DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

George W. Buckley
Chairman, President and Chief Executive Officer
3M Corporate Headquarters
3M Center
St. Paul, MN 55144-1000

Re: NDA 20-014
Maxair™ Autohaler™ (pirbuterol acetate inhalation aerosol)
MACMIS ID # 14551

WARNING LETTER

Dear Mr. Buckley:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a flashcard (AH-7090) for Maxair™ Autohaler™ (pirbuterol acetate inhalation aerosol) (Maxair Autohaler) submitted by 3M Pharmaceuticals (3M) under cover of Form FDA 2253. The flashcard is false or misleading in that it presents efficacy claims for Maxair Autohaler, but fails to communicate any risks associated with its use and fails to present the approved indication. In addition, the flashcard makes unsubstantiated claims. Thus, the flashcard misbrands the drug in violation of Sections 502(a) and 201(n) of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a) and 321(n); cf 21 C.F.R. §202.1(e)(3)(i). Your flashcard raises public health and safety concerns through its complete omission of risk information for Maxair Autohaler by suggesting the drug is safer than has been demonstrated.

Background

According to the FDA-approved product labeling (PI), Maxair Autohaler "is indicated for the prevention and reversal of bronchospasm in patients 12 years of age and older with reversible bronchospasm including asthma. It may be used with or without concurrent theophylline and/or corticosteroid therapy."

The PI also states that Maxair Autohaler is associated with numerous important risks, including the following (in pertinent part):

WARNINGS

Cardiovascular

MAXAIR AUTOHALER, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Paradoxical Bronchospasm

MAXAIR AUTOHALER can produce paradoxical bronchospasm, which can be life threatening….It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister or vial.

PRECAUTIONS

General

Since pirbuterol is a sympathomimetic amine, it should be used with caution in patients with cardiovascular disorders, including ischemic heart disease, hypertension, or cardiac arrhythmias, in patients with hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines or who have convulsive disorders.

Drug Interactions

Other short-acting beta adrenergic aerosol bronchodilators should not be used concomitantly with MAXAIR AUTOHALER because they may have additive effects.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: Pirbuterol 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 pirbuterol on the vascular system may be potentiated.

Beta Blockers: Beta adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as MAXAIR AUTOHALER, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta blockers. However, under certain circumstances, e.g., as 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.

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.

ADVERSE REACTIONS

CNS: nervousness (6.9%), tremor (6.0%), headache (2.0%), dizziness (1.2%).
Cardiovascular: palpitations (1.7%), tachycardia (1.2%).
Respiratory: cough (1.2%).
Gastrointestinal: nausea (1.7%).

Omission of Material Facts

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The flashcard is misleading because it presents claims for Maxair Autohaler but fails to present any risk information or the approved indication.

The flashcard includes the following claims:

- "**Maxair™ Autohaler™ helps your patients breathe easier**"
- "Breath-actuated inspiratory flow rate of 30 LPM delivers particles to the lung.[1]"
- "Deposition of the particles to the lung is increased threefold using Autohaler delivery system.[2]"
- "**The inhaler that's easier to use and use correctly**[1,3,4]"
- "Easier to teach…Easier to use…400 doses"
- Presentation of the Maxair Autohaler device adjacent to an image of drug lung deposition with the disclaimer, "The clinical significance of lung deposition data is unknown"

(original emphasis).

However, the flashcard entirely omits risk information for Maxair Autohaler, including the most serious and frequently occurring risks associated with the drug. In addition, the flashcard fails to present the approved indication for Maxair Autohaler. The statement, "Please see full prescribing information" in small type at the lower left-hand corner on the back side of the flashcard does not mitigate these misleading presentations (cf. 21 C.F.R. §202.1(e)(3)(i)).

Unsubstantiated Superiority Claims

The front side of the flashcard claims that "**Maxair™ Autohaler™ helps . . .patients breathe easier**." As support for this claim, the flashcard states that Maxair Autohaler's "Breath-actuated inspiratory flow rate of 30 LPM delivers particles to the lung[1]" and that the "Deposition of the particles to the lung is increased threefold using Autohaler delivery system.[2]" The back side of the flashcard contains a picture of the Maxair Autohaler device overlapping with an image of lung deposition of radio-labeled drug. The image consists of two sets of lungs, one showing little drug coverage and the other with almost total drug coverage, with the disclaimer, "The clinical significance of lung deposition data is unknown."

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[1] Grossman J, Tinkelman DG, Ziment I. Pirbuterol acetate administered via breath-actuated inhaler compared with albuterol administered via MDI with a spacing device. www.Medscape.com. 1997; Article ID No. M R C3019.0.
[2] Newman SP, Weisz AW, Talaee N, et al. Improvement of drug delivery with a breath-actuated pressurized aerosol for patients with poor inhaler technique. *Thorax*. 1991;46(10):712-716.
[3] Larsen JS, Hahn M, Kochevar JW, et al. Administration errors with a conventional metered-dose inhaler versus a novel breath-actuated device. *Annals Allergy*. 1993;71(2):103-106.
[4] Kelloway JS, Wyatt R. A cost-effectiveness analysis of breath-actuated metered-dose inhalers. *Manage Care Interface*. 1997;10(9):99-107.

The claim that "Maxair™ Autohaler™ helps . . . patients breathe easier" is misleading. The totality of the presentation on the front and back sides of the flashcard implies that, by increasing drug lung deposition, Maxair Autohaler helps patients breathe easier compared to other drugs. This superiority claim has not been demonstrated by substantial evidence or substantial clinical experience. In fact, one of the references cited[1] to support these claims demonstrated similar efficacy between Maxair Autohaler and albuterol administered via metered-dose inhaler (MDI) with no clinical differences in asthma control. The other reference cited[2] did not specifically evaluate Maxair Autohaler. In general, drug deposition studies have not been shown to characterize drug delivery to the site of action well enough to imply clinical efficacy or safety. The disclaimer, "The clinical significance of lung deposition data is unknown" does not mitigate these misleading presentations.

The front side of the flashcard also contains the claims, "**The inhaler that's easier to use and use correctly[1,3,4]**…Easier to teach…Easier to use…" These claims are misleading because they state that Maxair Autohaler is easier to use, easier to use correctly, and easier to teach compared to all other types of inhalers, when this has not been demonstrated. None of the cited references were adequately designed to assess the proposed claims (e.g., none specified "ease of use" as the primary endpoint). In addition, the last reference cited[4] was not specifically designed to evaluate the proposed claims because the primary endpoint was "drug use as measured by canister weights" with the objective of "assessing direct and indirect costs."

FDA is not aware of any evidence to support these claims. If you have data to support them, please submit the data to FDA for review.

Conclusion and Requested Action

For the reasons discussed above, the flashcard misbrands Maxair Autohaler in violation of the Act. 21 U.S.C. §§ 352(a) and 321(n); cf. 21 C.F.R §202.1(e)(3)(i).

DDMAC requests that 3M immediately cease the dissemination of violative promotional materials for Maxair Autohaler such as those described above. Please submit a written response to this letter on or before November 2, 2006, stating whether you intend to comply with this request, listing all violative promotional materials for Maxair Autohaler 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 comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional material. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301-796-9877. In all future correspondence regarding this matter, please refer to MACMIS ID # 14551 in addition to the NDA number. 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 Maxair Autohaler 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 Abrams, RPh, MBA
Division 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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