# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**NDA 22-249**

# CROSS DISCIPLINE TEAM LEADER REVIEW

# Cross-Discipline Team Leader Review

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| **Date** | *March 20th, 2008* |
| **From** | Amna Ibrahim MD |
| **Subject** | Cross-Discipline Team Leader Review |
| **NDA # (Supp #)** | 22249 (S-000) |
| **Proprietary / Established (USAN) names** | Bendamustine (Treanda) |
| **Dosage forms /strength** | 100-mg vials of bendamustine HCL as white to off-white lyophilized powder |
| **Proposed Indication(s)** | For the treatment of patients with chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established. |
| **Recommended:** | Approval |

*This an amended CDTL review. The additions are provided in italics in this review and are based on the new information.*

**1 Introduction**

A single, open-label, multicenter, randomized trial has been submitted as the major trial to support the approval of bendamustine (Treanda®) for the treatment of patients with CLL. The clinical team recommends approval of this NDA on the basis of an improvement in Overall Response Rates (ORR) and Progression-free Survival (PFS).

In this study, Bendamustine was compared to Chlorambucil as a comparator in a treatment-naïve population. The choice of comparator was influenced by the drugs approved in Europe for this indication, where the trial was conducted. Fludarabine, one of the most active drugs for this disease was approved only for second-line use. FDA does not require the use of a standard of care in a randomized study.

Bendamustine is a bifunctional nitrogen mustard derivative. Nitrogen mustard and its derivatives are alkylating agents which dissociate into electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties. The bifunctional covalent linkage can lead to cell death via several pathways. The exact mechanism of action of bendamustine remains unknown.

CLL is a disease that mainly affects the older population, the median age being 72 at diagnosis. Over the past few decades, there has been little progress in prolonging survival of patients with CLL, and it remains an incurable disorder. Because the patients generally have a good long term prognosis and treatment does not change the outcome of disease, a "watch and wait" approach is often used before initiation of treatment. Factors which generally prompt the initiation of therapy include the presence of disease-related symptoms, massive and/or progressive lymphadenopathy or hepatosplenomegaly, bone marrow failure, or recurrent infections. The lymphocyte doubling time should be considered in the total clinical picture but not used as the primary criterion. The routine availability of peripheral blood lymphocyte immunophenotyping has facilitated the diagnosis of CLL in patients with a monoclonal lymphocytosis. Three main phenotypic features define B-CLL: the predominant population shares B-cell markers (CD19, CD20, and CD23) with the CD5 antigen, in the absence of other pan-T-cell markers; the B cell is monoclonal with regard to expression of either κ or *h;* and surface immunoglobulin (sIg) is of low density. Not only are these characteristics generally adequate for a

precise diagnosis, but, importantly, they distinguish CLL from uncommon disorders such as PLL, hairy-cell leukemia, mantle-cell lymphoma, and other lymphomas[1].

The National Cancer Institute-Sponsored Working Group (NCI-WG) published guidelines for the diagnosis and criteria for response for CLL[1]. The peripheral blood should exhibit an increase in the number of small mature-appearing lymphocytes to >5,000/μl. The bone marrow aspirate smear must show >30% of all nucleated cells to be lymphoid. Although a bone marrow examination is rarely required to make the diagnosis of CLL in general practice, it may be evaluable prior to the start of treatment in order to define prognostic factors. Subsequently, a bone marrow examination is indicated primarily to evaluate response to treatment or to assess normal elements if there is an unexplained anemia or thrombocytopenia[1]. Although not approved for this indication, Fludarabine-based regimens are generally used for treatment-naïve patients in the US. Chlorambucil and cyclophosphamide are approved for this patient population. For further details regarding first-line treatment options, please see Medical Officer's Review (MOR).

2. **Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status**

Bendamustine hydrochloride was developed in the 1960s in former East Germany, but was never systematically studied in patients until the 1990s[2]. Per applicant, although it has been used for a variety of malignancies in Germany for over 30 years, re-approval was required by the German law post reunification due to regulatory requirements in the German Democratic Republic. Bendamustine is currently marketed in Germany and Bulgaria.

This randomized study was conducted entirely in Europe by Ribosepharm GmbH, and per applicant, is Cephalon Inc. acquired the rights and using their own statistical analysis plan (SAP), analyzed and submitted the NDA to FDA. This SAP and its approach were discussed with the FDA in a preNDA meeting. FDA asked for details of the SAP, and did not agree (or disagree) to the design due to insufficient information. In an earlier EOP2 meeting with Cephalon, FDA agreed to accept a single randomized study and encouraged the use of an independent response review committee for efficacy evaluation. For further details regarding the regulatory history, please see Dr. Qin Ryan's Medical Officer's Review (MOR). There was no Special Protocol Assessment (SPA) conducted for the protocol.

3. **CMC/Microbiology**

The CMC review was completed by Ravindra K. Kasliwal Ph.D., and cosigned by Ravi Harapanhalli on 2/27/2008. Their recommendation is as below:

"The application is recommended for an approval action for chemistry, manufacturing and controls under section 505 of the Act, provided trademark and labeling acceptability has been determined by Office of Drug Safety (DMETS) and provided the manufacturing sites are deemed acceptable for cGMP compliance. The product quality microbiology has recommended approval on 06-Feb-2008. The recommendation for Office of Compliance regarding the acceptability of the manufacturing facilities is pending as of the date of this review."

3.1 General product quality considerations

According to the microbiology reviewer, Anastasia G. Lolas, M.S., and co-signed by Stephen Langille Ph.D., this NDA is recommended for approval (Date archived: 2/6/2008) from microbiology point of view.

3.2 Facilities review/inspection

*According to C. Cruz, the facilities inspection was found acceptable (memo dated March 17th, 2008).*

3.3Other notable issues

Per CMC review, the company has not provided data showing compatibility of the constitution solution, Sterile Water for Injection, USP, with other commonly available diluents such as [redacted] .The data (assay and impurity profile) should be provided as part of the phase 4 commitment within 6 months of approval of the application (comment for company is provided at the end of this review).

It is recommended in the CMC review that the following be included in the action letter:

"We remind you of your agreement in an amendment dated 12-Feb-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."

**4. Nonclinical Pharmacology/Toxicology**

Pharmacology/Toxicology Review and Evaluation was signed by Anwar Goheer Ph.D. and cosigned by team leader John Leighton Ph.D. on 2/27/2008. According to the review, the nonclinical studies are sufficient to support the approval of this NDA. Excerpt from his review states:

"A. Recommendation on approvability: The non-clinical studies submitted to this NDA provide sufficient information to support the use of Treanda ® (bendamustine hydrochloride) for the treatment of patients with chronic lymphocytic leukemia (CLL)."
"B. Recommendation for nonclinical studies: No additional non-clinical studies are required."
"C. Recommendations on labeling: A separate review will be conducted."

4.1 General nonclinical pharmacology/toxicology considerations

According to Dr Goheer's review, "Bendamustine hydrochloride [Treanda®, Cytostasan® (Germany), and Ribomustine® (Germany)] belongs to bifunctional nitrogen mustards. Nitrogen mustard and its derivatives are alkylating agents which dissociate into electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties. The bifunctional covalent linkage produced can lead to cell death via several pathways. The precise mechanism of action of bendamustine has not been fully characterized."

4.2 Carcinogenicity

As observed in Dr. Goheer's review, bendamustine is a genotoxic alkylating agent. Oral administration for four days induced mammary carcinoma and pulmonary adenomas in mice."

4.3 Reproductive toxicology

Dr. Goheer's review also stated that embryo-fetal developmental studies were not conducted by the sponsor. During embryo-fetal developmental toxicity study, intraperitoneal administration of bendamustine produced embryotoxic and teratogenic effects in mice.

4.4 Other notable issues

Per Dr. Goheer's review, nonclinical safety issues relevant to clinical use were reduction in WBC and lymphocytes were observed in a dose related manner during pivotal repeat dose toxicity studies in rats and dogs. Treatment related microscopic changes were seen in kidneys (tubular degeneration/necrosis) in both species. Cardiomyopathy (focal/multifocal) was observed in male rats only. Heart rates of dogs at 6.6 mg/kg/day were reduced during cycle 2 (2 males & 1 female, 3/6 animals). A vigilant monitoring of QT prolongation is warranted until more clinical experience is gained. Bendamustine is mutagenic, carcinogenic, and teratogenic like other nitrogen mustard alkylating agents. There are no outstanding issues noted in Dr Goheer's review.

## 5 Clinical Pharmacology/Biopharmaceutics

Julie Bullock, Ph.D. was the clinical pharmacology reviewer for this NDA. Her recommendations were as follows:

"This NDA is considered to be deficient from a clinical pharmacology perspective due to the lack of data available regarding pharmacokinetics at the proposed dose, dose proportionality, human excretion and metabolism, effect on QT prolongation, in-vivo drug-drug interactions, and in-vitro p-glycoprotein screens." She recommended that the NDA will be considered acceptable pending the sponsor's agreement to four Phase 4 commitments. "No pharmacokinetic data was obtained at the proposed dose (100 mg/m2 IV over 30-mins) in the proposed CLL patient population. In addition, there were no formal PK dose ranging studies, and no multiple dose pharmacokinetic assessments. A mass-balance study in humans was initiated in 2008. Completion of the mass balance study, assessment of QT prolongation, [redacted], in-vitro p-gp substrate and inhibition screens, and in-vivo interaction studies with a CYP1A2 inhibitor and inducer will be phase 4 commitments. The completion of renal and/or hepatic studies will depend on the outcome of the mass balance evaluation." Dr. Bullock's review was cosigned by Brian Booth Ph.D. on 2/22/2008.

5.1 General clinical pharmacology/biopharmaceutics considerations:

The Clinical pharmacology assessments were mostly based on Studies conducted in patients with Non-Hodgkin's Lymphoma (NHL). As noted by Dr. Booth, Team Leader/Deputy Director, Clinical Pharmacology, "the dose in this patient population is 20% higher than the dose used for CLL patients (100 mg/m$^2$). In the NHL patients, the higher dose was infused for 1 hour (twice as long as CLL patients) and had an elimination half-life of about 5 hours. The Cmax was approximately 5600 ng/ml, and the AUC was approximately 6600 ng·hr/ml. No information is available from these studies regarding the dose proportionality of bendamustine. Bendamustine generates two active metabolites, named M3 and M4. However, concentrations of these metabolites in vivo appear to be 1/10 (M3) and

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