DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation
and Research
1401 Rockville Pike
Rockville MD 20852-1448

94735d

CBER-04-008

May 25, 2004

BY FACSIMILE AND CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER

Jan Robertson, Manager
Global Regulatory Affairs
Baxter Healthcare Corporation
One Baxter Way
Westlake Village, CA 91362

Re: BLA STN #125063
ADVATE [Antihemophilic Factor (Recombinant) Plasma/Albumin Free Method (rAHF-PFM)]

Dear Ms. Robertson:

The Advertising and Promotional Labeling Branch (APLB) in the Food and Drug Administration's Center for Biologics Evaluation and Research (CBER) has reviewed a sell sheet (#HYL986) and patient brochures (#HYL1009, and #HYL956) for ADVATE [Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method] submitted by Baxter Healthcare Corporation (Baxter) under cover of Form FDA 2253. The sell sheet and brochures are false or misleading under sections 502(a) and 201(n) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 352(a), 321(n)) because they fail to reveal material facts and contain unsubstantiated claims with respect to other antihemophilic factors. The sell sheet and brochures could encourage use of Advate in conditions other than those for which FDA has found the product safe and effective.

Background

According to the FDA-approved professional labeling (PI), Advate is a purified glycoprotein that is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line. Advate is indicated in hemophilia A (classical hemophilia) for the prevention and control of bleeding episodes and in the perioperative management of patients with hemophilia A. Advate is not indicated for the treatment of von Willebrand's disease.

Contraindications for Advate include known hypersensitivity to mouse or hamster proteins. In addition, the PI states that side effects that have been reported with the infusion of Advate include a strange taste in the mouth, itching, dizziness, headache, catheter-related infection, cold shivers, hot flashes, diarrhea, sweating, nausea, pain in the upper abdomen, chest pain, prolonged bleeding after postoperative drain removal, decreased hematocrit,

swelling of limbs, swelling of joints, shortness of breath, fever, decreased factor VIII levels and postoperative unspecified blood clot at the site of surgery.

Failure to Reveal Material Facts

The sell sheet and one of the patient brochures (#HYL1009) contain the text, "Good to excellent efficacy in 86% of bleeds," without providing risk information. Providing the PI with these promotional materials, by itself, fails to include sufficient qualifying information about such risks.

Additionally, in a question and answer section, the text reads: "Does [Advate] have any side effects? So far in clinical studies, patients had no serious adverse events related to ADVATE rAHF-PFM. Also, there were no reported cases of allergic-type hypersensitivity in patients who were receiving therapy with ADVATE rAHF-PFM." While these statements may be true, the omission of non-serious adverse events contained in the PI minimizes the risks of this drug.

Unsubstantiated Claims

One of the patient brochures (#HYL956) states that the product offers "unsurpassed pathogen safety in hemophilia A therapy." We are concerned that this claim could be interpreted to mean that no other hemophilia A therapy offers better pathogen safety than Advate. To the extent that you may have data suggesting otherwise, we invite you to submit it. FDA is unaware of any comparative data supporting the claim that no other hemophilia A therapy offers better pathogen safety than Advate.

One of the patient brochures (#HYL1009) contains the text, "It's a major advance on a major advance," and this brochure and the sell sheet contain the header "Breakthrough treatment for Hemophilia A." These statements suggest that Advate is safer or more effective than other treatments for hemophilia A. FDA is unaware of substantial evidence or substantial clinical experience supporting this claim. In addition, there are other approved non-plasma derived products that are manufactured without proteins from human or animal sources and albumin.

Conclusions and Requested Actions

The sell sheet and patient brochures misbrand Advate within the meaning of sections 502(a) and 201(n) of the Act (21 U.S.C. 352(a), 321(n)) because they fail to reveal material facts and contain unsubstantiated claims and are, therefore, false or misleading.

We request that Baxter immediately cease the dissemination of violative promotional materials for Advate such as those described above. Please submit a written response to this letter within ten (10) business days of the date of this letter stating whether you intend to comply with this request, listing all violative promotional materials for Advate 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 audiences that received the violative promotional materials. Please

direct your response to me at the Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Compliance and Biologics Quality, HFM-600, 1401 Rockville Pike, Rockville, Maryland 20852-1448. In all future correspondence regarding this matter, please refer to the BLA/STN number and to CBER-04-008. We remind you that only written communications are considered official responses.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Advate 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,

James S. Cohen, J.D.
Acting Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Enclosures

A- Sell Sheet (#HYL986)
B- Patient Brochure (#HYL1009)
C- Patient Brochure (#HYL956)