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APPLICATION NUMBER:
22-203

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA 22-303
Submission Date: 28-December 2007; 6-March-2008;14-May-2008
Brand Name: Treanda®
Generic Name: Bendamustine hydrochloride
Formulation: Injection
Clinical Pharmacology Reviewer: Qi Liu, Ph.D.
Clinical Pharmacology Team Leader: Brian Booth, Ph.D.
Pharmacometric Team Leader: Yaning Wang, Ph.D.
OCP Division: Division of Clinical Pharmacology 5
ORM Division: Division of Drug Oncology Products
Sponsor: Cephalon
Submission Type; Code: Original NDA; 000
Dosing regimen: 120 mg/m² infused intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, for 6-8 cycles
Indication: For the treatment of patients with indolent B-cell non-Hodgkin's lymphoma (NHL) who have progressed during or following treatment with rituximab or a rituximab-containing regimen.

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1 EXECUTIVE SUMMARY

The current New Drug Application (NDA 22-303) has been submitted in support of registration of Treanda® (bendamustine hydrochloride, an alkylating drug) for the treatment of patients with indolent B-cell non-Hodgkin's lymphoma (NHL) who have progressed during or following treatment with rituximab or a rituximab-containing regimen. Treanda® was approved by the FDA on 20-March-2008 for the treatment of patients with chronic lymphocytic leukemia (NDA 22-249). NDA 22-249 was considered acceptable from a clinical pharmacology perspective as the sponsor has agreed to the following Phase 4 commitments: (1) conducting the mass-balance study, (2) investigating the QT prolongation potential, (3) conducting the drug-drug interaction (DDI) study with fluvoxamine, (4) evaluating the effects of smoking on bendamustine pharmacokinetics, and (5) conducting in vitro p-glycoprotein screens (see the Approval letter for NDA 22-249, dated 20-March-2008).

To support the approval for the treatment of NHL, the sponsor submitted data from 16 clinical studies, among which the Phase 3 Study SDX-105-03 is considered the pivotal study and the Phase 2 Study SDX-105-01 is considered a supportive study. Both studies used the same dosage regimen for bendamustine (120 mg/m² iv infusion on days 1 and 2 of a 21-day cycle for a minimum of 6 cycles with additional cycles allowed with no evidence of disease progression).

The only new clinical pharmacology information submitted in the current submission is the exposure-response analysis conducted for the Phase 3 Study SDX-105-03. No exposure measures were found to be significant predictors of responder status, duration of response, or progression-free survival within the studied exposure range. Among the safety endpoints evaluated in the PK/PD analyses, nausea was the only safety endpoint that was found to be statistically significantly related to bendamustine exposure.

1.1 RECOMMENDATIONS

The NDA is considered acceptable from a clinical pharmacology perspective.

Please see Section 3 for detailed labeling recommendations.

Signatures:

Qi Liu,
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 5

Brian Booth, Ph.D.
Deputy Division Director & Acting Team Leader
Division of Clinical Pharmacology 5

Cc: DDOP: CSO - D Pease; MTL - A Ibrahim; MO - Q Ryan, V Kwitkowski
DCP-5: Reviewers - Q Liu; PM TL: Y Wang; Acting TL & DDD - B Booth;
DD - A Rahman

1.2 CLINICAL PHARMACOLOGY SUMMARY

TREANDA (bendamustine hydrochloride) for Injection is an alkylating drug. Following a single IV dose of bendamustine hydrochloride, C_{max} typically occurred at the end of infusion. In humans, the mean steady state volume of distribution (V_{ss}) was approximately 25 L. Bendamustine clearance in humans is approximately 700 mL/minute. *In-vitro* metabolism indicates that bendamustine is metabolized via CYP1A2 to form two active metabolites M3 and M4. Based on the clinical pharmacokinetic data, the two metabolites M3 and M4 are present at concentrations 10- and 100-fold lower than that of the parent compound, respectively. After a single dose of 120 mg/m² bendamustine IV over 1-hour, the intermediate t_{1/2} of the parent compound is approximately 40 minutes. The mean apparent terminal elimination t_{1/2} of M3 and M4 are approximately 3 hours and 30 minutes respectively. Preclinical radiolabeled bendamustine studies showed that approximately 90% of drug administered was recovered in excreta primarily in the feces.

To support the approval for the treatment of NHL, the sponsor submitted data from 16 clinical studies, among which the Phase 3 Study SDX-105-03 is considered the pivotal study and the Phase 2 Study SDX-105-01 is considered a supportive study. Both studies used the same dosage regimen for bendamustine (120 mg/m² iv infusion on days 1 and 2 of a 21-day cycle for a minimum of 6 cycles with additional cycles allowed with no evidence of disease progression).

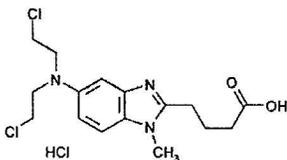
The only new clinical pharmacology information submitted in the current submission is the pharmacokinetic/pharmacodynamic (PK/PD) analyses for the efficacy and safety in NHL patients conducted for the Phase 3 Study SDX-105-03. Based on logistic regression and graphical analyses, no exposure measures (AUC or C_{max}) were significant predictors of responder status within the studied exposure range. Exploratory graphical analyses demonstrated no relationship between duration of response (DR) and measures of exposure, whereas a potential relationship between progression-free survival (PFS) and exposure up to 30-60 weeks was observed. However, the relationship was not statistically significant. Among the safety endpoints evaluated in the PK/PD analyses, nausea was the only safety endpoint that was found to be statistically significantly related to bendamustine exposure. No correlation was observed between exposure and other three safety endpoints assessed (fatigue, vomiting and neutropenia) within the studied exposure range.

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

1. Structural formula:



2. Established name: bendamustine Hydrochloride, CEP-18083

3. Molecular Weight: 394.7

4. Molecular Formula: C₁₆H₂₁Cl₂N₃O₂HCl

5. Chemical Name: 1H-Benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1-methyl-, monohydrochloride

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Bendamustine, a purine analog alkylating agent, was synthesized to combine the activities of the purine antimetabolite, benzimidazole, with the alkylating properties of the bifunctional mechlorethamine nitrogen mustard. The precise mechanism of action of the drug in humans has not been fully characterized. Bendamustine has been approved for the treatment of chronic lymphocytic leukemia (CLL). Bendamustine is being developed for the treatment of patients with indolent B-cell non-Hodgkin's lymphoma (NHL) who have progressed during or following treatment with rituximab or a rituximab-containing regimen.

2.1.3 What are the proposed dosage and route of administration?

The recommended dosing regimen for bendamustine in the treatment of CLL is 100 mg/m² IV over 30-minutes on Days 1 and 2 every 28 days for up to six cycles.

The recommended dosing regimen for bendamustine in the treatment of NHL is 120 mg/m² infused intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, for 6-8 cycles.

2.2 GENERAL

2.3 CLINICAL PHARMACOLOGY

2.3.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

To support the approval for the treatment of NHL, the sponsor submitted data from 16 clinical studies, among which the Phase 3 Study SDX-105-03 is considered the pivotal study and the Phase 2 Study SDX-105-01 is considered a supportive study. The two studies shared similar study designs (multicenter, nonrandomized, open-label, single-agent studies). Both Studies SDX-105-01 and SDX-105-03 included adult patients with relapsed, rituximab-refractory, indolent NHL. Both studies used the same dosage regimen for bendamustine (120 mg/m² iv infusion on days 1 and 2 of a 21-day cycle for a minimum of 6 cycles with additional cycles allowed with no evidence of disease progression). One hundred and two patients were enrolled in study SDX-105-03. Seventy-seven patients were enrolled in study SDX-105-01.

The only new clinical pharmacology information submitted in the current submission is the exposure-response

analyses conducted for the Phase 3 Study SDX-105-03.

2.3.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

In the pivotal phase 3 study SDX-105-03:

The primary efficacy variables were overall response rate (ORR) and duration of response (DR). ORR was defined as the proportion of patients who achieved a best response of complete response (CR), unconfirmed complete response (CRu), or partial response (PR) during the study.

The secondary efficacy variable was progression-free survival (PFS). PFS for each patient was defined as the time interval from the date of first study drug dose to the first documentation of disease progression, change of therapy, or death regardless of cause, whichever occurred first. Patients without disease progression, change of therapy, or death were censored at the date of last known progression-free assessment.

A baseline assessment of NHL was performed within 28 days before cycle 1, day 1. Assessments of patient response to bendamustine treatment were performed at week 6 (day 42) and week 12 (day 84), and then every 12 weeks thereafter, with a window of ± 3 days around each timepoint, until the patient completed or discontinued treatment. After a patient completed or discontinued treatment for any reason, an end-of-treatment assessment was performed within 28 days after the last dose of study drug, unless the patient had experienced a treatment delay due to toxicity, in which case the assessment was performed within 2 weeks of the decision to discontinue the patient from treatment.

2.3.3 Exposure-response

2.3.3.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Pharmacokinetic/Pharmacodynamic (PK/PD) analyses were conducted for the efficacy of bendamustine in NHL patients using data from the Phase 3 Study SDX-105-03. No exposure measures were significant predictors of responder status, duration of response (DR) and progression-free survival (PFS) within the studied exposure range.

Study SDX-105-03 was a phase 3, multicenter, open label, 6-treatment cycle, single-agent study in patients with indolent NHL refractory to rituximab. In this study, bendamustine was administered as a 60-minute *iv* infusion at a dose of 120 mg/m² on day 1 and day 2 of 6 consecutive 21-day treatment cycles. If a patient was continuing to experience clinical benefit at cycle 6, as assessed by the investigator, the patient received up to 2 additional cycles of bendamustine. The primary efficacy variables were overall response rate (ORR) and DR. The secondary efficacy variable was PFS.

Responder Status: Of the 80 patients in the PK/PD efficacy analysis, 68 patients (85%) were responders after treatment with bendamustine. Based on logistic regression analysis, no exposure measures were significant predictors of responder status within the studied exposure range.

DR: The mean DR (standard deviation) was 31.60 (18.27) weeks and ranged from 0.1 to 77 weeks. Kaplan-Meier plots of DR were constructed by categorizing each exposure into 2 groups using the median cycle 1 exposure measure. Only responder patients were included in the plots since non-responders had no duration of response. Graphical analyses demonstrated no relationship between DR and exposure. Kaplan-Meier analysis resulted in no statistically significant relationship between DR and the exposure measures.

PFS: The mean PFS (standard deviation) was 35.79 (18.42) weeks and ranged from 2.9 to 83 weeks. Kaplan-Meier plots of PFS were constructed by categorizing each exposure into 2 groups using the median cycle 1 exposure. Exploratory graphical analyses demonstrated an initial trend for a relationship between exposure measures and PFS up to 30-60 weeks. However, Kaplan-Meier analysis resulted in no statistically significant relationship.

For details of the analyses, refer to the pharmacometric review in the Appendix.

2.3.3.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Pharmacokinetic/Pharmacodynamic (PK/PD) analyses were conducted for safety of bendamustine in NHL patients using data from the Phase 3 Study SDX-105-03. The analyses included three safety adverse events (fatigue, nausea, and vomiting) and one laboratory abnormality (neutropenia). These adverse events/ laboratory abnormality were selected due to the fact that they are known to be frequently associated with bendamustine treatment. Among them, nausea was the only safety endpoint that was found to be statistically significantly related to bendamustine exposure.

Fatigue: Of the 80 patients in the PK/PD safety analyses, 45 patients (56%) had at least 1 occurrence of fatigue during the treatment period. Exploratory graphical analyses and logistic regression analysis showed that no exposure measures were statistically significant predictors of the probability of fatigue within the studied exposure range.

Nausea: A total of 59 patients (74%) had at least 1 occurrence of nausea during the treatment period. Logistic regression analysis showed that cycle 1 bendamustine C_{max} and cycle 1 composite C_{max} (weighted sums of C_{max} based on the relative potency of bendamustine and its two active metabolites, M3 and M4) were both statistically significant predictors (p-value=0.013 and p-value=0.013) of the probability of the nausea. Since both exposures were equally significant, cycle 1 bendamustine C_{max} was deemed the more appropriate exposure measure, given that cycle 1 composite C_{max} is composed mostly of bendamustine, and because the 2 measures were highly correlated (r>0.99).

Vomiting: A total of 25 patients (31%) had at least 1 occurrence of vomiting during the treatment period. Exploratory graphical analyses and logistical regression analysis showed that no exposure measures were statistically significant predictors of the probability of the vomiting within the studied exposure range.

Grade 3 and 4 Neutropenia: Weekly hematology measurements were planned in this study. For each patient cycle, the lowest laboratory ANC measurement was taken and graded based on NCI toxicity criteria. Only patients with a grade of 3 or 4 neutropenia were classified as having neutropenia. Boxplots of bendamustine AUC measures at each cycle demonstrated that patients with neutropenia had slightly higher bendamustine AUCs during cycles 1 through 3. During cycles 4 through 6, similar bendamustine AUC measures were observed in patients with and without neutropenia.

For details of the analyses, refer to the pharmacometric review in the Appendix.

2.3.3.3 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Based on the exposure-response analysis conducted for the Phase 3 Study SDX-105-03, no exposure measures were found to be significant predictors of responder status, duration of response, or

progression-free survival within the studied exposure range. Among the safety endpoints evaluated in the PK/PD analyses for the same study, nausea was the only safety endpoint that was found to be statistically significantly related to bendamustine exposure.

The sponsor used the results of the pivotal Phase 3 study SDX-105-03 and the supportive Phase 2 Study SDX-105-01 to demonstrate that bendamustine at 120 mg/m² iv infusion on days 1 and 2 of a 21-day cycle for 6-8 cycle is an effective treatment for patients with NHL.

3 DETAILED LABELING RECOMMENDATIONS

The entirety of the Applicant's Proposed Package Insert appears in the Appendices. We recommend some modifications to the sponsor's proposed labeling change (the sponsor's proposed labeling change is highlighted in yellow, and FDA's modification is in bold blue text as below).

Addition of the following sub-section in CLINICAL PHARMACOLOGY section:

12.4 Pharmacokinetics/Pharmacodynamics

(b) (4)



Based on the Pharmacokinetics/Pharmacodynamics analyses of data from NHL

patients, a correlation was observed (b) (4)

between nausea and bendamustine C_{max} (b) (4)

