DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-249 **NDA APPROVAL**

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

Dear Ms. Marchione:

Please refer to your new drug application (NDA) dated September 19, 2007, received September 20, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for TREANDA® (bendamustine hydrochloride) for Injection, for intravenous infusion.

We acknowledge receipt of your submissions dated October 3, 18, 22, 24, 26, November 1, 2, 9, 15 (2), 27, 28, December 10 and 17, 2007, January 7 (2), 8, 11, 14, 15, 17, 18, 23, 24, 25, 28, 31, February 12, 13, 14, 20, 22, 25, 28, March 3, 6, 7, 12, 13 (2), 14, 17 (2), 18 (electronic) and 19 (4 electronic), 2008.

This new drug application provides for the use of TREANDA® (bendamustine hydrochloride) for Injection, for intravenous infusion, for the treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established.

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

An expiration dating period of 24 months is granted when stored as recommended in the approved product labeling. You may extend the expiration dating based on accrual of real-time stability data and report this in an annual report for this NDA.

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."

We acknowledge your March 13, 2008, submission containing final printed carton and container labels.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

This application was not referred to the Oncologic Drugs Advisory Committee because the improvements in response rate and progression-free survival with bendamustine compared to chlorambucil were clinically and statistically robust and the safety profile is comparable to other therapies used for the treatment of CLL.

We remind you of your postmarketing study commitments in your submission dated March 19 (electronic), 2008. 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) B-CLL 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, 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, 2008
   Study Start: December, 2008
   PK Report Submission: December, 2009
   Final Report Submission: March, 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, 2008
   Study Start: December, 2008
   Final Report Submission: June, 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, 2010
   Study Start: September, 2010
   PK Report Submission: January, 2012
   Final Report Submission: July, 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, 2010
   Study Start: September, 2010
   PK Report Submission: July, 2012
   Final Report Submission: December, 2012

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

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

7. Cephalon commits to assess the physico-chemical compatibility of Treanda with the following diluents as admixtures to reconstituted TREANDA: [redacted] 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 should be prominently labeled "**Postmarketing Study Commitment Protocol**," "**Postmarketing Study Commitment Final Report**," or "**Postmarketing Study Commitment Correspondence**."

We also remind you of your agreement dated February 12, 2008, to initiate change controls for all the documents impacted by the revision to the maximum hold time not to exceed [redacted] and to submit appropriate post-approval correspondence reflecting this change in the next annual report.

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) 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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

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

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

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

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, please call Frank H. Cross, Jr., Regulatory Project Manager, at (301) 796-0876.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Office Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

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

/s/

Robert Justice
3/20/2008 10:23:41 AM

Richard Pazdur
3/20/2008 10:46:28 AM