DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

CBER-04-009 May 27, 2004

VIA FACSIMILE AND CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER

Mr. Robert Taub
President
OMRIX biopharmaceuticals, Ltd.
200 Chaussee De Waterloo
1640 Rhode-St-Genese
Belgium

Re: BLA STN #125010
Crosseal™ [Fibrin Sealant (Human)]

Dear Mr. Taub:

The Advertising and Promotional Labeling Branch (APLB) in the Food and Drug Administration's Center for Biologics Evaluation and Research (CBER) has reviewed a convention panel for Crosseal™ [Fibrin Sealant (Human)] submitted by the American Red Cross (ARC) on behalf of OMRIX biopharmaceuticals, Ltd. (OMRIX) under cover of Form FDA 2253. The convention panel is 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 it omits risk information. By failing to include sufficient qualifying information on risks, you have encouraged the potentially unsafe use of Crosseal. In addition, OMRIX has failed to submit promotional materials to CBER at the time of the initial dissemination.

Background

Crosseal is a single-use kit consisting of two packages: one containing one vial each of frozen sterile solutions of Biological Active Component (BAC) and Thrombin and the other containing the sterile spray application device. The two components are mixed and applied topically as described in the Dosage and Administration section of the FDA-approved professional labeling (PI). The PI states that "Crosseal is indicated as an adjunct to hemostatis in patients undergoing liver surgery, when control of bleeding by conventional surgical techniques, including suture, ligature and cautery, is ineffective or impractical. Crosseal is not indicated for the treatment of massive and brisk arterial bleeding." Crosseal is manufactured by OMRIX and distributed by ARC.

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

- Information from a black box warning: "WARNING: Crosseal™ must not be used in contact with cerebrospinal fluid (CSF) or dura mater."
- "Crosseal is contraindicated in individuals known to have anaphylactic or severe systemic reaction to human blood products."
- "Do not inject Crosseal™ directly into the circulatory system or tissue."
- "Because this product is made from human plasma, it may carry the risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent."

Failure to Reveal Material Facts

The convention panel includes the headline,

> For fast hemostasis
> CROSSEAL. RIGHT AT THE MOMENT YOU NEED IT

and also states: "The first all human, bovine-free fibrin sealant." Although the convention panel refers the reader to the "complete product information sheet" for risk and "usage" information, the panel itself fails to provide any risk information, including the contraindications and warnings quoted above. Providing the PI near the convention panel, by itself, fails to include sufficient qualifying information on the panel about such risks.

In addition, the lack of specific definition of the meaning of "fast hemostasis" is misleading, because the time of hemostasis is a material fact.

Finally, the convention panel misleadingly implies that Crosseal is indicated for hemostasis treatment when, according to the PI, it is indicated only as an adjunct to hemostasis in patients undergoing liver surgery, when control of bleeding by conventional surgical techniques is impractical. As noted in the PI, Crosseal is contraindicated in certain patients.

Failure to Submit Post-Marketing Reports at the Time of Dissemination

In violation of 21 CFR 601.12(f)(4), OMRIX has failed to submit its promotional materials to APLB at the time of initial dissemination of such materials. The Form FDA 2253 you submitted with your convention panel indicates that this piece was disseminated five months before you submitted it to APLB. Please immediately revise your practices to ensure submission of promotional materials to FDA at the time of initial dissemination of the labeling.

Conclusion and Requested Actions

Your convention panel misbrands Crosseal within the meaning of section 502(a) and 201(n) of the Act (21 U.S.C. 352(a), 321(n)) because it fails to reveal material facts and is therefore false or misleading.

We request that OMRIX immediately cease the dissemination of violative promotional materials for Crosseal 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 Crosseal 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-04-009. 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 Crosseal 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

cc: American Red Cross

Enclosure A: convention panel
Enclosure B: Crosseal package insert