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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

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

August 25, 2008

CBER-08-003

VIA FACSIMILE AND CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER

Jeffrey S. Aronin
President and Chief Executive Officer
Ovation Pharmaceuticals, Inc.
Four Parkway North
Deerfield, IL 60015

Re: BLA STN #101246
PANHEMATIN® (hemin for injection)

Dear Mr. Aronin:

The Office of Compliance and Biologics Quality (OCBQ) in the Food and Drug Administration's Center for Biologics Evaluation and Research has reviewed Leave Behind Porphyria Letters for Healthcare Providers (PHT094b & PHT094c) for PANHEMATIN® (hemin for injection) submitted by your firm under cover of Form FDA 2253. These promotional materials are misleading because they fail to reveal material facts regarding the most serious and important risks associated with the use of PANHEMATIN and present misleading efficacy claims. Thus, the materials misbrand Panhematin in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(a) and 321(n), and FDA implementing regulations, *Cf.* 21CFR 202.1 (e)(3)(i), and 202.1 (e)(6)(i). By failing to include sufficient risk information and presenting misleading efficacy claims, you encourage the potentially unsafe use of PANHEMATIN.

Background

The INDICATIONS AND USAGE section of the approved product labeling (PI) for Panhematin states:

> PANHEMATIN (hemin for injection) is indicated for the amelioration of recurrent attacks of acute intermittent porphyria temporally related to the menstrual cycle in susceptible women... PANHEMATIN is not indicated in porphyria cutanea tarda.

The PI also contains a black box warning which states:

> PANHEMATIN should only be used by physicians experienced in the management of porphyrias in hospitals where the recommended clinical and laboratory diagnostic and monitoring techniques are available. PANHEMATIN therapy should be considered after an appropriate period of alternate therapy (i.e., 400 g glucose/day for 1 to 2 days).

The PI includes additional detailed risk information including contraindications, warnings, precautions, and adverse reactions.

Failure to Reveal Material Facts

The promotional materials (letters for Healthcare Providers) include the indication for PANHEMATIN; but fail to include the most serious and important risk information necessary for the safe administration of this product including the contraindications and certain adverse reactions contained in the PI. In determining whether promotional materials are misleading, FDA takes into consideration not only the representations made or suggested in such materials, but also the extent to which the promotional materials fail to reveal facts that are material in light of these representations or that are material with respect to the consequences that may result from the use of the product (21 U.S.C. § 321(n)). Specifically, for both promotional pieces, you fail to include the following important risk information:

- Contraindications: "Panhematin is contraindicated in patients with known hypersensitivity to this drug."

- Adverse Reactions: "Reversible renal shutdown has occurred with administration of excessive doses."

In addition, the fact that the PI accompanies the promotional material is not sufficient to rectify this omission of important risk information (21 CFR 202.1 (e)(3)(i)).

Misleading Efficacy Claims

Promotional materials are false or misleading if they contain representations or suggestions that are not approved or permitted for use in the labeling that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience.

Specifically, the statement "100% positive chemical response" [1-5] presented under "[Panhematin] is effective" is misleading because it implies clinical significance, and the references cited to support this claim do not constitute substantial evidence or substantial clinical experience. According to the PI, the exact mechanism by which hematin produces symptomatic improvement in patients with acute episodes of hepatic porphyrias has not been elucidated. The PI also states that Panhematin therapy for the acute porphyrias in not curative. Therefore, it is misleading to suggest that a positive chemical response to Panhematin has clinical significance. Further, the references cited describe individual case studies and include responses from males and individuals with other types of porphyria (e.g., variegate porphyria and hereditary coproporphyia), which is inconsistent with the approved population for Panhematin. According to the PI, "Panhematin is indicated for the amelioration of recurrent attacks of acute intermittent porphyria temporally related to the menstrual cycle in susceptible women." Furthermore, according to the references, subjects treated with hemin did not always respond clinically or chemically. In fact, there were reported deaths in the referenced studies [1,2,3,5] after treatment with hemin. If you have other data consisting of substantial evidence to support such a claim for the approved population for Panhematin, please submit the data to FDA for review.

Additionally, the claim that Panhematin "Is the only FDA-approved therapy for the treatment of the acute porphyrias (AIP, VP, HCP)" is misleading because it suggests that Panhematin is effective in the treatment of all acute porphyrias. The presentation of the indication at the bottom of the letter does not correct this overall misleading presentation.

Conclusion and Requested Actions

For the reasons discussed above, your promotional materials misbrand PANHEMATIN in violation of the Act, 21 U.S.C. 352(a) and 321(n) and FDA implementing regulations, *Cf.* 21 CFR 202.1 (e)(3)(i), and 202.1 (e)(6)(i).

OCBQ requests that Ovation Pharmaceuticals, Inc. immediately cease the dissemination of these violative promotional materials for PANHEMATIN, as well as promotional materials with the same or similar claims and representations. Please submit a written response 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 PANHEMATIN, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we further request 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

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[1] Watson, CJ, et al. Adv Intem Med 1978;23:265-286.
[2] Pierach CA, et al. Klin Wochenschr. 1980;58:829-832.
[3] Lamon JM, Frykholm BC, Hess RA, Tschudy DP. Medicine (Baltimore). 1979;58:252-269.
[4] Lamon JM, et al. Clin Res. 1977;25(3);471A
[5] McColl KEL, Moore MR, Thompson GG, Goldberg A. QJ Med.1981;50:161-174.

the audience(s) that received the violative promotional material. 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-08-003. 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 PANHEMATIN 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,

Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Enclosures: Letters for Healthcare Providers PHT094b & PHT094c