CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205580Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

Application Number	NDA 205580 SDN 38
Letter Date of Submission	January 31, 2018
Product Name (Trade and generic, code)	Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL)
Route of Administration	Intravenous Injection
Proposed Indication	Treatment of Chronic Lymphocytic Leukemia (CLL) and Indolent B-Cell non-Hodgkin Lymphoma (NHL)
Submission Type	Resubmission Class 1
Sponsor	Eagle Pharmaceuticals, Inc.
Related Applications	NDA205580 SDN 8
Prior Reviews (Application number, Submission type, Date)	NDA 205580, (b) (4) , May 29, 2014

On September 6, 2013, Eagle Pharmaceuticals, Inc. submitted a 505(b)(2) New Drug Application (NDA 205580) for Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL) in a 500 mL admixture for the treatment of Chronic Lymphocytic Leukemia (CLL) and Indolent B-Cell non-Hodgkin Lymphoma (NHL). The Agency gave a tentative approval on July 2, 2014. The approval was tentative due to CMC, labeling and patent rights infringement issues.

Dr. Y-J. Moon reviewed (DARRTS 5/29/2014) the clinical pharmacology information in the 2013 submission. Dr. Moon's review states (indented):

> Although the Eagle bendamustine HCl product has a higher concentration (25 mg/mL) than the reconstituted listed drug (LD) (5 mg/mL), after dilution in the admixture vehicle the concentration is the same between the two products. Therefore, the actual dose that will be administered to patients and the infusion time to administer that dose has not changed. A request for waiver for requirement to conduct bioequivalence testing is included in this NDA.
>
> ONDQA-Biopharmaceutics review stated (DARRTS Communication date: 5/13/14) that the Applicant provided appropriate information/data justifying that the higher osmolality range of their product (when compared to that of the listed product), will not have an impact on the clinical safety profile of their proposed bendamustine HCl product. Also it was stated that the absence of mannitol and inclusion of monothioglycerol, propylene glycol, and PEG 400 in the proposed formulation does not affect the distribution and/or elimination of bendamustine HCl (when compared to those of the listed product) and that the Applicant's response included evidence from literature supporting the safety of the intravenous infusions of bendamustine HCl solutions containing the proposed

concentrations of monothioglycerol, propylene glycol, and PEG 400. ONDQA-Biopharmaceutics recommended approval and granted a Biowaiver.
This submission contains no new clinical pharmacology information for review. NDA 205580 is recommended for approval from the standpoint of clinical pharmacology.

Recommendation

This submission contains no new clinical pharmacology information for review. Consistent with clinical pharmacology's 2013 recommendation, NDA 205580 is recommended for approval from the standpoint of clinical pharmacology.

Signatures

Christy S John, Ph.D. Reviewer Division of Clinical Pharmacology V	Gene Williams, Ph.D. Team Leader Division of Clinical Pharmacology V
Cc:	DHP: RPM – L. Wall; MO – A. Schwarsin; MTL – A. de Claro
	DCP-V: DDD – B. Booth; DD – A. Rahman

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/s/

CHRISTY S JOHN
03/20/2018

GENE M WILLIAMS
03/20/2018
I concur with the recommendation

Clinical Pharmacology Memorandum	
NDA	205580 SDN 8
Submission Date:	6 September 2013
Drug Name:	Bendamustine HCL, 100 mg/4 mL (25 mg/mL)
Sponsor:	Eagle Pharmaceuticals, Inc.
OCP Reviewers:	Young Jin Moon, Ph.D.
OCP Team Leader:	Julie M. Bullock, Pharm.D.

This 505(b)(2) application relies on the FDA's finding of safety and effectiveness for the listed drug, TREANDA® (bendamustine HCl) marketed by Teva Pharmaceuticals under the approved NDA 22249. Bendamustine HCl, an alkylating agent, is approved for the treatment of chronic lymphocytic leukemia (CLL) and indolent Non-Hodgkin Lymphoma (NHL). Dosing regimen is 100 mg/m^2 infused intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles for CLL and 120 mg/m^2 infused intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles for NHL.

Eagle's Bendamustine HCl is intended for the same indications and by the same dosing regimen. The difference and similarity of the two products are detailed as follows.

TREANDA (bendamustine HCl) for Injection has two vial sizes, 100 mg of bendamustine HCl lyophilized powder in a 20 mL amber glass vial and 25 mg of bendamustine HCl lyophilized powder in a 8 mL amber glass vial. Both have the exact same compositions. Eagle's Bendamustine HCl Injection, 25 mg/mL has only one presentation as 100 mg of bendamustine HCl in 4 mL solution in a 5 mL clear glass vial. A comparison between the TREANDA 100 mg presentation and Eagle Bendamustine HCl, 25 mg/mL is provided in Table 1 below.

Table 1. Comparison of Treanda 100 mg Vial and Eagle's Bendamustine HCl Injection, 25 mg/mL (100 mg/4 mL)

Product	**Treanda (bendamustine HCl) for Injection (100 mg vial)**		**Bendamustine HCl Injection, 25 mg/mL (100 mg/4 mL)**	
Dosage Form	Lyophilized powder		Sterile Solution	
Composition	***Ingredients***	***Amount per vial***	***Ingredient***	***Amount per vial***
	Bendamustine HCl	100 mg	Bendamustine HCl	100 mg
	Mannitol, USP	170 mg	Monothioglycerol, NF	20 mg
			Propylene Glycol, USP	0.4 mL
			Polyethylene Glycol 400 (PEG 400), NF*	QS to 4 mL

(b) (4)

The preparation of the product solutions for infusion is different as follows.

Table 2. Comparison of Preparation and Final Solution for Infusion

Product		Treanda (bendamustine HCl) for Injection (100 mg vial)		Bendamustine HCl Injection, 25 mg/mL (100 mg/4 mL)	
Reconstitution		Reconstituted with sterile water for injection to yield a solution of 5 mg/mL		No reconstitution is needed (A ready to dilute solution of 25 mg/mL)	
Further Dilution prior to Infusion		Withdraw require 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 require dose and dilute into 500 mL bag of 0.9% Sodium Chloride Injection, USP or 0.45% Sodium Chloride/2.5% Dextrose Injection, USP.	
Final Solution for Infusion*	Admixture Concentration Covering Dose Range	0.2 mg/mL	0.6 mg/mL	0.2 mg/mL	(b) (4) mg/mL
	pH	(b) (4)			
	Osmolarity (mOsm/kg)				

Although the Eagle bendamustine HCl product has a higher concentration (25 mg/mL) than the reconstituted listed drug (LD) (5 mg/mL), after dilution in the admixture vehicle the concentration is the same between the two products. Therefore, the actual dose that will be administered to patients and the infusion time to administer that dose has not changed. A request for waiver for requirement to conduct bioequivalence testing is included in this NDA.

ONDQA-Biopharmaceutics review stated (DARRTS Communication date: 5/13/14) that the Applicant provided appropriate information/data justifying that the higher osmolality range of their product (when compared to that of the listed product), will not have an impact on the clinical safety profile of their proposed bendamustine HCl product. Also it was stated that the absence of mannitol and inclusion of monothioglycerol, propylene glycol, and PEG 400 in the proposed formulation does not affect the distribution and/or elimination of bendamustine HCl (when compared to those of the listed product) and that the Applicant's response included evidence from literature supporting the safety of the intravenous infusions of bendamustine HCl solutions containing the proposed concentrations of monothioglycerol, propylene glycol, and PEG 400. ONDQA-Biopharmaceutics recommended approval and granted a Biowaiver.

This submission contains no new clinical pharmacology information for review. NDA 205580 is recommended for approval from the standpoint of clinical pharmacology.

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/s/

YOUNG J MOON
05/29/2014

JULIE M BULLOCK
05/29/2014

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 205580	**Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	September 6, 2013		
Division:	Division of Hematology Products	**Team Leader:** Angelica Dorantes, PhD	
Applicant:	Eagle Pharmaceuticals, Inc.	**Acting Supervisor:** Richard Lostritto, PhD	
Trade Name:	TBD	**Date Assigned:**	September 6, 2013
Established Name:	Bendamustine HCl concentrate for Injection	**Date of Review:**	May13, 2014
Indication:	For the treatment of patients with: • Chronic lymphocytic leukemia (CLL). • Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.	**Type of Submission:** Resubmission of original New Drug Application – 505(b)(2)	
Dosage form/ strengths	Concentrated solution for IV infusion/ 25 mg/mL		
Route of Administration	IV infusion		
Type of Review:	Biowaiver Request		

SUBMISSION:

The Applicant is seeking approval of a New Drug Application (NDA) for Bendamustine HCl concentrate for Injection under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. This 505(b)(2) application relies on the FDA's previous findings of safety and efficacy for the listed drug, Treanda® for Injection (bendamustine hydrochloride for injection) marketed by Cephalon (a subsidiary of Teva Pharmaceutical) under the approved NDA 22249 and NDA 22303. The proposed formulation is a ready-to-dilute solution, and will not require reconstitution as is the case for the listed drug, Treanda®, which is a lyophilized powder. The proposed product is a self-preserving, multiple-use drug containing vial.

BIOPHARMACEUTICS INFORMATION:

The proposed bendamustine HCl Injection has a different presentation from the listed Treanda® product and was designed as a concentrated liquid to eliminate the reconstitution

step during preparation of the product for administration. The proposed product is intended for the same indications and has the same active ingredient, final admixture bendamustine HCl concentration, dose, dosing regimen, and route of administration as the reference drug. The differences and similarities of the two products are summarized as follows:

Comparison of the Formulations for the Listed and Proposed Drug Products

Product	**Listed Product** **Treanda (bendamustine HCl) for Injection (100 mg vial)**		**Proposed Product** **Bendamustine HCl Injection, 25 mg/mL (100 mg/4 mL)**	
Dosage Form	Lyophilized powder		Sterile Solution	
Composition	***Ingredients***	***Amount per vial***	***Ingredient***	***Amount per vial***
	Bendamustine HCl	100 mg	Bendamustine HCl	100 mg
	Mannitol, USP	170 mg	Monothioglycerol, NF	20 mg
			Propylene Glycol, USP	0.4 mL
			Polyethylene Glycol 400 (PEG 400), NF*	QS to 4 mL

(b) (4)

Comparison of the preparation, stability and final solution for infusion

Product		**Listed Product** **Treanda (bendamustine HCl) for Injection (100 mg vial)**		**Proposed Product** **Bendamustine HCl Injection, 25 mg/mL (100 mg/4 mL)**	
Reconstitution		Reconstituted in 20 mL sterile water for injection to yield a solution of 5 mg/mL		No reconstitution is needed (A ready to dilute solution of 25 mg/mL)	
Storage Condition before dilution		The reconstituted solution must be transferred to the infusion bag within 30 minutes of reconstitution.		A partially used vial is proposed to be stable for up to 28 days when stored in its original carton at refrigeration (2-8°C or 36-46°F).	
Further Dilution prior to Infusion		Withdraw require 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 require dose and dilute into 500 mL bag of 0.9% Sodium Chloride Injection, USP or 0.45% Sodium Chloride/2.5% Dextrose Injection, USP.	
Storage Condition after dilution		Stable for 24 hours when stored refrigerated (2-8°C or 36-47°F) or for (b) (4) hours when stored at room temperature (15-30°C or 59-86°F) and room light (per approved label).		Proposed to be stable for 24 hours when stored refrigerated (2-8°C or 36-47°F) or for 3 hours when stored at room temperature (15-30°C or 59-86°F) and room light.	
Final Solution for Infusion*	**Admixture Concentration Covering Dose Range**	**0.2 mg/mL**	**0.6 mg/mL**	**0.2 mg/mL**	(b) (4) **mg/mL**
	pH	(b) (4)			
	Osmolarity (mOsm/kg)				

Despite the formulation differences with regards to the inactive ingredients between the listed drug, Treanda for Injection and the proposed product, the Applicant claims that both products as administered to the patient (i.e. final admixture) are similar in terms of the physicochemical properties, pH and osmolality.

The difference in inactive ingredients in terms of concentration, for a maximum dose of 324 mg (based upon a 2.7 m^2 patient) is shown in the following table:

Listed Product **Treanda for Injection** **(after Reconstitution, 5 mg/mL)**		**Proposed Product** **Eagle Bendamustine HCl** **(concentrate 25 mg/mL)**	
Formulation Volume to deliver 324 mg bendamustine HCl: 65 mL		Formulation Volume to deliver 324 mg bendamustine HCl: 13 mL	
Final Admixture Volume: 565 mL		Final Admixture Volume: 513 mL	
Ingredients	Concentration in 500 mL admixture	Ingredient	Concentration in 500 mL admixture
Bendamustine HCl	**0.6 mg/mL**	**Bendamustine HCl**	(b) (4) **mg/mL**
		Monothioglycerol, NF	0.13 **mg/mL**
Mannitol, USP	1.0 mg/mL	Propylene Glycol, USP	0.0025 mL/mL
		Polyethylene Glycol 400 (PEG 400), NF	0.023 mL/mL

BIOWAIVER REQUEST:

The NDA includes a request for a waiver of the CFR requirement to submit data from an *in vivo* bioequivalence study, based on the similarity between the proposed product and the listed product.

Based on 21 CFR 320.22(b)(1) such a waiver can be granted if the drug product:

i) Is a parenteral solution intended solely for administration by injection, and
ii) Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

In further support of the Biowaiver, the solubility of bendamustine HCl was determined in normal saline (0.9% NaCl). For the bendamustine HCl salt, normal saline was chosen since it is a poor solvent relative to 0.45% saline/2.5% dextrose due to the potential for a common ion (Cl-) effect. The solubility of bendamustine at 25°C was determined to be 3.97 mg/mL. The solubility increases further due to the addition of propylene glycol in the proposed admixture (> 4 mg/mL). These results show that the proposed drug product admixture (up to and including the maximum dose) is a true solution of bendamustine HCl (no precipitation).

ASSESSMENT OF THE BIOWAIVER REQUEST:

According to CFR 320.22(b), for certain drug products the in vivo bioavailability (BA) or bioequivalence (BE) of the drug product may be self-evident and FDA can waive the requirement for the submission of in vivo BA or BE data of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident if the drug product meets the following:

Is a parenteral solution intended solely for administration by injection, and

Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

The proposed bendamustine HCl for injection product, when diluted, contains the same concentration of active ingredient but different inactive ingredients compared to the diluted listed product, Treanda. In support of the Biowaiver request, the pH and osmolality comparison data were provided. These data showed very similar pH values for the diluted solutions of the proposed and the listed drug products; but with respect to osmolarity, the data showed a lower osmolality range (b) (4) mOsm/kg) for the diluted listed product when compared to the proposed diluted product (b) (4) mOsm/kg). With regards to the diluted drug product stability, both the listed and the proposed diluted drug products appear to be unstable and show degradation of the active ingredient, bendamustine HCl. This degradation occurs regardless of the difference in the inactive ingredients.

Since a justification/information was needed to support that; **1)** the observed difference in the osmolality range of the proposed drug product when compared to that of the listed product did not have any clinical impact, and **2)** the differences in the inactive ingredients (i.e., absence of mannitol and inclusion of monothioglycerol, propylene glycol, and PEG 400 in the proposed formulation) did not affect the distribution and/or elimination of bendamustine HCl, the following **Information Request** was conveyed to the Applicant in the NDA's filing letter dated 9/16/13:

1. Provide a justification for the difference in osmolality between your proposed diluted drug product and the reference diluted drug product. Include information demonstrating that the observed difference in osmolality does NOT affect the safety profile of your bendamustine HCl product.

2. Provide information indicating whether the absence of mannitol and inclusion of monothioglycerol, propylene glycol, and PEG 400 in your proposed formulation affect or NOT the distribution and/or elimination of bendamustine HCl (when compared to those of the RLD product). Also, submit evidence from literature supporting the safety of the intravenous infusions of bendamustine HCl solutions containing the proposed concentrations of monothioglycerol, propylene glycol, and PEG 400.

On 10/15/13, the Applicant addressed the IR comments and submitted the following information:

1. The osmolality values reported in the admixture study are summarized here:

Comparison of Treanda 100 mg Vial and Eagle's Bendamustine HCl Injection, 25 mg/mL (100 mg/4 mL) Admixtures:

Product	Eagle	Treanda	Eagle	Treanda	Eagle	Treanda	Eagle	Treanda
Admixture Vehicle	0.9% NaCl		2.5% Dextrose/ 0.45%NaCl		0.9% NaCl		2.5% Dextrose/ 0.45%NaCl	
BDM HCl Concentration (mg/mL)	0.2		0.2		(b) (4)		(b) (4)	
Measured Osmolality (mOsm/kg)[a]	(b) (4)							
Volume of admixture after addition of drug product (mL)[b]								
Estimated Molality (moles/kg								
BDM HCl	(b) (4)							
Mannitol								
Monothioglycerol								
PG								
PEG 400								

[a] n=2 per set of vehicle/concentration combinations
[b] Assumes ideal mixing and volumes are additive

As a point of reference, the osmolality of normal saline is approximately 300 mOsmol/kg. The osmolality of serum (human) normally ranges from 287 to 300 mOsmol/kg. The proposed admixture drug product's osmolality is hypertonic and always higher than that of Treanda which is consistently hypotonic.

The potential of formulation changes (including osmolality) to impact the safety profile was addressed in preclinical studies. The hemolytic properties of Eagle Bendamustine HCl Concentration for Injection were assessed *in vitro* with human whole blood. A comparison to the listed drug, Treanda, was also investigated. Additionally, a local irritation study in rabbits was conducted to assess potential local irritation that could arise from these admixtures. The results of these studies indicate that Bendamustine HCl Injection (Eagle) is not hemolytic at bendamustine HCl concentrations of 0.7 to 5.6 mg/mL.

These concentrations exceed the approved clinical administration concentration of Treanda (admixture: up to (b) (4) mg/mL). There was no evidence of venous irritation after intravenous administration of Bendamustine HCl Injection at concentrations up to 5.6 mg/mL (for a total dose of 5 mg/kg). Perivenous administration of Bendamustine HCl Injection (diluted in saline) at 3.2 to 5.6 mg/mL resulted in observations of local irritation (with evidence of reversibility). The severity of the irritation observed was more notable than that seen with Treanda. This observation is consistent with a dose and/or concentration relationship for the perivascular tolerance of bendamustine HCl as illustrated by an increase in perivascular irritation potential seen with higher doses/

concentrations of bendamustine HCl administered in pilot studies, and is unlikely due to the osmolarity of treatments as administered. Finally, the range of osmolality values noted for the final admixtures of Eagle's bendamustine HCL injection product ((b) (4) mOsm/kg) are well within the range observed for commonly administered IV products, and are also within the range for which the risk of injection/infusion related complication (such as phlebitis) would be considered low. Gazitua *et.al.,* classified three risk levels for phlebitis caused by infusate osmolarity, in which the lowest risk was observed for solutions less than 450 mOsm/L. The Infusion Nursing Society (INS) recommends an upper limit of 500 mOsm/L for peripheral vein tolerance (with higher values permissible when administration is into fast-flowing major vessels).

2. Recently, a new version of Treanda (bendamustine HCl) Injection, a liquid formulation (as a nonaqueous solution) for intravenous infusion (after dilution in saline or dextrose saline), was approved for marketing in the US. This new liquid formulation contains 90 mg/mL of bendamustine HCl, 324 mg/mL propylene glycol and 586 mg/mL N,N, dimethylacetamide (DMA). Mannitol, which is in the lyophilized Treanda formulation, has been eliminated in the new version. The pharmacokinetic profile relating to distribution and elimination for bendamustine remains the same between the two products. Nonclinical evidence also suggests that the absence of mannitol and presence of propylene glycol does not impact the distribution and/or elimination of bendamustine:

Pharmacokinetic Parameters of Bendamustine in Cynomolgus Monkeys after 3 mg/kg IV Bendamustine Hydrochloride:

Parameter	TREANDA	Formulation (b) (4)
Co, ng/mL	8664 ± 3841	10716 ± 2033
C_{max}, ng/mL	6037 ± 2456	7380 ± 1170
t_{max}, hr	0.083 [0.083 for all]	0.083 [0.083 for all]
AUC_{0-t}, ng*hr/mL	2313 ± 800	2853 ± 398
$AUC_{0-\infty}$, ng*hr/mL	2314 ± 800	2854 ± 398
λ_z, hr^{-1}	1.220 ± 0.111	1.295 ± 0.108
$t_{1/2}$	0.57	0.54
CL, L/hr/kg	1.27 ± 0.40	0.96 ± 0.14
V_z, L/kg	1.04 ± 0.36	0.74 ± 0.05
V_{ss}, L/kg	0.34 ± 0.11	0.26 ± 0.05
$MRT_{0-\infty}$, hr	0.26 ± 0.02	0.27 ± 0.02

Based upon the reported information, the elimination of mannitol and the addition of propylene glycol did not cause a change in the reported distribution nor elimination of bendamustine or its metabolites. The amount of propylene glycol administered at the maximum bendamustine HCl dose at a concentration of 0.7 mg/mL from Treanda (bendamustine HCl) Injection is 1166 mg. This value is comparable to the maximum amount of propylene glycol to be administered via the Eagle product, 1238 mgs. Therefore, a change in distribution or elimination of bendamustine would not be expected from such a small difference in the amount of propylene glycol (as no change was evident following inclusion of PG in the Treanda liquid product).

PEG 400 has been reported to affect renal elimination of drugs at intravenous doses of 1000 to 2000 mg/kg. The dose of PEG 400 from the Eagle product (in a 120 mg/m2 bendamustine HCl dose) is well below these values, ~173 mg/kg for a 70 kg patient. As noted in the Treanda package insert, there was no "meaningful" effect of renal impairment on the pharmacokinetics of a high dose of bendamustine HCl (120 mg/m2). Further, Dubbelmen and coworkers found that renal clearance of bendamustine ranged from 6.6 to 29.9 mL/min and renal excretion was minor (3% of dose), concluding that accumulation was not likely in cancer patients with renal impairment due to dose administration schedule and short half-life of bendamustine. This would suggest that even if PEG 400 negatively impacted renal elimination of drugs at 173 mg/kg, bendamustine elimination would not be affected. Furthermore, Johnson and coworkers studied the effects of PEG 400 on P-glycoprotein mediated efflux of digoxin and the cytochrome P450 (CYP3A) mediated metabolism of verapamil. The results of that work indicated that although PEG 400 does affect these enzyme systems it lacks the potency of typical enzyme inhibitors. Egger-Heigold examined the potential of PEG 200 to modify the blood distribution and protein binding of model compounds *in vitro*. PEG 200 did not modulate the blood distribution or protein binding of the compounds studied. Based upon the available information, PEG 400 impact on bendamustine metabolism, distribution or elimination would not be expected. A literature search on the effects of monothioglycerol on the pharmacokinetics of drugs, specifically disposition and elimination, has been performed. Relevant references were not found. Monothioglycerol is a commonly used antioxidant in parenteral products. Monothioglycerol as with the other excipients in the Eagle product, PG and PEG 400, are listed in the FDA CDER database on Inactive Ingredients (IIG) for Approved Drug Products for parenteral administration.

Reviewer's Assessment of Applicant's Responses: SATISFACTORY

1. The Applicant provided appropriate information/data justifying that the higher osmolality range of their product (when compared to that of the listed product), will not have an impact on the clinical safety profile of their proposed bendamustine HCl product. The Medical Reviewer, Dr. Adam George, has indicated that he agrees with this conclusion.(see his review in DARRTS dated 5/13/14).

2. The provided information adequately supports the Applicant's response stating that the absence of mannitol and inclusion of monothioglycerol, propylene glycol, and PEG 400 in the proposed formulation does not affect the distribution and/or elimination of bendamustine HCl (when compared to those of the listed product). Also, the response included evidence from literature supporting the safety of the intravenous infusions of bendamustine HCl solutions containing the proposed concentrations of monothioglycerol, propylene glycol, and PEG 400.

RECOMMENDATION:

ONDQA-Biopharmaceutics had reviewed the overall information/data supporting the approval of the Biowaiver request and considers that the provided information is adequate and acceptable.

A waiver from the CFR's requirement to provide data from an *in vivo* bioequivalence study for the IV route of administration is granted. From the Biopharmaceutics perspective, NDA 205580 for Bendamustine HCl for Injection (25 mg/mL) is recommended for APPROVAL.

Signature	**Signature**
Elsbeth Chikhale, Ph.D.	Angelica Dorantes, Ph.D.
Biopharmaceutics Reviewer	Biopharmaceutics Team Leader
Office of New Drug Quality Assessment	Office of New Drug Quality Assessment

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/s/

ELSBETH G CHIKHALE
05/13/2014

ANGELICA DORANTES
05/13/2014