CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-203

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review
Amendment

Date of amendment:	October 28, 2008
From	Amna Ibrahim MD
Subject	Cross-Discipline Team Leader Review
NDA #/Supplement#	22303/000
Applicant	Cephalon, Inc.
Date of Submission	December 12th, 2007
PDUFA Goal Date	October 31st, 2008
Proprietary Name / Established (USAN) names	Bendamustine hydrochloride/Treanda
Dosage forms / Strength	For intravenous use/ single-use 20 mL vials containing 100 mg bendamustine hydrochloride
Proposed Indication(s)	for treatment of patients with indolent B-cell non-Hodgkin's lymphoma (NHL) that have progressed on or within 6 months of treatment with rituximab or a rituximab-containing regimen
Recommended:	Approval

The sentence with the strike through is deleted from page 7 of the original CDTL review, as in the paragraph below.

As expected due to the dosage difference, the rate of adverse reactions is higher in the NHL study than in the CLL study, although caution is advised in drawing conclusions from cross-comparisons. Ms Kwitkowski notes in the clinical review that the population in the NHL study had been previously treated and this may also be a contributing factor. Overall, 68 (68%) patients had dose reductions or dose delays in the major NHL study, most commonly due to neutropenia and thrombocytopenia. Adverse reactions caused deaths in three patients ~~within 30 days of drug administration.~~ These were pulmonary alveolar hemorrhage concurrent with grade 3 thrombocytopenia, neutropenic sepsis and CMV pneumonia.

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

/s/

Amna Ibrahim
10/28/2008 05:41:24 PM
MEDICAL OFFICER

Cross-Discipline Team Leader Review

Date	October 17, 2008
From	Amna Ibrahim MD
Subject	Cross-Discipline Team Leader Review
NDA #/Supplement#	22303/000
Applicant	Cephalon, Inc.
Date of Submission	December 12th, 2007
PDUFA Goal Date	October 31st, 2008
Proprietary Name / Established (USAN) names	Bendamustine hydrochloride/Treanda
Dosage forms / Strength	For intravenous use/ single-use 20 mL vials containing 100 mg bendamustine hydrochloride
Proposed Indication(s)	for treatment of patients with indolent B-cell non-Hodgkin's lymphoma (NHL) that have progressed on or within 6 months of treatment with rituximab or a rituximab-containing regimen
Recommended:	Approval

1. Introduction

Two single arm studies have been submitted to support the approval of bendamustine (Treanda®) for treatment of patients with indolent B-cell non-Hodgkin's lymphoma (NHL) who have progressed on or within 6 months of treatment with rituximab or a rituximab-containing regimen. The clinical team recommends approval of this NDA on the basis of an improvement in Overall Response Rates (ORR) and Duration of Response observed in the larger of these two studies.

NHL is the fifth most common cancer in the United States. It is a heterogenous disease. In 2008, it is estimated that over 50,000 new cases will be diagnosed and approximately 20,000 will die from the disease in the United States. The NHL can be divided by prognostic groups into the indolent lymphomas and the aggressive lymphomas. Approximately 35-40% of NHL patients have indolent lymphoma. This variety of lymphoma occurs more often in patients between the ages of 40 and 70. Fewer than 5% of people with NHL are children. It occurs somewhat more often in men than women. For most people, the cause of NHL is unknown. Though patients with advanced indolent NHL cannot be cured by conventional therapies, patients may live a decade or more with disease, during which time there may initially be watchful waiting or patients may receive multiple treatments.

Improvement in progression-free survival and overall survival has been reported with the use of rituximab and patients expressing CD-20 antigen generally get treated with rituximab, often in combination with chemotherapy. Once the patient is refractory to treatment with rituxan, treatment options are less clear. Purine nucleosides (such as Fludarabine and cladribine), alkylating agents (for example doxorubicin, mitoxantrone, cyclophosphamide and chlorambucil) and corticosteroids are active in NHL. In addition to these agents, Bexxar and Zevalin have been approved for rituximab-refractory NHL. In patients with NHL refractory to rituximab, clinically relevant response rate combined with a meaningful duration of response can be considered clinical benefit.

2. Background

Per applicant, bendamustine, a purine analog alkylating agent, was synthesized as a hybrid molecule intended to combine the activities of the purine antimetabolite, benzimidazole, with the alkylating properties of the bifunctional mechlorethamine nitrogen mustard. It is a bifunctional mechlorethamine

derivative containing a purine-like benzimidazole ring. Mechlorethamine and its derivatives form electrophilic alkyl groups. These groups form covalent bonds with electron-rich nucleophilic moieties, resulting in interstrand DNA crosslinks. The bifunctional covalent linkage can lead to cell death via several pathways. Bendamustine is active against both quiescent and dividing cells. The exact mechanism of action of bendamustine remains unknown.

Bendamustine hydrochloride was developed in the 1960s in former East Germany, but was not systematically studied in patients until the 1990s. 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. In February 2008, bendamustine was approved for the treatment of patients with CLL based on an improvement in progression-free survival in a randomized study. Mundipharma has also filed a marketing application in Europe (using the decentralized procedure) for the use of bendamustine for the treatment of patients with CLL. The dose approved for the CLL indication (100 mg/m^2 infused intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles) is lower than for the proposed NHL indication (120 mg/m^2 administered on Days 1 and 2 of a 21-day cycle, for up to 8 cycles).

In the initial clinical study of single-agent bendamustine in patients with rituximab-refractory indolent NHL, durable responses and an acceptable safety profile were observed. Based on the encouraging results from this study a second larger single arm study was designed in consultation with the USFDA. This second and larger study was the subject of a Special Protocol Assessment (SPA) and the major study design elements for this study were agreed upon by this Division. It was conducted in patients with indolent B-cell non-Hodgkin's lymphoma (NHL) that have progressed on or within 6 months of treatment with rituximab or a rituximab-containing regimen. The primary endpoint of response rate and duration of response were based on the assessments of a central, blinded committee, the "Independent Review Committee" (IRC). The two single arm studies were submitted to support the proposed indication.

3. CMC

According to the CMC review by Ravi Kasliwal PhD,cosigned by Sarah Pope PhD signed on 10/17/2008, "*The chemistry, manufacturing and controls (CMC) section of this NDA has been referenced to the Treanda NDA 22-249 submitted by Cephalon on 19-Sep-2007 and approved on 20-Mar-2008. The CMC information remains the same except that the company has added 2.5% dextrose / 0.45% sodium chloride as a diluent (following reconstitution in vials using sterile water for injection) in addition to 0.9% sodium chloride which was approved in NDA 22-303*".

Dr. Kasliwal also states that "*The trademark was determined to be acceptable under NDA 22-249 review. The Office of Compliance issued an overall acceptable recommendation on 10-Oct-2008*". Dr. Kasliwal concluded that "*Based on the review of additional compatibility data and the previous review of CMC information under NDA 22-249, this application is recommended for an approval action for chemistry, manufacturing and controls under section 505 of the Act*".

For other details of product quality, refer to the CMC review of Treanda in NDA 22303 and NDA 22249.

4. Nonclinical Pharmacology/Toxicology

According to the review of Anwar Goheer PhD signed on 10/22/208, cosigned by Leigh Verbois PhD, *"the non-clinical studies submitted to cross reference NDA 22-249 provide sufficient information to support the use of Treanda ® (bendamustine hydrochloride) 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."*

Dr Goheer states that "*Bendamustine hydrochloride [Treanda®, Cytostasan® (Germany), and Ribomustine® (Germany)] belongs to bifunctional nitrogen mustards. Nitrogen mustard and its derivatives are alkylating drugs 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.*"

Certain mechanisms of actions were not included in the label because of conflicting published reports.

5. Clinical Pharmacology/Biopharmaceutics

According to the clinical pharmacology review by Qi Liu PhD dated 10/27/2008, cosigned by Yaning Wang PhD and Brian Booth PhD

"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."

"The NDA is considered acceptable from a clinical pharmacology perspective."

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The applicant submitted two studies to support the efficacy of bendamustine for treatment of patients with indolent B-cell non-Hodgkin's lymphoma (NHL) that have progressed on or within 6 months of treatment with rituximab or a rituximab-containing regimen. Study SDX-105-03 will be called the major study for the purpose of this review. This study was designed after encouraging results were

observed in an earlier study SDX-105-01 called pilot study in this review. Due to certain weaknesses detailed later, the results from this pilot study were not used for labeling purposes.

According to the applicant, the major study was conducted at 24 study centers in the United States and 4 centers in Canada by 28 investigators from October 2005 through 16 July 2007. Efficacy was based on the assessments by a blinded independent review committee (IRC) and included overall response rate (ORR=CR+CRu+PR) and duration of response (DR). Independent Review Committee assessment was based on modified International Working Group response criteria (IWG-RC)

International Working Group Criteria for Response for NHL

Response category	Physical examination	Lymph nodes	Lymph node masses	Bone marrow
CR	Normal	Normal	Normal	Normal
CRu	Normal	Normal	Normal	Indeterminate
	Normal	Normal	>75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥50% decrease	≥50% decrease	Irrelevant
	Decrease in liver/spleen	≥50% decrease	≥50% decrease	Irrelevant
Relapse or progression	Enlarging liver or spleen , new sites	New or increased	New or increased	Reappearance

From Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas; JCO 17:1244-1253.

Modifications to IWG-RC specified that a persistently positive bone marrow in patients who met all other criteria for CR would be scored as PR. Bone marrow sample lengths were not required to be ≥20 mm for this study. In addition, there were several other minor differences from the IWG-RC.

Patients were treated with 120 mg/m^2 on day 1 and day 2 in treatment cycles that were repeated every 21 days for up 8 cycles. Some criteria required for enrollment as noted in the applicant's study report were:

- The patient had documented relapsed indolent B-cell NHL.
- The patient had disease documented to be refractory to rituximab treatment. Patients could receive additional systemic treatment after the qualifying rituximab regimen and had received treatment with at least 1 previous chemotherapy regimen.
- The patient was at least 18 years old at the time of informed consent, had a bidimensionally measurable disease with at least 1 lesion measuring 2.0 cm or more in a single dimension, had a bone marrow biopsy within 28 days of the first dose of study treatment, had a World Health Organization (WHO) performance status of 0 to 2.
- In patients with thrombocytopenia attributable to bone marrow involvement with NHL, the patient had an absolute neutrophil count (ANC) of 1000 cells/mm^3 or more and a platelet count of 100,000 cells/mm^3 or more, or platelet count 75,000 cells/mm^3 or more, had a creatinine clearance of more than 30 mL/min as determined by Cockroft-Gault calculation, had adequate hepatic function.