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

October 12, 2004

CBER-05-002

VIA FACSIMILE AND CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER

Mr. Paul Hartmann
Director, Regulatory Affairs
Aventis Behring L.L.C.
1020 First Avenue
P.O. Box 61501
King of Prussia, PA 19406-0901

Re: BLA STN # 125078
Zemaira™[alpha$_1$-proteinase inhibitor (human)]

Dear Mr. Hartmann:

The Office of Compliance and Biologics Quality (OCBQ) in the Food and Drug Administration's Center for Biologics Evaluation and Research (CBER) has reviewed convention panels (IO#102-8524) for Zemaira™[alpha$_1$-proteinase inhibitor (human)] submitted by Aventis Behring L.L.C. (Aventis Behring) under cover of Form FDA 2253. The convention panels 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 omit risk information. By failing to include sufficient qualifying information on risks, you have encouraged the potentially unsafe use of Zemaira.

Background

According to the FDA-approved professional labeling (PI), Zemaira is a highly purified human alpha$_1$-proteinase inhibitor derived from human plasma. It is supplied as a lyophilized preparation for injection. The PI states:

> Zemaira™ is indicated for chronic augmentation and maintenance therapy in individuals with alpha$_1$-protienase inhibitor (A_1-PI) deficiency and clinical evidence of emphysema .... Clinical data demonstrating the long-term effects of chronic augmentation therapy of individuals with Zemaira™ are not available. Safety and effectiveness in pediatric

patients have not been established. Zemaira™ is not indicated as therapy for lung disease patients in whom severe congenital A_1-PI deficiency has not been established.

Specific examples of risk information contained in the PI include the following:

- "Zemaira™ is contraindicated in individuals with a known hypersensitivity to any of its components. Zemaira™ is also contraindicated in individuals with a history of anaphylaxis or severe systemic response to A_1-PI products. Individuals with selective IgA deficiencies who have known antibodies against IgA (anti-IgA antibodies) should not receive Zemaira™, since these patients may experience severe reactions, including anaphylaxis, to IgA that may be present in Zemaira™."
- "Because Zemaira™ is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent."
- "In clinical studies, the following treatment-related adverse reactions were reported: asthenia, injection site pain, dizziness, headache, paresthesia, and pruritus."

Failure to Reveal Material Facts

The convention panels contain headlines and text specifying this product's indication for use and infusion information but fail to provide any risk information. Among the claims made on the panels are the statements: ". . . management of A1-PI therapy . . ." and ". . . offers half or less the infusion time of other Alph-1 therapies." Although the convention panels state, "Please see full prescribing information available at this booth," the convention panels themselves fail to provide the risk information noted above. Providing the PI near the convention panels, by itself, fails to include sufficient qualifying information on the convention panels about such material risks.

Conclusion and Requested Actions

The convention panels misbrand Zemaira within the meaning of section 502(a) and 201(n) of the Act (21 U.S.C. 352(a), 321(n)) in that they fail to reveal material facts and are, therefore, false or misleading.

OCBQ requests that Aventis Behring immediately cease the dissemination of promotional materials for Zemaira 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 Zemaira 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, 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-05-002. 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 Zemaira 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

Enclosure A: convention panels