CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208194Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Date: November 10, 2015
From: Christopher M. Sheth, PhD
Pharmacology/Toxicology Supervisor
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology and Oncology Products (OHOP)
Re: Approvability for Pharmacology and Toxicology
NDA: 208194
Drug: Bendamustine hydrochloride
Indications: Chronic lymphocytic leukemia and B cell non-Hodgkin lymphoma
Applicant: Eagle Pharmaceuticals, Inc.

I have examined the pharmacology/toxicology supporting review for bendamustine HCl conducted by Dr. Manning. I concur with Dr. Manning's conclusion that bendamustine HCl may be approved for the proposed indication.

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/s/

CHRISTOPHER M SHETH
11/10/2015

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 208194
Supporting document/s:	1
Applicant's letter date:	February 12, 2015
CDER stamp date:	February 13, 2015
Product:	Bendamustine hydrochloride (HCl)
Indication:	Chronic lymphocytic leukemia (CLL)
	B cell non-Hodgkin lymphoma (NHL)
Applicant:	Eagle Pharmaceuticals, Inc (EPI)
Review Division:	Division of Hematology Oncology Toxicology (DHOT) for Division of Hematology Products (DHP)
Reviewer:	Michael L Manning, PhD (DHOT)
Supervisor/Team Leader:	Christopher M Sheth, PhD (DHOT)
Division Director:	John Leighton, PhD, DABT (DHOT)
	Ann Farrell, MD (DHP)
Project Manager:	Laura Wall, MS, APHN, OCN

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 208194 are owned by EPI or are data for which EPI has obtained a written right of reference. Any information or data necessary for approval of NDA 208194 that EPI 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 reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 208194.

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1 Executive Summary

1.1 Introduction

Treanda® (bendamustine HCl) is an alkylating agent approved in 2008 for the treatment of two indications: 1) indolent B cell non-Hodgkin lymphoma (NHL) that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen, and 2) chronic lymphocytic leukemia (CLL). The Applicant, EPI, is seeking marketing approval for a liquid formulation of bendamustine HCl which can be administered as a 50 mL admixture over an infusion time of 10 minutes, whereas Treanda® must be administered as a 500 mL admixture over a 30-60 minute infusion time. Also unlike Treanda®, EPI's bendamustine HCl formulation may be diluted in a 5% dextrose solution. EPI's bendamustine HCl formulation is intended to be administered via the same route, at the same dose levels, and for the same indications as Treanda®.

In 2014 EPI received tentative marketing approval for (b) (4) bendamustine HC (b) (4) EPI has not submitted any new nonclinical studies since their previous NDA submission and subsequent tentative marketing approval. The nonclinical aspects of EPI's liquid formulation of bendamustine HCl was reviewed by Christopher M Sheth, PhD under NDA 205580. The current review examines the findings of high concentrations of bendamustine HCl but otherwise relies on the conclusions of Dr. Sheth's review.

1.2 Brief Discussion of Nonclinical Findings

EPI's liquid formulation of bendamustine HCl is (b) (4). In the current application, EPI is relying in part upon the Agency's previous findings of safety and efficacy for Treanda® as described in the drug's approved labeling. EPI's nonclinical testing strategy was designed in accordance with FDA/CDER Draft Guidance for Industry and Review Staff: *Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route* (March 2008). EPI submitted reports to assess the hemolytic and irritant potential of bendamustine HCl at a concentration of up to 5.6 mg/mL, the highest final admixture concentration covering the clinical dose range. These reports were previously reviewed by Dr. Sheth during the review of NDA 205580.

EPI conducted a GLP-compliant local tolerance study in rabbits evaluating the irritation potential of bendamustine HCl administered by intended (intravenous, IV) and unintended (perivascular, PV) routes of administration. IV administration of EPI's bendamustine HCl, Treanda®, and their respective placebos were associated with a similar degree of minor trauma and do not represent a toxicologically significant concern. PV administration of EPI's bendamustine HCl was associated with local macroscopic and microscopic irritation that was not observed with Treanda® or either placebo. The irritation extended up to 2 cm from the injection site and was followed by

epidermal hyperplasia, consistent with normal tissue repair processes. The clinical relevance of findings limited to the PV route of administration is uncertain.

The hemolytic potential of EPI's bendamustine HCl was assessed alongside Treanda® and their respective placebos in a GLP-compliant study. Human whole blood was incubated with test articles at a 1:1 ratio for 30 minutes at 37ºC. No hemolysis was observed in any of the samples tested, except for the positive control.

1.3 Recommendations

1.3.1 Approvability

From the Pharmacology/Toxicology perspective, bendamustine HCl, administered as a 50mL admixture over an infusion time of 10 minutes, may be approved for the proposed indications.

1.3.2 Additional Non Clinical Recommendations

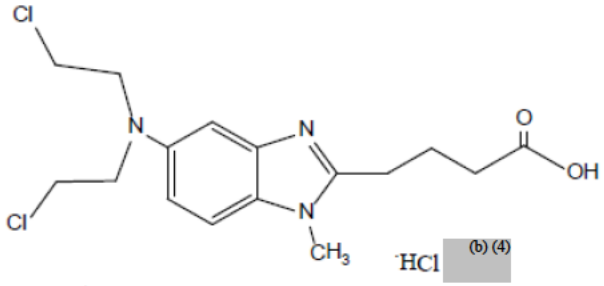
None

1.3.3 Labeling

The nonclinical sections of the label will be comparable to the label of the listed drug Treanda®.

2 Drug Information

2.1 Drug

CAS Registry Number:	3543-75-7
Generic Name:	Bendamustine HCl
Code Name:	Not applicable
Chemical Name:	1H-Benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-methyl-,hydrochloride (1:1)
Molecular Formula:	$C_{16}H_{21}Cl_2N_3O_2 \cdot HCl \cdot$ (b) (4)
Molecular Weight:	(b) (4) g/mol
Structure:	
Pharmacologic Class:	Alkylating drug

2.2 Relevant INDs, NDAs, BLAs and DMFs

- IND 116448 (bendamustine HCl concentrate for injection): nonclinical information contained in the current NDA was previously submitted to IND 116448.

- NDA 205580 (bendamustine HCl [redacted] for injection): EPI received tentative marketing approval for [redacted] bendamustine HCl on July 2, 2014.
- NDA 022249 (Treanda®): Cephalon Inc received marketing approval for the lyophilized powder formulation of bendamustine HCl on March 20, 2008.
- DMF [redacted] (bendamustine HCl)

2.3 Drug Formulation

EPI's bendamustine HCl drug formulation (see Table 1) [redacted] EPI is seeking approval of bendamustine HCl when administered as a 50 mL admixture over an infusion time of 10 minutes (see Table 2), whereas Treanda® is administered as a 500 mL admixture over an infusion time of 30 minutes (CLL) or 60 minutes (NHL). EPI is proposing bendamustine HCl to be diluted in 50 mL of one of the following diluents:

- 0.9% Sodium Chloride Injection, USP; or
- 2.5% Dextrose/0.45% Sodium Chloride Injection, USP; or
- 5% Dextrose Injection, USP.

In contrast, Treanda® is to be diluted in 500 mL of one of the following diluents:

- 0.9% Sodium Chloride Injection, USP; or
- 2.5% Dextrose/0.45% Sodium Chloride Injection, USP.

Table 1: Comparison of Treanda® (lyophilized powder and sterile solution) and EPI's bendamustine HCl formulation

Product	Treanda® (bendamustine HCl) for injection (100 mg vial[a])		Treanda® (bendamustine HCl) injection, 90 mg/mL (180 mg/2 mL[b])		EPI bendamustine HCl injection, 25 mg/mL (100 mg/4 mL)	
Dosage form	Lyophilized powder		Sterile solution		Sterile solution	
How supplied	Single use vial		Single use vial		Multi-use vial (up to 28 days after initial use)	
Composition	**Ingredients**	**Amount per vial**	**Ingredients**	**Amount per vial**	**Ingredients**	**Amount per vial**
	BDM HCl	100 mg	BDM HCl	180 mg	BDM HCl	100 mg
	Mannitol, USP	170 mg	Propylene Glycol, USP	648 mg	Monothioglycerol, NF	20 mg
			N,N-Dimethylacetamide (DMA), EP	1172 mg	Propylene Glycol, USP	[redacted]
					Polyethylene Glycol 400 (PEG 400), NF[c]	

BDM = bendamustine; DMA = N,N-Dimethylacetamide; EP = European Pharmacopeia; HCl = hydrochloride; NF = National Formulary; PEG = polyethylene glycol; USP = United States Pharmacopeia

[a] Treanda® (bendamustine HCl) for injection (Lyophilized) is also available in a 25 mg vial which has the same product composition.

[b] Treanda® (bendamustine HCl) injection (Sterile Solution) is also available in a 45 mg/0.5 mL vial, which has the same product composition.

[c] PEG 400 acidity may be modified using sodium hydroxide (NaOH) in water-for-injection solution.

Table 2: Comparison of Treanda® (lyophilized powder and sterile solution) and EPI's bendamustine HCl preparation and final solution properties

Product	Treanda® (bendamustine HCl) for injection (100 mg vial)[a]	Treanda® (bendamustine HCl) injection 90 mg/mL (180 mg/2 mL vial)[b]	EPI bendamustine HCl injection 25 mg/mL (100 mg/4 mL vial)
Reconstitution	Reconstitute with sterile water for injection to yield a solution of 5 mg/mL	No reconstitution needed	No reconstitution needed
Further dilution before infusion	Withdraw required dose and dilute into 500 mL bag of: 0.9% Sodium Chloride Injection, USP, or 0.45% Sodium Chloride /2.5% Dextrose Injection, USP	Withdraw required dose and dilute into 500 mL bag of: 0.9% Sodium Chloride Injection, USP, or 0.45% Sodium Chloride /2.5% Dextrose Injection, USP	Withdraw required dose and dilute into 50 mL bag of: 0.9% Sodium Chloride Injection, USP, or 0.45% Sodium Chloride /2.5% Dextrose Injection, USP, or 5% Dextrose Injection, USP
Infusion duration	30-60 minutes	30-60 minutes	10 minutes
Final admixture concentration covering dose range	0.2 mg/mL to 0.6 mg/mL	0.2 mg/mL to 0.7 mg/mL	1.85 mg/mL to 5.6 mg/mL
pH of final admixture	3.4 to 3.9[c]	(Not measured)	3.2[d]
Admixture stability	24 hours when stored refrigerated (2-8°C [36-46°F]) or 3 hours when stored at room temperature (15-30°C [59-86°F]) and room light	24 hours when stored refrigerated (2-8°C [36-46°F]) or 2 hours when stored at room temperature (15-30°C [59-86°F]) and room light	24 hours when stored refrigerated 2-8°C [36-46°F]) or 3 hours [5% dextrose, USP] when stored at room temperature (15-30°C [59-86°F]) and room light or 6 hours [0.9% Sodium Chloride Injection, USP, or 0.45% Sodium Chloride/2.5% Dextrose Injection, USP] when stored at room temperature (15-30°C [59-86°F]) and room light

HCl = hydrochloride; USP = United States Pharmacopeia
[a] Treanda® lyophilized product, also available in 25 mg vial
[b] Treanda® liquid product, also available in 45 mg vial
[c] Reference: (b) (4)
[d] Reference: Toxicology Rabbit Local Tolerance Study No.13-2342

2.4 Comments on Novel Excipients

The excipients contained in EPI's current bendamustine HCl drug formulation (for 50 mL admixture) (b) (4)

2.5 Comments on Impurities/Degradants of Concern

The impurities contained in EPI's current bendamustine HCl drug formulation (for 50 mL admixture) (b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population for EPI's bendamustine HCl is identical to that of Treanda®. EPI is proposing bendamustine HCl to be administered as a 50 mL admixture over an infusion time of 10 minutes, whereas Treanda® is to be administered as a 500 mL admixture over an infusion time of 30 minutes (CLL) or 60 minutes (NHL). Otherwise, the proposed dosing regimen for EPI's bendamustine HCl (b) (4) Treanda®.

2.7 Regulatory Background

Treanda® is marketed by Cephalon Inc and first received FDA approval on March 20, 2008 for the lyophilized powder formulation of bendamustine HCl (NDA 022249). On September 13, 2013, Cephalon Inc received FDA approval for the liquid formulation of Treanda®. On July 2, 2014 EPI received tentative approval for (b) (4) bendamustine HCl under NDA 205580.

A pre-NDA meeting was held with EPI on December 17, 2014 at which the Agency instructed EPI to submit a new NDA to obtain approval of the low-volume admixture of bendamustine HCl. No non-clinical issues were discussed at this meeting.

EPI's low-volume admixture of bendamustine HCl received Orphan Drug Designation for both chronic lymphocytic leukemia (CLL) and NHL indications on July 2, 2014 [NHL-ODD#14-4303 and CLL-ODD#14-4318].

3 Studies Submitted

3.1 Studies Reviewed

Study Title	eCTD Module
Hemolytic Properties of Test and Reference Formulations of Bendamustine Hydrochloride in Human Whole Blood (# 8280095)	4.2.3.7
Single Dose Intravenous and Perivascular Tolerance Study of Bendamustine Containing Formulations in Male Rabbits (# 13-2342)	4.2.3.6

3.2 Studies Not Reviewed

Study Title	eCTD Module
Hemolytic Properties of Test and Reference Formulations of Bendamustine Hydrochloride in Human Whole Blood (# 8264313)	4.2.3.7
Single Dose Intravenous and Perivascular Tolerance of Bendamustine-Containing Formulations in Male Rabbits (# 12-2298)	4.2.3.6
Single Dose Perivascular Tolerance of Bendamustine-Containing Formulations in Male Rabbits with a 21-Day Recovery Period (# 12-2311)	4.2.3.6

3.3 Previous Reviews Referenced

The nonclinical aspects of EPI's current liquid formulation of bendamustine HCl were reviewed by Christopher M Sheth, PhD under NDA 205580 (Reference ID: 3425918). No new nonclinical studies have been submitted since Dr. Sheth's review. This review examines the findings of high concentrations of bendamustine HCl but otherwise relies on the conclusions of Dr. Sheth's review.

4 Pharmacology

No pharmacology studies were submitted.

5 Pharmacokinetics/ADME/Toxicokinetics

No pharmacokinetic/ADME/toxicokinetic studies were submitted.

6 General Toxicology

No general toxicology studies were submitted.

7 Genetic Toxicology

No genetic toxicology studies were submitted.

8 Carcinogenicity

No carcinogenicity studies were submitted.

9 Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies were submitted.

10 Special Toxicology Studies

EPI's bendamustine HCl [redacted] (b) (4) approved drug substance with a proposed route of administration [redacted] (b) (4) the listed drug. EPI's nonclinical testing strategy was designed in accordance with FDA/CDER Draft Guidance for Industry and Review Staff: *Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route* (March 2008). EPI submitted reports to assess the hemolytic and irritant potential of bendamustine HCl at a concentration of up to 5.6 mg/mL, the highest final admixture concentration covering the clinical dose range.

Hemolysis study:

The hemolytic potential of EPI's bendamustine HCl was compared to that of Treanda® using human whole blood as a substrate. Test samples were prepared as follows:

- EPI's bendamustine HCl (25 mg/mL) was diluted with saline across a range from 0.7 to 5.6 mg/mL;
- Treanda® was diluted with saline to 0.61 mg/mL;
- Human plasma was used for negative control;

– 1% Saponin was used for positive control.

Human whole blood was collected on the day of testing from a fasted volunteer and incubated with test articles at a 1:1 ratio for 30 minutes at 37ºC. Samples were centrifuged and hemolysis was evaluated by spectrophotometric analysis for hemoglobin in the supernatant. No hemolysis was observed in any of the samples tested, except for the positive control (see Table 5 in Dr. Sheth's review).

Local tolerance study:

The single dose IV and PV tolerance of EPI's bendamustine HCl was compared to that of Treanda® in rabbits. The study was intended to assess the irritation potential for intended (IV) and unintended (PV) routes of administration.

Male albino New Zealand white rabbits were 4.5 to 5.5 months of age and weighed 2.8 to 3.2 kg at the initiation of dosing. Three rabbits/group received a single dose of IV or PV administered test article and corresponding placebo in the left and right ear, respectively. EPI's bendamustine HCl and Treanda® were administered at a concentration of 5.6 mg/mL and 0.6 mg/mL, respectively (see Table 3). EPI's bendamustine HCl was administered as an IV infusion over 10 minutes in accordance with the proposed label while Treanda® was administered as an IV infusion over 30 minutes in accordance with the currently approved label. To evaluate the unintended route of administration, test articles and corresponding placebos (250 µL) were injected PV to simulate extravasation. Rabbits were observed for 96-hours post-dose, after which animals were sacrificed for further macroscopic and microscopic examination of both ears.

Table 3: Local tolerance study: summary of experimental design

Group	Dose					Number of male animals			
	Route	Dose[a] (mg/kg IV or mg PV)	Volume (mL per dose)	BDM conc.[a] (mg/mL)	Infusion duration minute/rate (mL/min)	Total	Left ear[a]	Right ear[a]	96-hour necropsy
1 = Treanda® / Treanda® placebo	IV	5	25	0.6	30/0.83[b, c]	3	3	3	3
2 = BDM in saline / BDM placebo	IV	5	2.7	5.6	10/0.27[b, c]	3	3	3	3
3 = Treanda® / Treanda® placebo	PV	0.15	0.25	0.6	NA	3	3	3	3
4 = BDM in saline / BDM placebo	PV	1.4	0.25	5.6	NA	3	3	3	3

BDM = bendamustine hydrochloride
[a]Doses represent active pharmaceutical ingredient as administered to the left ear. Placebo formulations (0 mg; 0 mg/mL) were administered to the right ear. For the IV groups the dose was presented as mg/kg, for the PV groups the dose was presented as mg administered.
[b]These rates assumed a rabbit body weight of 3 kg. The rate/minute was adjusted in accordance with the actual body weight to reach the 5 mg/kg target in the specified infusion duration (of either 10 or 30 minutes)

[c]As the volumes and infusion rates changed based on the body weights, the following dose volumes were used: 8.3 mL/kg (5 mg/kg ÷ 0.6 mg/mL) for Group 1; 0.89 mL/kg (5 mg/kg ÷ 5.6 mg/mL) for Group 2. For consistency, the same dose volumes were used for the placebos.
The first day of dosing was defined as Day 1 of the study.

IV administration of EPI's bendamustine HCl, Treanda®, and their respective placebos were well tolerated at all concentrations. The types and degree of findings were typical of the trauma associated with injection procedures and do not represent a toxicologically significant concern (see Table 4).

PV administration of EPI's bendamustine HCl was associated with local irritation that was not observed with Treanda® or either placebo. The irritation extended up to 2 cm from the injection site and was characterized by macroscopic scabs and red discoloration, and microscopic findings of moderate to marked edema/collagen degeneration, slight mixed inflammation, minimal to slight hemorrhage and slight to moderate epidermal pustules and erosion/ulceration of the overlying epidermis. During the 96-hour post-dose observation period epidermal hyperplasia was noted, consistent with normal tissue repair processes.

Table 4: Local tolerance study: dermal, macroscopic, and microscopic findings of test article and placebo preparations

	Treanda ® in saline (0.6 mg/mL)	Treanda ® placebo in saline	BDM in saline (5.6 mg/mL)	BDM placebo in saline	Treanda ® in saline (0.6 mg/mL)	Treanda ® placebo in saline	BDM in saline (5.6 mg/mL)	BDM placebo in saline
Dose (route)	5 mg/kg (IV)		5 mg/kg (IV)		0.15 mg (PV)		1.4 mg (PV)	
Number of animals	3		3		3		3	
Noteworthy findings								
Died/euthanized moribund	0	0	0	0	0	0	0	0
Body weight (%)	-	-	-	-	-	-	-	-
Dermal evaluation								
Erythema slight	1	0	1	1	0	0	1	2
Erythema moderate	1	1	1	0	0	0	1	0
Bruising	0	0	0	0	0	0	1	0
Eschar	0	0	0	0	0	0	0	1
Gross pathology								
Discolored	0	0	2	1	0	0	2	2
Scab	2	1	0	0	0	0	1	2
Histopathology (injection site)								
Edema/collagen degeneration	1	2	0	0	1	1	3	2
Mixed inflammation	0	0	0	1	0	1	2	0
Hemorrhage	1	1	1	0	0	1	2	1
Hyperplasia, epithelial	0	0	0	0	0	0	2	0

	Treanda ® in saline (0.6 mg/mL)	Treanda ® placebo in saline	BDM in saline (5.6 mg/mL)	BDM placebo in saline	Treanda ® in saline (0.6 mg/mL)	Treanda ® placebo in saline	BDM in saline (5.6 mg/mL)	BDM placebo in saline
Dose (route)	5 mg/kg (IV)		5 mg/kg (IV)		0.15 mg (PV)		1.4 mg (PV)	
Epidermal pustule, erosion/ulceration	0	0	0	0	0	0	2	0
Scab	0	0	1	0	0	0	2	0
Thrombus	0	0	0	1	0	0	0	0
Histopathology (2 cm d stal to injection site)								
Edema/collagen degeneration	1	1	0	0	0	0	3	0
Mixed inflammation	0	0	0	0	0	0	2	0
Hemorrhage	0	0	0	0	0	0	2	0
Hyperplasia, epithelial	0	0	0	0	0	0	2	0
Epidermal pustule, erosion/ulceration	0	0	0	0	0	0	1	0
Scab	0	0	0	0	0	0	1	0
Histopathology (4 cm d stal to injection site)								
Edema/collagen degeneration	0	0	0	0	0	0	2	1
Mixed inflammation	0	0	0	0	0	0	1	0
Hemorrhage	0	2	1	0	1	0	1	0

BDM = bendamustine hydrochloride

11 Integrated Summary and Safety Evaluation

See Executive Summary

12 Appendix/Attachments

None

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

/s/

MICHAEL L MANNING
10/01/2015

CHRISTOPHER M SHETH
10/01/2015