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APPLICATION NUMBER:

NDA 22-249

MEDICAL REVIEW(S)

CLINICAL REVIEW ADDENDUM

Application Type:	NDA
Submission Number:	22249
Submission Code:	000
Letter Date:	09/19/07
Stamp Date:	09/20/07
PDUFA Goal Date:	03/20/07
Reviewer Names:	Qin Ryan, MD, PhD (Efficacy) Virginia Kwitkowski, MS, RN, CRNP (Safety)
Date of Addendum:	03/18/08
Established Name:	bendamustine hydrochloride
(Proposed) Trade Name:	TRENDA ®
Therapeutic Class:	Alkylating agent
Applicant:	Cephalon
Priority Designation:	P
Formulation:	IV
Dosing Regimen:	100 mg/m2, Days 1 & 2, q28 days
Indication:	Treatment for CLL
Intended Population:	Chemotherapy naïve patients

Amendment Summary:

After the completion of the NDA review, the Applicant submitted additional information regarding the following:

1. Study 02CLLIII financial disclosures
2. Treatment dose modification information

This amendment is to include the reviewers' assessments of the new information. Amendments to Clinical Review sections 3.3, Financial Disclosure and 9.2 Labeling Recommendations are listed below.

After the initial review completion, an investigation for drug-induced liver injury was undertaken with the results prepared as an amendment to section 7.4.2 Laboratory Findings.

Efficacy Review Addendum

In section 3.3 Financial Disclosures in the original NDA review, it was stated that the financial disclosures could not be obtained for the following studies: 02CLLIII, 99CLL2E (BG), 99CLL2E (DE), 98B02, 20BEND1, 20BEN 03, 98B02W, 93BOP01, 94BP01, 96BMF02/1, 98B03, BE04, based on the initial NDA submission. However, upon FDA request, the applicant requested financial disclosures per the FDA recommended format through the original sponsor of study 02CLLIII. The collected disclosure information was submitted as an amendment to the NDA. Among the 45 principal investigators (PIs), 43 of them as well as the available sub-investigators from their sites submitted financial disclosures indicating no personal financial interest in the study drug. Of the 2 remaining PIs, one was deceased and one is on vacation. Based on the information provided in this NDA, there were 11 patients enrolled from the sites of the 2 PIs whose financial disclosures are not yet available. Excluding enrollments from the deceased PI, 6 patients (or 2% of the total enrollment of study 02CLLIII) were treated by an investigator who has not provided financial disclosure information. The applicant will continue to collect this information and submit it to the Agency as soon as the last one is available.

The available information does not suggest that the study results would be influenced by financial interest since no personal financial interest was reported by any of the investigators. Due to the small number of investigators for whom financial disclosure information is not available and the small number of patients enrolled by these investigators, it is unlikely that the information not available to date would influence FDA's interpretation of the study results.

Safety Review Addendum

The following text is added to Section 7.4.2, Laboratory Findings:

An exploration of the datasets submitted to the Cephalon NDA 22249 (Treanda for CLL) was undertaken to search for potential cases of Drug Induced Liver Injury (DILI) per the "Draft Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation". The clinical chemistry dataset was explored to identify any patients that met Hy's Law definition. Briefly, Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by more frequent 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control agent or placebo.

2. Among subjects showing such aminotransferase (AT) elevations, often with ATs much greater than 3xULN, some subjects also show elevation of serum total bilirubin (TBL) to >2xULN, without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity >2xULN).

3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.

In the dataset exploration, no cases that met these criteria were found.

These results do not exclude the potential for DILI due to the small sample size, but no evidence for DILI was identified during this data exploration.

The following text is added to Section 9.2, Labeling Recommendations:

The original proposed product information label that was submitted by Cephalon recommendations for dose reductions in the case of toxicities. FDA proposed the following language for the Dosage and Administration section

Cephalon expressed concern that if these recommendations were followed verbatim, patients would be undertreated. Cephalon proposed the following text for the label:

- "Dose modifications for hematologic toxicity: consider a 50% dose reduction for Grade 3 or greater toxicity; if Grade 3 or greater toxicity recurs, consider a 75% dose reduction. (2.2)
- Dose modifications for non-hematologic toxicity: 50% dose reduction for clinically significant Grade 3 toxicity. (2.2)
- Dose re-escalation may be considered. (2.2)"

FDA asked Cephalon to provide an evaluation of how the dose reductions were handled in the 02CLLIII protocol to justify the above labeling recommendations.

Cephalon provided the following evaluation summary:

The main findings from this analysis were as follows:

1. The occurrence of Grade 2 and Grade 3/4 hematologic toxicities, as graded by the standard NCI-CTC, did not result in dose reduction for the majority of patient-cycles. Of the patient-cycles with Grade 2 and Grade 3/4 hematologic toxicity, 69% and 64% of the subsequent cycles were administered at >90% of the planned dose, respectively. Of the patient-cycles with Grade 2 and Grade 3/4 hematologic toxicity excluding leucopenia and lymphocytopenia (which are both related to disease), 58% and 53% of the subsequent cycles were administered at >90% of the planned dose, respectively.

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/s/

Virginia Kwitkowski
3/18/2008 05:02:59 PM
MEDICAL OFFICER
Signing as Acting Clinical Team Leader

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