DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

MAY 21 1999

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# 7961

Dear Mr. Wachholz:

As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed various health professional promotional launch materials disseminated by Sepracor Inc. (Sepracor) (i.e., journal ad/7SEP7059, reminder journal ad/7SEP114, sales aid/7SEP7058, and dear doctor letter) for Xopenex 0.63 mg (levalbuterol HCl) Inhalation Solution, the (R)-enantiomer (isomer) of racemic albuterol (that contains a 50:50 mixture of the (R,S) mirror-image isomers).

We have determined that these materials make 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, these promotional materials violate the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Many of the same issues objected to below were the subject of a March 26, 1999 untitled DDMAC letter to Sepracor on its initial promotion of Xopenex.

False or Misleading Tagline "The *Right B*-Agonist" Suggests Clinical Superiority

The overall tone of these materials, as reflected by the above tagline, suggests or implies that Xopenex is superior in safety and efficacy to racemic albuterol containing a 50:50 mixture of the mirror-image isomers, because of Xopenex's single-isomer molecular structure. However, as previously objected to on March 26, 1999, this type of overall message of product superiority overstates the safety and efficacy of Xopenex and is inconsistent with the approved product labeling. Xopenex 0.63 mg was only demonstrated to be clinically comparable to 2.5 mg racemic albuterol sulfate, 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. Therefore, these implied superiority claims are false or misleading because they are not supported by substantial evidence.

Furthermore, the tagline is misleading because contextual information describing a limitation of efficacy about the 0.63 mg dose of Xopenex is omitted (i.e., for patients who do not respond to the 0.63 mg usual starting dose, the 1.25 mg dose is available with close monitoring recommended for adverse systemic effects).

Misleadingly Broad Characterizations of Xopenex Benefit and (S)-Isomer Deficiencies

- "We Wiped Out The (S)-Isomer. Your Patients Don't Need It"
- "Discover Xopenex—and Deliver the B-Agonist Your Patients Need"
- "Racemic (R,S) Albuterol is a 50:50 mixture of mirror-image isomers; only one provides the clinical benefit"
- "Benefits of (R)-Isomer (right isomer)...Provides the therapeutic bronchodilatory effect"
- "Xopenex contains only the therapeutically effective right (R)-isomer"
- "Xopenex allows you to prescribe less medicine and achieve excellent results, making it the *right* B-agonist in the treatment or prevention of bronchospasm"
- "The world's first pure, single-isomer B-agonist"

As previously objected to on March 26, 1999, these types of claims are misleading because they are 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. Such claims are inconsistent with preclinical data in the approved product labeling which only "suggest that most of the bronchodilatory effect of racemic albuterol is due to the (R)-enantiomer" and from clinical data in the approved product labeling that demonstrate only clinical comparability rather than equivalence between Xopenex and racemic albuterol Therefore, the above claims misleadingly overstate the overall efficacy of Xopenex.

Moreover, the "world's first pure single-isomer B-agonist" characterization is clinically irrelevant and thus misleading. There is no (S)-isomer because it is not part of the active chemical. 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 "purity" is viewed in terms product impurities.

Unsubstantiated Equivalence is an Overstatement of Efficacy, Implied General Superiority

- "Discover Xopenex—Equally Effective At ¼ Of The Dose of Racemic Albuterol"

The above claim overstates the product's efficacy and is a misleading implied safety and efficacy superiority claim because the 0.63 mg usual starting dose of Xopenex was only demonstrated to be clinically comparable to racemic albuterol 2.5 mg, according to the approved product labeling.

Furthermore, the "1/4 dose" comparison to racemic albuterol lacks context and is misleading because some patients do not respond adequately to the Xopenex 0.63 mg starting dose and may benefit from the 1.25 mg dose of Xopenex. However, the approved product labeling recommends that patients receiving the higher dose should be monitored closely for adverse systemic effects (and the risks of such effects should be balanced against the potential for improved efficacy). Therefore, the above claim is misleading because it omits this important limitation on efficacy and safety.

Lack of Fair Balance

All of the promotional pieces lack adequate fair balance in content and presentation. All of these materials omit the following important balancing risk information pertinent to this beta-agonist: the warning that Xopenex can produce paradoxical bronchospasm that may be life-threatening; a general statement referring the health professional to the approved product labeling for information regarding drug interactions between Xopenex and various classes of drugs (beta-blockers, monoamine oxidase inhibitors, or tricyclic antidepressants); and a statement referring the health professional to the approved product labeling that due to its cardiovascular-effects, Xopenex should be used with caution in certain types of patients. Furthermore, the adverse events disclosure lacks context because it does not identify the specific percent incidences for the listed adverse events and this information, where it is disclosed, is not presented with a prominence and readability reasonably comparable to the benefit claims.

Sepracor should immediately cease its distribution and use of all promotional Xopenex materials that contain these or similar violative claims. Your written response should be received no later than June 4, 1999, and should list all similarly violative materials and description of your method of discontinuation.

Your response should be directed 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# 7961 in addition to the NDA number.

Sincerely,

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