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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

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

/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.

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