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

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September 14, 2004

CBER-04-016

VIA FASCIMILE AND CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER

Craig B. Mendelsohn, M.D., J.D.
Medical Director
ZLB Bioplasma Inc.
801 N. Brand Blvd., Suite 1150
Glendale, CA 91203

Re: BLA STN #125070
Rhophylac® [Rh_o(D) Immune Globulin Intravenous (Human)]

Dear Dr. Mendelsohn:

The Food and Drug Administration's Center for Biologics Evaluation and Research (CBER) has reviewed a sales brochure and a Patient Q&A for Rhophylac® [Rh_o(D) Immune Globulin Intravenous (Human)] (copies enclosed) submitted by ZLB Bioplasma Inc. (ZLB) under cover of Form FDA 2253. We also reviewed a promotional web site maintained by or on behalf of ZLB (http://www.rhophylacusa.com/) (excerpt enclosed). These materials fail to reveal material facts regarding Rhophylac and, therefore, misbrand the drug within the meaning of the Federal Food, Drug, and Cosmetic Act (the Act). See 21 U.S.C. §§ 352(a), 352(n), and 321(n).

Your failure to provide appropriate risk information misleads consumers and professionals to believe that Rhophylac is safer than has been demonstrated in the approved populations and encourages its unsafe use in those for whom it is contraindicated.

Background

Rhophylac is a sterile Rh_o(D) Immune Globulin Intravenous (Human) solution in a prefilled, ready to use syringe for either intravenous or intramuscular injection. The FDA-approved professional labeling (PI) states that Rhophylac is recommended for the suppression of Rh isoimmunization in non-sensitized Rh_o(D)-negative women, for Rhesus prophylaxis in case of obstetric complications, for Rhesus prophylaxis in case of invasive procedures during pregnancy, and for the suppression of Rh isoimmunization in

Rh_o(D)-negative individuals transfused with Rh_o(D)-positive Red Blood Cells (RBCs) or blood components containing Rh_o(D)-positive RBCs.

Specific examples of risk information contained in the PI include, but are not limited to, the following:

- A statement that "Rhophylac® is contraindicated in persons with hypersensitivity to human globulin."
- The following warning: "Rhophylac® is made from human plasma. Products made from human plasma may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the CJD [Creutzfeldt-Jakob Disease] agent."
- The following precaution: "For postpartum use, Rhophylac® is intended for maternal administration. It should not be given to the newborn infant. The product is not intended for use in Rh_o(D)-positive individuals. Patients should be observed for at least 20 minutes after administration."
  The following Adverse Reactions: "Mild and transient fever, malaise, headache, cutaneous reactions and chills occur occasionally. In rare cases, nausea, vomiting, hypotension, tachycardia, and allergic or anaphylactic type reactions, including dyspnea and shock are reported, even when the patient has shown no hypersensitivity to previous administration."

Failure to Reveal Material Facts

The main parts of your webpage, sales brochure, and patient Q&A make claims of safety and effectiveness, but fail to provide risk information, including the contraindications, warnings, precautions, and adverse reaction information noted above (except that the webpage does contain the warning regarding human plasma, and page 2 of the sales brochure states that the product is "[p]repared from only US donor plasma," but does not contain the whole warning). Although this information appears in the PI accompanying the sales brochure and patient Q&A, and is linked to the webpage, this is insufficient to make the effectiveness claims appearing in the main parts of these items non-misleading. The main parts of the Q&A and webpage include references to the full prescribing information; however, this statement is not sufficient to provide the appropriate qualification or pertinent information for the effectiveness claims made in the main parts of these items. Cf. 21 CFR 202.1(e)(3)(i). The webpage, sales brochure, and patient Q&A fail to reveal material facts within the meaning of Section 201(n) of the Act and, therefore, are misleading and cause Rhophylac to be misbranded under the Act. 21 U.S.C. §§ 321(n), 352(a), 352(n).

Conclusion and Requested Action

The cited materials misbrand Rhophylac within the meaning of the Act because they fail to reveal material facts regarding the risks associated with the use of this product and are, therefore, misleading. 21 U.S.C. §§ 321(n), 352(a), 352(n).

We request that ZLB immediately cease the dissemination of promotional materials for Rhophylac 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 promotional materials for Rhophylac such as those described above, and explaining your plan for discontinuing use of such materials. Because the violation described above is 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, facsimile at 301-827-3528. In all future correspondence regarding this matter, please refer to the BLA/STN number and to CBER-04-016. 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 Rhophylac 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- Web Page
B- Sales Brochure
C- Patient Q&A