

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-203**

**PHARMACOLOGY REVIEW(S)**



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION**

NDA NUMBER:	22-303
SERIAL NUMBER:	001
DATE RECEIVED BY CENTER:	01/17/2008
PRODUCT:	Treanda® (bendamustine hydrochloride)
INTENDED CLINICAL POPULATION:	Non-Hodgkin' Lymphoma (NHL). Approved by the FDA on March 20, 2008 for Chronic Lymphocytic Leukemia (CLL).
SPONSOR:	Cephalon, Inc.
DOCUMENTS REVIEWED:	Electronic submission
REVIEW DIVISION:	Division of Drug Oncology Products (HFD-150)
PHARM/TOX REVIEWER:	M. Anwar Goheer, Ph.D.
PHARM/TOX SUPERVISOR:	Leigh Verbois, Ph.D.
DIVISION DIRECTOR:	Robert Justice, M.D., M.S.
PROJECT MANAGER:	Milinda Vialpando

Date of review submission to Division File System (DFS):   October 22, 2008

## EXECUTIVE SUMMARY

I. **Recommendations**

- A. Recommendation on approvability: 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.
- B. Recommendation for nonclinical studies: No additional non-clinical studies are required.
- C. Recommendations on labeling: Recommendations to the sponsor's proposed labeling are given below.

II. **Summary of nonclinical findings**

A. **Brief overview of nonclinical findings:** 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.

**Pharmacology:** The cytotoxic activity of bendamustine, bendamustine impurities, and bendamustine degradation products had been studied in human tumor cell lines. The antineoplastic activity of bendamustine was tested *in vivo* in xenograft models. In both *in vivo* and *in vitro* tests, bendamustine showed cell cycle effects analogous to other alkylating drugs including cyclophosphamide and chlorambucil.

**Safety pharmacology:** During safety pharmacology testing, bendamustine at 20 and 25 mg/kg affected urine output, urinary electrolyte (kaliuretic and natriuretic) and glomerular filtration rate (creatinine clearance) in Sprague Dawley rats, suggesting dysfunction of glomerular filtration. Histopathology lesions in the kidney were also found in the pivotal rat and dog studies described below. Bendamustine hydrochloride perfused at concentrations of 1.5 and 7.5 µg/mL in isolated canine Purkinje fibers had no statistically significant effect on action potential parameters. Bendamustine at 20 µM and 200 µM significantly inhibited the hERG tail current amplitude and caused a significant deceleration of the tail current decay time constant in HEK 293 cells stably expressing the potassium channel. No effects on hERG channel were seen at 2 µM. The clinical significance of these findings are not clear. However, cardiotoxicity was also noted upon histopathological evaluation in the rat and dog pivotal toxicity studies. Heart failure was also noted in the clinical trials. This finding may translate into adverse effects that need to be fully explored in future clinical trials. A QT evaluation in patients is planned as part of post-marketing (phase 4 commitments).

**Pharmacokinetics:** Bendamustine was metabolized by both dog and human microsomes mainly by Phase 1 metabolism to produce an oxidative metabolite and an N-desmethyl metabolite. These processes appeared to be CYP1A2 mediated. Two active circulating metabolites in human and dog liver preparations were  $\gamma$ -hydroxybendamustine (M3) and N-desmethylbendamustine (M4). The highest tissue levels of bendamustine were in the kidney and liver. The mass balance study in rats showed that significant radioactivity was recovered in both feces (~50%) and urine (~37%). The majority of radioactivity was eliminated rapidly and remained constant from 1 hour to 24 hours.

**Toxicology:** During traditional toxicity assessment, the acute (single dose) toxicity studies were conducted in mice and rats to determine the lethal doses using various routes and are reported in the literature (non-GLP). Bendamustine at 80, or 160 mg/kg/day by stomach tube for 28 consecutive days produced 50% mortalities in rats. Body weight gain and food consumption decreased in a dose dependent manner. Total white blood count and lymphocytes partly recovered in the surviving animals during the recovery phase. There was a dose dependent atrophy of the thymus and inhibition of bone marrow hematopoiesis. Bendamustine at 40 and 60 mg/kg by stomach tube for 90 consecutive days produced 70% and 100% mortalities in Wistar rats, respectively, between week 7 and 14. Prior to death, respiration was impaired and the abdomen of the animals was extremely swollen. White blood cells and lymphocytes were decreased in bendamustine animals. Histopathologically, lymph nodes, spleen and thymus were atrophic.

**Pivotal repeat dose toxicity studies** of 15-weeks intermittent dosing were conducted in Sprague-Dawley rats and beagle dogs (GLP). Male and female Crl:CD (SD) rats (20/sex/group) were dosed bendamustine at 5, 10, or 15 mg/kg/day via 30 minute intravenous infusion once daily for 3 consecutive days in each of five dose cycles. Each dose cycle consisted of 21 days (3 dose days followed by 18 non-dose days). Mortalities (28) occurred in control and test animals throughout the study. Swollen ventral abdomens were observed in control and treated animals. This may be due to infusion apparatus and decreased white blood counts observed in the bendamustine treated groups. Hematological evaluations showed a dose-related decrease in white blood cell and absolute lymphocyte counts. Treatment related microscopic changes were in the kidney (tubular degeneration/ necrosis), heart (cardiomyopathy, focal/multifocal, in male animals only), and bone marrow hyperplasia (femur and sternum). As pointed out in the Pharmacokinetic section, the kidney had high levels of bendamustine and was a significant route of excretion. Bone marrow hyperplasia was not dose-related (4 animals given 5 mg/kg/dose, 1 female given 10 mg/kg/dose, and 1 male given 15 mg/kg/day). All animals with bone marrow hyperplasia died at unscheduled intervals and absence of it in surviving animals suggests that the findings were not test article related or that the timing of the observation was not optimal. The plasma concentrations of bendamustine and both metabolites (M3 & M4) were dose-related over the dose range evaluated. Systemic exposure to bendamustine did not appear to differ consistently with respect to the sex of the animal or the day of dosing. The apparent  $t_{1/2}$  values ranged from 0.14 to 0.36 hr. Concentrations of M3 and M4 were typically below the limit of quantitation by 2 and 1 hour, respectively, after the start of the infusion.

Bendamustine hydrochloride was administered to beagle dogs (3/sex/group) at dosage levels of 1.65, 3.3 or 6.6 mg/kg/day by 30 minute daily intravenous infusion over 4 consecutive days for a total of three treatment cycles. Each cycle was followed by a 31 days recovery period. Three high dose animals (2 males & 1 female) showed deterioration of health and were killed on humane grounds during the recovery phase of the second treatment. Remaining high dose animals were killed on day 29 of this period. Brown/yellow liquid vomitus was noted in treated animals. Body weight loss and reduction in food consumption were noted in both sexes in a dose-related manner. Heart rates were reduced during cycle 2 at 6.6 mg/kg/day (2 males & 1 female, 3/6 animals). Myocardial interstitial inflammation, left atrioventricular valve hemorrhage and leukocytosis were observed in high dose animals. Reduction in WBC counts and lymphocytes were observed in a dose-related manner. Bone marrow suppression (decreased myeloid cells) was observed in animals sacrificed on humane grounds. Lymphoid tissues of high dose animals showed marked or severe changes indicating immunosuppression. Bendamustine also affected testes (seminiferous tubular atrophy), and resulted in mucosal congestion and hemorrhage in the intestines. Systemic exposure was demonstrated at all three dose levels and was dose proportional in cycle 3.

**Genetic toxicology:** Bendamustine induced mutation in Ames test with or without metabolic activation. In the *in vitro* chromosome aberration assay using human lymphocytes, bendamustine produced chromosome aberrations in the presence and absence of metabolic activation. Bendamustine also induced a significant increase in the incidence of micronucleated polychromatic erythrocytes in male and female rats. Hydroxy bendamustine (M3) in the presence and absence of metabolic activation also induced structural chromosomal aberration in human lymphocytes *in vitro*. Therefore, bendamustine is a genotoxic alkylating agent.

**Carcinogenicity:** Although study design in the published paper (Arch Geschwulstforsch 1974; 43(1):16-21) was not adequate to fully assess the carcinogenic potential of bendamustine, intraperitoneal injections of bendamustine for four days produced peritoneal sarcoma in mice. Oral administration for four days induced mammary carcinoma and pulmonary adenomas in mice. Pulmonary adenoma showed signs of malignancy accompanied by pleural rupture dedifferentiation. The evaluations of carcinogenic potentials for oncology drugs are usually not required.

**Developmental and reproductive toxicity:** Embryo-fetal developmental studies were not conducted by the sponsor. Published non-GLP studies referenced by the sponsor have not been adequately conducted to fully evaluate the developmental toxicity of bendamustine. During embryo-fetal developmental toxicity study, intraperitoneal administration of bendamustine produced embryotoxic and teratogenic effects in mice. Malformations observed included exencephaly, cleft palates, and dwarfism (decreased body weights). Bendamustine (ip administration) also caused external (bent/circinate tail) and internal (hydronephrosis and hydrocephalus) malformation in Wistar rats. These developmental findings clearly demonstrate bendamustine as a nitrogen mustard alkylating agent.

**Local tolerance:** Perivenous injection of bendamustine at a concentration of 0.6 or 1.0 mg/ml or intra-arterial injection at a concentration of 0.2 or 0.6 mg/mL produced local irritation at the injection sites in the ear of New Zealand White rabbits.

**B. Pharmacologic activity:** 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. This bifunctional covalent linkage produced can lead to cell death via several pathways. The exact mechanism of action of bendamustine remains unknown.

**C. Nonclinical safety issues relevant to clinical use:** 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; a clinical study is planned as a part of post-marketing. Bendamustine is mutagenic, carcinogenic, and teratogenic like other nitrogen mustard alkylating drugs.

## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### 2.6.1 INTRODUCTION AND DRUG HISTORY

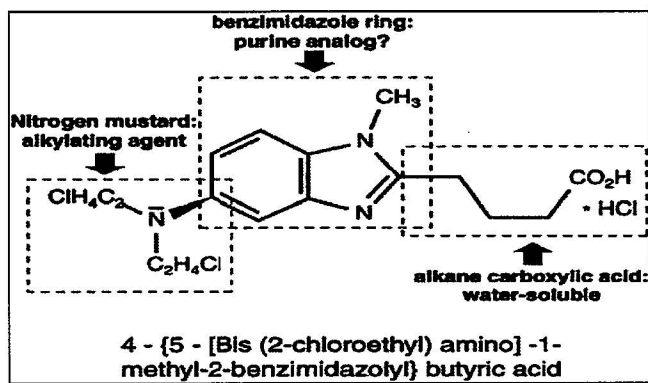
**NDA number:** 22-303  
**Review number:** 1  
**Sequence number/date/type of submission:** 001 / 05-14-2008 / NDA  
**Information to sponsor:** Yes (X) No ( )  
**Sponsor and/or agent:** Cephalon, Inc.  
 41 Moores Road, Frazer, PA 19355  
**Manufacturer for drug substance:** (b) (4)

**Reviewer name:** M. Anwar Goheer, Ph.D.  
**Division name:** Division of Drug Oncology Products  
**HFD #:** 150  
**Review completion date:** 10-22-2008

#### Drug:

**Trade name:** Treanda  
 Cytostasan<sup>®</sup> (Germany) and Ribomustine<sup>®</sup> (Germany)  
**Generic name:** N/A  
**Code name:** BM1, CEP-18083, ID00039, ID00275, ID08736, IMET3393,  
 M000275, M000039, M008736, SDX-105, and ZIMET3393  
**Chemical name:** Bendamustine hydrochloride.  
 1H-Benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1-methyl- monohydrochloride, or  
 2-Benzimidazole butyric acid, 5-[bis(2-chloroethyl)amino]-1-methyl-, monohydrochloride.  
**CAS registry number:** 3543-75-7  
**Molecular formula/molecular weight:** C<sub>16</sub>H<sub>21</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub>.HCl /  
 358.3 (free base) and 394.7 (hydrochloride)

#### Structure:



**Relevant INDs/NDAs/DMFs:** IND 67,554, NDA 22-249  
**Drug class:** Cytotoxic alkylating agent  
**Intended clinical population:** Non-Hodgkin's Lymphoma (NHL)  
**Clinical formulation:** Lyophilized powder for injection (100 mg/vial)

## Composition of drug product

Component	Reference to Standard	Function	Amount per Vial
Bendamustine HCl	In house standard	Active Ingredient	100 mg
Mannitol	USP	(b) (4)	170 mg
(b) (4)	ACS		-
Water for Injection <sup>a</sup>	USP		-

<sup>a</sup> Removed during (b) (4)

(Excerpted from the sponsor's submission)

**Route of administration:** Intravenous infusion over 60 minutes

**Proposed Use:** Treanda® is indicated for the treatment of patients with indolent B-cell non-Hodgkin's lymphoma who have progressed during or following treatment with rituximab or a rituximab-containing regimen. The recommended dose is 120 mg/m<sup>2</sup> administered as an intravenous infusion over 60 minutes on days 1 and 2 of a 21 days cycle, for 6-8 cycles.

**Disclaimer:** Tabular and graphical information are constructed by the reviewer unless cited otherwise.

This NDA was submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Treanda (bendamustine hydrochloride).

**Data reliance :** Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-303 are owned by Cephalon Inc. or are data for which Cephalon has obtained a written right of reference. Any information or data necessary for approval of NDA 22-303 that Cephalon does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Cephalon does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-303.