DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-249/S-002
NDA 22-303

Cephalon, Inc.
Attention: Carol S. Marchione
Senior Director and Group Leader
41 Moores Road
Frazer, PA 19355

Dear Ms. Marchione:

Please refer to your supplemental new drug application dated March 30, 2009, received March 31, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Treanda® (bendamustine hydrochloride) for Injection, 100 mg.

We acknowledge receipt of your submissions dated March 20, March 26, April 6, and April 9, 2009.

This supplemental new drug application provides for revising the package insert to include reports of adverse events of Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN).

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 22-249/S-002."

We remind you of your outstanding postmarketing study commitments listed in the March 20, 2008, approval letter. These commitments are listed below.

1. Cephalon commits to providing an updated study report of Protocol 02CLLIII titled *"Phase III, Open-Label, Randomized, Multicenter Efficacy and Safety Study of Bendamustine Hydrochloride Versus Chlorambucil in Treatment-Naive Patients with (Binet Stage B/C) BCLL Requiring Therapy"* at data cut off date in May 2008. Response rate, progression-free survival, overall survival and safety updates will be provided in this study report.

   Protocol Submission: N/A
   Study Start: N/A
   Final Report Submission: February 28, 2009

2. Cephalon commits to submitting the results and data from the ADME Study 1039 titled "An Open-Label Study to Investigate the Pharmacokinetics (Distribution, Metabolism, and Excretion) of Bendamustine Hydrochloride Following Intravenous Infusion of [$_{14}$C]Bendamustine Hydrochloride in Patients With Relapsed or Refractory Malignancy (Hematologic or Nonhematologic)". Results from this study may indicate a need for dedicated renal and/or hepatic organ impairment studies.

   Protocol Submission: May 31, 2008
   Study Start: December 31, 2008
   Final Report Submission: March 31, 2010

3. Cephalon commits to conducting a study to assess the potential for bendamustine to prolong the QT interval in patients. The QT plan will be submitted prior to initiation for IRT review and concurrence.

   Protocol Submission: July 31, 2008
   Study Start: December 31, 2008
   Final Report Submission: June 30, 2010

4. Since bendamustine is a CYP1A2 substrate *in vitro*, Cephalon agrees to perform an *in vivo* drug interaction study of the ability of fluvoxamine (CYP1A2 inhibitor) to alter the pharmacokinetics of a single dose of bendamustine. The necessity to conduct this study will be predicated upon the results from Study 1039.

   Protocol Submission: March 31, 2010
   Study Start: September 30, 2010
   Final Report Submission: July 31, 2012

5. Since bendamustine is a CYP1A2 substrate *in vitro*, Cephalon agrees to perform an *in vivo* drug interaction study of the ability of smoking (CYP1A2 inducer) to alter the pharmacokinetics of a single dose of bendamustine. The necessity to conduct this study will be predicated upon the results from Study 1039.

   Protocol Submission: March 31, 2010
   Study Start: September 30, 2010
   Final Report Submission: December 31, 2012

6. Cephalon commits to conducting *in vitro* screens to determine if bendamustine is a p-glycoprotein substrate or inhibitor.

   Protocol Submission: March 31, 2008
   Study Start: September 30, 2007
   Final Report Submission: June 30, 2008

7. Cephalon commits to assess the physico-chemical compatibility of Treanda with the following diluents as admixtures to reconstituted TREANDA: (b) (4) (b) (4) sodium chloride).

Protocol submission: April 1, 2008
Study start: May 15, 2008
Final Report: September 1, 2008

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the revised labeling, and has determined that it contains significant new risk information relating to Treanda. We are hereby informing you that all promotional materials for Treanda that include representations about Treanda should be revised to include the new information immediately. These revisions should include prominent disclosure of the important new information regarding the increased risk of severe skin toxicity in a manner consistent with the Warnings and Precautions and Adverse Reactions section of the revised PI. If you have any questions about the promotion of your drug products, please contact the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications by facsimile at (301) 594-6771 or at HFD-42, Room 8B-45, 5600 Fishers Lane, Rockville, MD 20857.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Drug Oncology Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Milinda Vialpando, Regulatory Project Manager, at (301) 796-1444.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure: Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Amna Ibrahim

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