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Approval Package for:

APPLICATION NUMBER:

NDA 22-249/S-1

Trade Name:	Treanda
Generic or Proper Name:	bendamustine hydrochloride, for Injection, 100 mg
Sponsor:	Cephalon, Inc.
Approval Date:	May 1, 2009
Indication:	provides for the addition of a new 25 mg vial

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NDA 22-249/S-1

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APPLICATION NUMBER:

NDA 22-249/S-1

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-249/S-001

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 August 27, 2008, received August 28, 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 August 27, 2008 and November 19, 2008.

This supplemental new drug application provides for the addition of a 25 mg vial for the use of Treanda® (bendamustine hydrochloride) for Injection for the treatment of patients with Chronic Lymphocytic Leukemia and for the treatment of patients with indolent B-cell non-Hodgkin's lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

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-001."

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

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