DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

J. Martin Carroll
President and Chief Operating Officer
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

RE: NDA #19-085
Atrovent® (ipratropium bromide) Inhalation Aerosol
NDA #20-291
Combivent® (ipratropium bromide and albuterol sulfate) Inhalation Aerosol
MACMIS # 11245

WARNING LETTER

Dear Mr. Carroll,

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a consumer-directed promotional labeling piece (CB-8740-3) for Atrovent® (ipratropium bromide) Inhalation Aerosol and Combivent® (ipratropium bromide and albuterol sulfate) Inhalation Aerosol in the Winter 2003, volume 7, number 3 version of Breathe Well (a house organ disseminated to consumers by Boehringer Ingelheim Pharmaceuticals, Inc.) submitted by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) under cover of Form FDA 2253. This labeling piece is false or misleading because it makes unsubstantiated effectiveness claims for, and omits material facts about, Atrovent and Combivent, in violation of section 502(a) of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(a). See 21 U.S.C. 321(n).

Background

The Indications and Usage sections of the approved product labeling (PI) for Atrovent and Combivent state:

> Atrovent (ipratropium bromide) Inhalation Aerosol is indicated as a bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema.
>
> Combivent Inhalation Aerosol is indicated for use in patients with chronic obstructive pulmonary disease (COPD) on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator.

Atrovent is associated with the following risks, as described in the Contraindications, Warnings, and Precautions sections of the PI (in pertinent part):

> **Contraindications.** Atrovent is contraindicated in patients with a history of hypersensitivity to soya lecithin or related food products such as soybean and peanut.
>
> **Warnings.** Atrovent is not indicated for the initial treatment of acute episodes of bronchospasm where rapid response is required.
>
> **Warnings. Immediate Hypersensitivity Reactions.** Immediate hypersensitivity reactions may occur after administration of ipratropium bromide or albuterol sulfate, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.
>
> **Precautions. General. Effects Seen with Anticholinergic Drugs.** Atrovent should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction.

Combivent is associated with the following risks, as described in the Contraindications, Warnings, and Precautions sections of the PI (in pertinent part):

> **Contraindications.** Combivent is contraindicated in patients with a history of hypersensitivity to soya lecithin or related food products such as soybean and peanut.
>
> **Warnings. Paradoxical Bronchospasm.** Combivent can produce paradoxical bronchospasm that can be life threatening. If it occurs, the preparation 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.
>
> **Warnings. Cardiovascular Effect.** The albuterol sulfate contained in Combivent, like 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 Combivent Inhalation Aerosol at recommended doses, if they occur, discontinuation of the drug may be indicated. In addition, beta-adrenergic agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. Therefore, Combivent should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias and hypertension.
>
> **Precautions. General. Effects Seen with Anticholinergic Drugs.** Combivent contains ipratropium bromide and, therefore, should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy or bladder-neck obstruction.
>
> **Precautions. General. Effects Seen with Sympathomimetic Drugs.** Preparations containing sympathomimetic amines such as albuterol sulfate should be used with caution in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus and in patients who are unusually responsive to sympathomimetic amines. Beta-adrenergic agents may also

produce significant hypokalemia in some patients (possibly through intracellular shunting) which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Unsubstantiated Effectiveness Claims

The labeling piece presents the prominent claims, "Anticholinergics. Essential for COPD" and "The COPD Essentials." These claims suggest that anticholinergics are essential for the treatment of COPD, and that COPD is not appropriately treated without an anticholinergic. This is false or misleading, because COPD can be treated without using anticholinergics.

In addition, the labeling piece fails to present material facts concerning limitations on the safety and effectiveness of Atrovent and Combivent in COPD therapy. Specifically, it fails to disclose that Atrovent is indicated as a bronchodilator only for maintenance treatment of bronchospasm in patients with COPD, and that Combivent is only indicated for use in patients with COPD who are on a regular bronchodilator and who continue to have evidence of bronchospasm and require a second bronchodilator. The asterisked statement, "Maintenance therapy," which is presented in small type at the bottom left-hand side of the page, does not remedy this misleading presentation because the content of this claim fails to communicate that Atrovent and Combivent have been found safe and effective to treat only one specific aspect of the COPD disease process (i.e., symptoms of bronchospasm), and fails to include the indication and limitations of Atrovent and Combivent. In addition, the disclaimer lacks sufficient prominence to adequately qualify the claims described above.

Omission of Risk Information

The labeling piece presents effectiveness claims for Atrovent and Combivent, refers the reader to www.thebreathingspace.com for more information, and contains the statement, "Please see Brief Summaries of Prescribing Information on accompanying pages." It provides no information about the risks described above. For the piece to be truthful and non-misleading, it must contain risk information in each part as necessary to qualify any safety or effectiveness claims made in that part. Because the piece makes effectiveness claims but contains no risk information, it is false or misleading under sections 352(a) and 201(n) of the Act, 21 U.S.C. 352(a), 321(n). Cf. 21 C.F.R. 202.1(e)(3)(i).

Conclusions and Requested Actions

Your labeling piece makes unsubstantiated effectiveness claims for, and omits material facts about, Atrovent and Combivent, and, therefore, misbrands these drugs under 21 U.S.C. 352(a) and 321(n).

DDMAC requests that BIPI immediately cease the dissemination of violative promotional materials for Atrovent and Combivent such as those described above. Please submit a written response to this letter on or before October 7, 2004, stating whether you intend to comply with this request, listing all violative promotional materials for Atrovent and Combivent such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a plan of action to disseminate truthful, non-misleading, and complete information to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer

to MACMIS # 11245 in addition to the NDA numbers. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Atrovent and Combivent comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, RPh, MBA
Director
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Thomas Abrams
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