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APPLICATION NUMBER:

205580Orig1s000

CLINICAL REVIEW(S)

Clinical Review
Division of Hematology Products

NDA #:	205580
SDN:	38
Drug(s):	bendamustine
Applicant:	Eagle
Primary Reviewer:	Alexandria Schwarsin, MD
Received Date:	January 31, 2018

This is a 505(b)(2) application. Clinical information for review was not included in the application. The clinical team participated in labeling meetings and agreed with the final Prescribing Information.

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/s/

ALEXANDRIA N SCHWARSIN
03/21/2018

YVETTE L KASAMON
03/21/2018

File Memorandum

NDA: 205580

Applicant: Eagle Pharmaceuticals, Inc.

Product: Bendamustine injection 100 mg/4 mL

Submission date: June 30, 2013

Review Completion Date: Electronic Stamp

Clinical reviewer: Adam George, PharmD.

Clinical team leader: Virginia Kwitkowski, M.S., R.N., A.C.N.P.-B.C.

Regarding: Clinical review of NDA 205580

Application background

The Applicant has submitted a 505(b)(2) application for a ready to dilute injection formulation of Bendamustine hydrochloride. The listed product Treanda® (bendamustine hydrochloride) is a lyophilized powder formulation which requires reconstitution. No clinical data investigating the use of the Applicant's proposed ready to dilute formulation were submitted with this application. On January 8, 2014 the Applicant submitted a 120 day safety update. (b) (4) [redacted] These data are not applicable to NDA 205580 (b) (4) [redacted]

During review of the application the biopharmaceutics review identified a potential clinical issue with the Applicant's proposed formulation in that the Applicant's formulation once diluted for administration has a higher osmolality than the listed product. The CMC discipline sent the Applicant an Information Request to provide justification for the difference in osmolality between the proposed diluted drug product and the reference diluted drug product. In their response the Applicant provided Table 1.

Table 1 Comparison of Treanda and Applicant Proposed 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)			
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

The Applicant addressed the potential of formulation changes (including osmolality) to impact the safety profile was addressed in preclinical studies. The hemolytic properties of the Applicant's formulation 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.

Reviewer comment: It is the opinion of this reviewer that the increased osmolality of the Eagle formulation of bendamustine will not result in a clinically meaningful increase in toxicities associated with administration of a hyperosmotic intravenous solution (i.e., phlebitis and/or infusion site reactions). In clinical practice chemotherapy is typically administered to patients via central venous access (e.g., peripherally inserted central catheter or Hickman catheter). Administration of chemotherapeutic agents through central venous access minimizes the risks of phlebitis associated with drugs that are hyperosmolar due the increased venous blood flow with central venous access. An article by Gazitua et al evaluated the risk of phlebitis based upon the osmolality of the infusate. The lowest identified risk group was solutions with an osmolarity lower than 450 mOsm/L. The upper limit for the range of osmolality with the proposed Eagle formulation is (b) (4) mOsm/kg.[1]

The listed drug Treanda is labeled for phlebitis and infusion site reactions which will also be communicated in the prescribing information for this (b)(2) formulation. In addition, it would not be feasible to conduct a clinical trial to quantify the possible increased risk of phlebitis with the Applicant's hyperosmolar formulation compared to Treanda as this would require an extremely large number of patients.

[1] Gazitua R, et al. Factors determining peripheral vein tolerance to amino acid infusions. *Arch Surg* 1979;114:897-900.

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