patients with more severe asthma or who do not respond to the usual starting dose of 0.63 mg. Additional objections to the fair balance statement are discussed under "Paragraph 11."

The claim "a duration of action that lasted up to 8 hours" is misleading because this finding was only demonstrated in "some patients." Furthermore, the claim lacks context to identify that there is a range for expected duration of efficacy (i.e., the mean duration of effect was approximately 5 hours for 0.63 mg Xopenex and approximately 6 hours for 1.25 mg Xopenex). As a rescue medication, a misleading duration of action claim presents safety concerns.

Paragraph 2:
"…removal of the unnecessary (S)-isomer results in a purer and more potent drug."
"…the (S)-isomer when exposed to the patient in racemic form has been shown to interfere with the overall efficacy of the (R) isomer."

First, the "purer drug" characterization is clinically irrelevant and thus misleading. The removal of the (S)-isomer that leaves only the (R)-isomer in the active molecule does not make this enantiomer any more "pure" than racemic albuterol, because "purer" is viewed in terms product impurities. There is no (S)-isomer because it is not part of the active chemical.

Second, regarding the characterization of Xopenex, the (R)- isomer albuterol, as "a more potent drug" compared to the standard racemic form of albuterol sulfate is misleading. Even the higher dosage of 1.25 mg Xopenex was not demonstrated to be statistically more effective than the

standard dose of racemic albuterol sulfate (2.5 mg). Although Xopenex 1.25 mg demonstrated the largest mean percent change from baseline in FEV1 compared to the other active treatments, this was not statistically significant. Furthermore, the usual starting dose of Xopenex 0.63 mg was only demonstrated to be clinically comparable to 2.5 mg racemic albuterol sulfate. Therefore, to characterize Xopenex, the (R)-isomer of albuterol sulfate, as a "more potent drug" is unsubstantiated and misleading. The second quoted statement "the (S)-isomer....has been shown to interfere with the overall efficacy of the (R) isomer" is misleading because it has not been demonstrated.

Paragraph 12: Racemic Drugs
"...In racemic albuterol, the (R)-isomer is exclusively responsible for the therapeutic effect and perfectly matches the human body's receptor. The (S)-isomer has been found to have no therapeutic benefit and poorly matches the body's receptor....Xopenex is the optically pure (R)-isomer version of racemic albuterol."

The above paragraph is misleading because it contains overly broad characterizations of the benefits of Xopenex as the (R)-isomer version of racemic albuterol, and of the deficiencies of the (S)-isomer within racemic albuterol in terms of overall efficacy. For the reasons discussed above, the "optically pure" characterization is misleading.

Paragraph 3:
"Patients treated with 0.63 mg of Xopenex demonstrated lung-function responses comparable to those treated with the standard clinical dose (2.5 mg) of racemic albuterol..."
"Generally, patients on 0.63 mg of Xopenex reported a lower incidence and severity of beta-mediated side effects, such as nervousness and tremor, compared with those taking 2.5 mg of racemic albuterol..."
"On both day 1 and 29, 1.25 mg of Xopenex demonstrated the largest mean percent change from baseline in FEV1 compared to the other active treatments."

The efficacy claim is misleading because "an overall improvement in lung function" is overly broad, given the single efficacy measurement tested (mean percent change from baseline in FEV1) and lacks context (i.e., "clinically comparable").

The safety superiority claim for Xopenex 0.63 mg is misleading and inconsistent with the approved product labeling that reported the incidence of these beta-mediated side effects to only be slightly less compared to the other active treatment groups. The clinical significance of these small differences is unknown.

The efficacy superiority claim for Xopenex 1.25 is misleading because the finding was not statistically significant and lacks fair balance by omitting that a slightly greater number of serious side effects, discontinuations due to side effects, and clinically significant

electrocardiogram (ECG) changes were reported in patients who received Xopenex 1.25 compared to the other active treatment groups.

Paragraph 6: "Levalbuterol is the first real advance in rescue asthma therapy in over 20 years."

This statement is false or misleading because it overstates the safety and efficacy of the product. According to the approved product labeling, the lower dosage strength of 0.63 mg for Xopenex was shown to be only clinically comparable to the approved dosage strength of racemic albuterol sulfate (2.5 mg), with only slightly less incidence of certain systemic beta-adrenergic side effects (e.g., tremor, nervousness), and only slightly less change in heart rate and plasma glucose. The clinical significance of these small differences is unknown and the remaining beta-adrenergic effects, including plasma potassium are not statistically significant from the other active treatments.

Paragraph 8: "For people with asthma, particularly with children…" "With Xopenex now available, some patients will no longer have to tolerate unwanted side effects such as shakiness and jitteriness, which can interfere with concentration and regular daily activities."

This paragraph is misleading because while it refers to children and families, it does not limit the discussion about Xopenex to patients who are adolescents aged 12 years and older. Furthermore, the safety claim is misleading because it is inconsistent with the approved product labeling, it is an overstatement of safety because these beta-adrenergic side effects are not eliminated by Xopenex (0.63 mg: nervousness 2.8%; 1.25 mg: nervousness 9.6%, tremor 6.8%), and it minimizes the risk associated with use of this product.

Paragraph 9: "Bronchodilators…immediate onset of action"

The "immediate" onset claim is misleading and lacks context because the mean time to onset of a 15% increase in FEV1 over baseline for Xopenex at 0.63 mg is 17 minutes and for Xopenex 1.25 mg it is 10 minutes. The mean time to peak effect for both doses was approximately 1.5 hours after 4 weeks of treatment.

Paragraph 11: "Side effects from Xopenex, like other beta-agonists, may include dizziness, nervousness, tremor, and dyspepsia. Patients with cardiovascular and convulsive disorders should use caution when administering the drug."

The clause "like other beta-agonists" minimizes the seriousness of the subsequent side effects information. In addition, the disclosure does not distinguish between the side effect profiles between the two dosage strengths of Xopenex. The risk statement about which types of patients who should use caution when taking Xopenex due to its cardiovascular-related effects lacks fair balance and should include all of the following conditions identified in the approved product

labeling (i.e., heart, blood, or seizure disorders, high blood pressure, diabetes, or an overactive thyroid).

Paragraph 13: "Xopenex is an example of an improvement in the performance of a marketed racemic drug through conversion to its single-isomer form"

Based on the objections to the claims cited in paragraph 3, the above claim is a misleading overstatement of safety and efficacy.

We request that the distribution and use of any materials containing these and similar violative claims cease immediately, including but not limited to, the removal of this press release from the PRNewswire website.

Sepracor should respond in writing no later than April 9, 1999, to the undersigned at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm 17-B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind Sepracor that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID # 7771 in addition to the NDA number.

Sincerely,

/S/

Joan Hankin, JD
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications