DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

September 21, 2006

John H. Klein
Chairman and Chief Executive Officer
DAVA Pharmaceuticals, Inc.
Parker Plaza
400 Kelby Street, 10th Floor
Fort Lee, NJ 07024

Re: ANDA # 76-130
VoSpire ER® (albuterol sulfate) Extended-Release Tablets
MACMIS ID # 14549

WARNING LETTER

Dear Mr. Klein:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a sample request letter (110) for VoSpire ER® (albuterol sulfate) Extended-Release Tablets (VoSpire ER) submitted by DAVA Pharmaceuticals, Inc. (DAVA) under cover of Form FDA 2253. The sample request letter is false or misleading in that it presents claims for VoSpire ER but fails to communicate any risks associated with its use, and presents unsubstantiated effectiveness claims. Thus, the sample request letter 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) & 321(n). Your sample request letter raises significant public health and safety concerns through its complete omission of risk information by suggesting that VoSpire ER is safer than has been demonstrated.

Background

According to the FDA-approved product labeling (PI), VoSpire ER is "indicated for the relief of bronchospasm in adults and children 6 years of age and older with reversible obstructive airway disease."

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

> **WARNINGS**
> **Cardiovascular Effects**
> ...albuterol extended-release tablets, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Paradoxical Bronchospasm
Albuterol extended-release tablets can produce paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs, albuterol extended-release tablets should be discontinued immediately and alternative therapy instituted.

PRECAUTIONS
General
Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines.

Drug Interactions
The concomitant use of albuterol extended-release tablets and other oral sympathomimetic agents is not recommended since such combined use may lead to deleterious cardiovascular effects....

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: Albuterol 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 albuterol 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 albuterol extended-release tablets, 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, cardio-selective 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.

Digoxin: Mean decreases of 16% to 22% in serum digoxin levels were demonstrated after single dose intravenous and oral administration of 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 albuterol 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 albuterol.

ADVERSE REACTIONS
The most frequent adverse reactions to albuterol are nervousness [8.5%],tremor [24.2%], headache [18.8%], tachycardia [2.7%], and palpitations [2.4%].

Omission of Material Facts

Promotional materials are misleading if they fail to reveal material facts with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The sample request letter contains claims related both to the drug itself and to its use for the treatment of asthma, but fails to present any risk information.

For example, the sample request letter states:

- "VoSpire ER® tablets are specially formulated to maintain plasma levels in patients with reversible obstructive airway disease by utilizing a controlled release of albuterol sulfate."
- "...we would like to provide you the opportunity to order **samples and information** about this long-acting bronchodilator, indicated for the relief of bronchospasm in adults and children 6 years of age and older."
- "Twice-daily dosing in an easy-to-swallow tablet"
- "One tablet provides up to 12 hours of bronchospasm control"
- "Compliance is enhanced by convenient twice daily oral administration"

(original emphasis).

While the sample request letter contains claims for VoSpire ER, it entirely omits risk information, including the most serious and frequently occurring risks associated with the drug.

Overstatement of Efficacy

As discussed above, the sample request letter includes the claim, "Compliance is enhanced by convenient twice daily oral administration." While twice daily dosing may be more convenient than products taken 4-6 times a day, this claim is misleading because it implies that characteristics of VoSpire ER and its dosage and administration cause patients to improve their compliance with treatment. FDA is not aware of any evidence supporting enhanced compliance rates with patients on VoSpire ER therapy in comparison to any other treatment. In fact, no references were cited to support this claim.

Conclusion and Requested Action

For the reasons discussed above, the sample request letter misbrands VoSpire ER in violation of the Act. 21 U.S.C. §§352(a) & 321(n).

DDMAC requests that DAVA immediately cease the dissemination of violative promotional materials for VoSpire ER such as those described above. Please submit a written response to this letter on or before October 5, 2006, stating whether you intend to comply with this request, listing all violative promotional materials for VoSpire ER 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 materials. 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 # 14549 in addition to the ANDA 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 VoSpire ER 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,

Thomas Abrams

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