DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Carol S. Marchione
Sr. Director & Group Leader, Regulatory Affairs
Cephalon, Inc.
41 Moores Road, P.O. Box 4011
Frazer, PA 19355

RE: NDA # 22-249
NDA # 22-303
Treanda® (bendamustine hydrochloride) for Injection
MACMIS ID # 17907

Dear Ms. Marchione:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a Pocket Dosing Card (dosing card) (TRE-2009P-PMC-00034) for Treanda (bendamustine hydrochloride) for injection (Treanda) submitted by Cephalon, Inc. (Cephalon) under cover of Form FDA-2253. This dosing card is false or misleading because it omits important risk information associated with the use of Treanda as well as important material information regarding dosing claims made by the card. Therefore, this promotional material misbrands Treanda in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(a) & 321(n). *Cf.* 21 CFR 202.1(e)(3)(i).

Background

According to the INDICATIONS AND USAGE section of its FDA-approved product labeling (PI):

> Treanda is indicated for the treatment of patients with chronic lymphocytic leukemia [CLL]. Efficacy relative to first line therapies other than chlorambucil has not been established.
>
> Treanda for Injection is indicated for the treatment of patients with indolent B-cell non-Hodgkin's lymphoma [NHL] that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

Treanda is associated with numerous serious risks, some of which can be fatal. For example, the PI includes contraindications regarding hypersensitivity (e.g., anaphylactic and anaphylactoid reactions) to bendamustine or mannitol and the following important information regarding warnings and precautions:

- Myelosuppression: Patients treated with Treanda are likely to experience myelosuppression. May warrant treatment delay or dose reduction. Monitor closely and restart treatment based on ANC and platelet count recovery. Complications of myelosuppression may lead to death.
- Infections: Infection, including pneumonia and sepsis, has been reported in patients in clinical trials and in post-marketing reports. Infection has been associated with hospitalization, septic shock and death. Monitor for fever and other signs of infection and treat promptly.
- Infusion Reactions and Anaphylaxis: Infusion reactions to Treanda have occurred commonly in clinical trials. Severe anaphylactic reactions have also occurred. Monitor clinically and discontinue drug for severe reactions. Ask patients about reactions after the first cycle. Consider pretreatment for cycles subsequent to milder reactions.
- Tumor Lysis Syndrome: The onset tends to be within the first treatment cycle of Treanda and without intervention, may lead to acute renal failure and death. Take precautions in patients at high risk. Allopurinol has also been used during the beginning of TREANDA therapy. However, there may be an increased risk of severe skin toxicity when TREANDA and allopurinol are administered concomitantly.
- Skin Reactions: Discontinue for severe skin reactions. Cases of Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some fatal, have been reported when TREANDA was administered concomitantly with allopurinol and other medications known to cause these syndromes.
- Other Malignancies: Pre-malignant and malignant diseases have been reported.
- Use in Pregnancy: Fetal harm can occur when administered to a pregnant woman. Women should be advised to avoid becoming pregnant when receiving TREANDA.

In addition, Treanda is associated with numerous adverse reactions. In particular, the most common non-hematologic adverse reactions (frequency ≥15%) for CLL are pyrexia, nausea and vomiting. The most common non-hematologic adverse reactions (frequency ≥15%) for NHL are nausea, fatigue, vomiting, diarrhea, pyrexia, constipation, anorexia, cough, headache, weight decreased, dyspnea, rash and stomatitis. The most common hematologic abnormalities (frequency ≥15%) for both indications are lymphopenia, anemia, leukopenia, thrombocytopenia, and neutropenia.

Furthermore, the Dosage and Administration and Warnings and Precautions sections of the PI state that dose delays, dose modifications, and reinitiation and discontinuation of Treanda therapy may be required for various hematologic and non-hematologic toxicities. For example, the PI includes the following information regarding dose delays, dose modifications and reinitiation of therapy for CLL and NHL, respectively:

> TREANDA administration should be delayed in the event of Grade 4 hematologic toxicity or clinically significant ≥ Grade 2 non-hematologic toxicity. Once non-hematologic toxicity has recovered to ≤ Grade 1 and/or the blood counts have improved [Absolute Neutrophil Count (ANC) ≥ 1 x 10^9/L, platelets ≥ 75 x 10^9/L], TREANDA can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted. Dose modifications for hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 50 mg/m^2 on Days 1 and 2 of each

cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 25 mg/m^2 on Days 1 and 2 of each cycle. Dose modifications for non-hematologic toxicity: for clinically significant Grade 3 or greater toxicity, reduce the dose to 50 mg/m^2 on Days 1 and 2 of each cycle. Dose re-escalation in subsequent cycles may be considered at the discretion of the treating physician.

TREANDA administration should be delayed in the event of a Grade 4 hematologic toxicity or clinically significant ≥ Grade 2 non-hematologic toxicity. Once non-hematologic toxicity has recovered to ≤ Grade 1 and/or the blood counts have improved [Absolute Neutrophil Count (ANC) ≥ 1 x 10^9/L, platelets ≥ 75 x 10^9/L], TREANDA can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted. Dose modifications for hematologic toxicity: for Grade 4 toxicity, reduce the dose to 90 mg/m^2 on Days 1 and 2 of each cycle; if Grade 4 toxicity recurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle. Dose modifications for non-hematologic toxicity: for Grade 3 or greater toxicity, reduce the dose to 90 mg/m^2 on Days 1 and 2 of each cycle; if Grade 3 or greater toxicity recurs, reduce the dose to 60mg/m^2 on Days 1 and 2 of each cycle.

Moreover, discontinuation of Treanda therapy may be necessary for severe infusion reactions and anaphylaxis as well as severe or progressive skin reactions as stated in the PI.

Omission of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to the consequences that may result from the use of the drug as recommended or suggested by the materials. The dosing card includes an extremely limited risk presentation under the header “Important safety information” (ISI) on the back cover. Importantly, this presentation omits critical details about the risks it discloses, including the context that some of these risks are frequent, severe and potentially **fatal**. For example, while the piece lists “myelosuppression” as an “adverse reaction”, it does not disclose any further information about this significant Warning. According to the PI, **98%** of patients experienced **Grade 3-4** myelosuppression in the two NHL studies, and **2% of patients died from myelosuppression-related adverse reactions**. Likewise, while the card lists the “adverse reaction” of “infections,” it fails to disclose any further information about this Warning. According to the PI, infection has been associated with **hospitalization, septic shock, and death**. This limited risk presentation is wholly inadequate to communicate the material risk information about Treanda, including risks that could potentially be ameliorated through interventions such as decreasing the dose or withholding treatment, and suggests that Treanda is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Omission of Material Fact

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. The dosing card omits

important material information related to the dosing claims on the front of the card. Specifically, it fails to communicate the potential need for dose delays, modifications, reinitiation and discontinuation of therapy for both hematologic and non-hematologic toxicities of Treanda. We note the statement on the bottom left corner of the front cover "Please see accompanying full Prescribing Information for dose modifications, interruptions, or discontinuation." However, the inclusion of this statement does not correct the misleading omission of material dosing information from the card itself.

Conclusion and Requested Action

For the reasons discussed above, the dosing card misbrands Treanda in violation of the Act, 21 U.S.C. 352(a) & 321(n). *Cf.* 21 CFR 202.1(e)(3)(i).

DDMAC requests that Cephalon immediately cease the dissemination of violative promotional materials for Treanda such as the dosing card described above. Please submit a written response to this letter on or before January 6, 2010, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Treanda that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS ID # 17907 in addition to the NDA number. We remind you that only written communications are considered official. The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Treanda comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

JuWon Lee, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22249	ORIG-1	CEPHALON INC	TREANDA
NDA-22303	ORIG-1	CEPHALON INC	TREANDA

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/s/

JUWON LEE
12/18/2009