CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208194Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	See electronic signature stamp
From	Janice Brown, M.S.
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 208194
Applicant	Eagle Pharmaceuticals, Inc.
Date of Submission	February 13, 2015 (received February 13, 2013)
PDUFA Goal Date	December 13, 2015
Proprietary Name / Established (USAN) names	BENDEKA (bendamustine hydrochloride)
Dosage forms / Strength	Injection, 100 mg/4 mL (25 mg/mL)
Proposed Indication(s)	For 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.
Recommended:	Approval, pending an acceptable recommendation from the Office of Study Integrity and Surveillance (OSIS) of the bioequivalence clinical site inspections

Include the following in the action letter:

A shelf life of 24 months is granted for Bendeka (bendamustine hydrochloride) Injection, when stored in refrigerator at 2 - 8°C (36 - 46°F), protected from light.

1. Introduction

Bendamustine hydrochloride (HCl) is a small molecule, alkylating agent approved for treatment of patients with chronic lymphocytic leukemia (CLL) and indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

The current application for Bendamustine HCl injection is submitted as a 505(b)(2) NDA. The proposed drug product is a ready-to-dilute solution, and does not require reconstitution, as is the case for the listed drug product, Treanda (bendamustine) for injection, which is a lyophilized powder. The proposed drug product is self-preserving and is intended for multiple-uses. (b) (4) the proposed bendamustine HCl injection also must be diluted in 500 mL of 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP prior to intravenous infusion.

2. Background

The subject of the current NDA application is a new formulation for bendamustine HCl. The applicant for this NDA is relying upon information in the public domain (labeling for approved bendamustine HCl product and published studies about bendamustine HCl) to support the safety and efficacy of the proposed product.

(b) (4) New information in NDA 208194 includes a modification of the dose preparation and administration, allowing administration of the product in a smaller volume (50 mL admixture) over a shorter time period (10 minutes), three options for admixtures, drug product stability data to support a 24 month shelf life, a BE study, and a safety and tolerability profile of bendamustine HCl injection when infused over 10 minutes in a 50 mL admixture volume.

Eagle received tentative approval for the companion NDA 205580, bendamustine HCl injection (b) (4) on July 2, 2014 for (b) (4) indolent B-cell NHL only.

3. CMC

Drug Substance: Bendamustine HCl is a (b) (4) nonspecific DNA alkylating agent. It is a bifunctional mechlorethamine derivative containing a purine-like benzimidazole ring. Mechlorethamine forms electrophilic alkyl groups that form covalent bonds with electron-rich nucleophilic moieties, resulting in interstrand DNA crosslinks. The bifunctional covalent linkage in the DNA leads to cell death.

The chemical name of bendamustine HCl is 1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1 methyl, monohydrochloride. Bendamustine HCl is a (b) (4) powder. (b) (4)

The CMC information for the drug substance was provided in DMF No. (b) (4) from (b) (4) The applicant provided adequate reference to their Type II DMF (b) (4) for information pertaining to the drug substance, bendamustine HCl. Bendamustine HCl is (b) (4) The DMF contains the necessary information related to manufacturing, characterization, physical properties, manufacture, process controls, analytical methods, specification, validation, container closure system, reference standard and stability data for bendamustine HCl. DMF (b) (4) was reviewed and found adequate to support the manufacture of a drug product as a solution dosage form by Joyce Crich, Ph.D. on May 6, 2014. There is no new quality update provided in the DMF since the last review.

Stability data supports a retest period of (b) (4) months for bendamustine HCl drug substance packaged (b) (4)

The NDA included minor drug substance updates and the drug substance reviewer found the information adequate to support the NDA 208194 (refer to the drug substance section of the integrated quality assessment signed by Nina Ni on September 21, 2015).

Drug Product: Bendeka (bendamustine HCl) injection is a ready-to-dilute non-aqueous solution formulation of Bendamustine HCl intended for intravenous administration after further dilution in 50 mL of either 0.9% Sodium Chloride Injection, USP, 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP.

Bendamustine is susceptible to hydrolysis and undergoes rapid degradation (b) (4) Polyethylene glycol 400 (PEG 400) (b) (4) propylene glycol (PG), (b) (4) Monothioglycerol is present at a concentration of 5 mg/mL (b) (4) Sodium hydroxide is used in the formulation to adjust the pH of PEG 400. The excipient levels, in terms of maximum daily dose in the drug product and the admixture are below the levels used in currently approved parenteral drug products.

A shelf life of 24 months is granted for Bendeka (bendamustine HCl) Injection, when stored refrigerated at 2 - 8ºC (36 - 46ºF), protected from light. Storage precautions are required as the

drug product is light sensitive. The primary container must be kept in the secondary packaging in order to protect the drug product from light. Accordingly, the following statement was put on the vial and carton labels: "*Retain in original package until time of use. Protect from light.*"

At the request of the CDTL, the drug product reviewer included the following information on the compatibility of the drug product and admixes in the infusion bags. The drug product review included the following information,

> "However, in the NDA 208194, the applicant did not provide compatibility study in terms of leachable/extractables for the diluted products which contain (b) (4) monothioglycerol, PG, and PEG 400 while prepared and stored in infusion bags. The in-use stability studies provided in the NDA 208194 mainly focused on the stability in terms of assay and degradation products of diluted bendamustine solutions while stored in infusion bags.
>
> Lack of compatibility study is deemed acceptable based on the following risk assessments:
>
> ☐ PG and monothioglycerol are present in the drug product at very low concentrations ((b) (4)%, respectively). (b) (4) PEG 400 is very hydrophilic and is present at no more than (b) (4)% in the admixture solutions. Thus, both formulation and admixtures are considered low risk in terms of extraction power.
>
> ☐ According to USP <88>, extraction in PEG 400 is not required for Class IV plastics. Therefore, the risk associated with presence of PEG 400 for Class IV plastics which is the proposed admixture bags is expected to be low given that USP <88> does not require PEG 400 extraction for Class IV plastics.
>
> ☐ The contact time for admixture solutions in the infusion bags is considered short which is no more than 6 hours at room temperature or no more than 24 hours at refrigerator. The total infusion time is only 10 minutes. Therefore, as a summary, the drug product is considered compatible with the proposed infusion bags as well as all the other commercially available transfer devices, including adaptor, syringe, filter, and tubing."

The CDTL agrees with this risk assessment.

No drug product issues which preclude approval were found and the drug product reviewer found the information adequate to support the approval of NDA 208194 (refer to the drug product section of the integrated quality assessment signed by Nina Ni on September 21, 2015).

Process Review – Drug Product: The manufacturing and packaging process of Bendamustine HCl Injection consists of the following unit operations:

(b) (4)

(b) (4)

The commercial batch size is (b) (4). Bendamustine HCl Injection is light sensitiv (b) (4)

(b) (4)

The drug product manufacturing process was reviewed and found acceptable and the process reviewer recommended approval of the NDA (refer to the process section of the integrated quality assessment signed by Vidya Pai on October 5, 2015).

Facilities review and inspection: There are no significant, outstanding manufacturing risks and the Office of Process and Facilities found the facilities acceptable. Based on the firm's inspectional history and district file review, the manufacturing facilities as listed below for NDA 208194 are acceptable.

Drug Substance Facilities

1. (b) (4) Acceptable Based on District Recommendation
2. (b) (4) Acceptable Based on Profile

Drug Product Facilities

1. (b) (4) Acceptable Based on District Recommendation
2. (b) (4) Acceptable Based on Profile

Microbiology Review: The drug product is (b) (4) The sterilization of the equipment and container closure is appropriately qualified and operated using validated loading patterns. Microbiological attributes, container-closure, package integrity, and the preservative effectiveness and bacterial endotoxin testing are adequate to support the microbiological quality for this drug product.

Bendamustine HCl is a multi-use vial. Although it does not contain any antimicrobial preservative, bendamustine HCl is bacteriostatic and does not support bacterial growth. The partially used vials are stable for up to 28 days when stored in its original carton under refrigeration (2°C - 8°C or 36°F - 46°F). Each vial is not recommended for more than six (6) dose withdrawals (see drug product review for the companion NDA by Erika A. Pfeiler on May 14, 2014). After first use, the partially used vial should be stored in original carton at 2 °C to 8 °C, and then discarded after 28 days. The in-use stability for the 50 mL diluted

product in 5% Dextrose Injection is 3 hours at room temperature and 24 hours at refrigerated conditions.

The microbiology section was reviewed and found acceptable (refer to the microbiology section of the integrated quality assessment signed by Vinayak Pawar, Ph.D. on October 14, 2015).

4. Nonclinical Pharmacology/Toxicology

According to the nonclinical review, "The nonclinical aspects of EPI's (b) (4) formulation of bendamustine HCl were reviewed by Christopher M. Sheth, Ph.D. 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."

The nonclinical review concluded that the "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."

An additional study evaluating 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.

The nonclinical reviewer recommended approval of the NDA for bendamustine HCL injection administered as a 50mL admixture over an infusion time of 10 minutes, for the proposed indications (see review by Michael Manning, Ph.D., final signature October 1, 2015).

Pharmacology/Toxicology has no concerns with the nonclinical findings and the excipients used for Eagle's bendamustine HCl injection at the defined level (b) (4)

5. Clinical Pharmacology/Biopharmaceutics

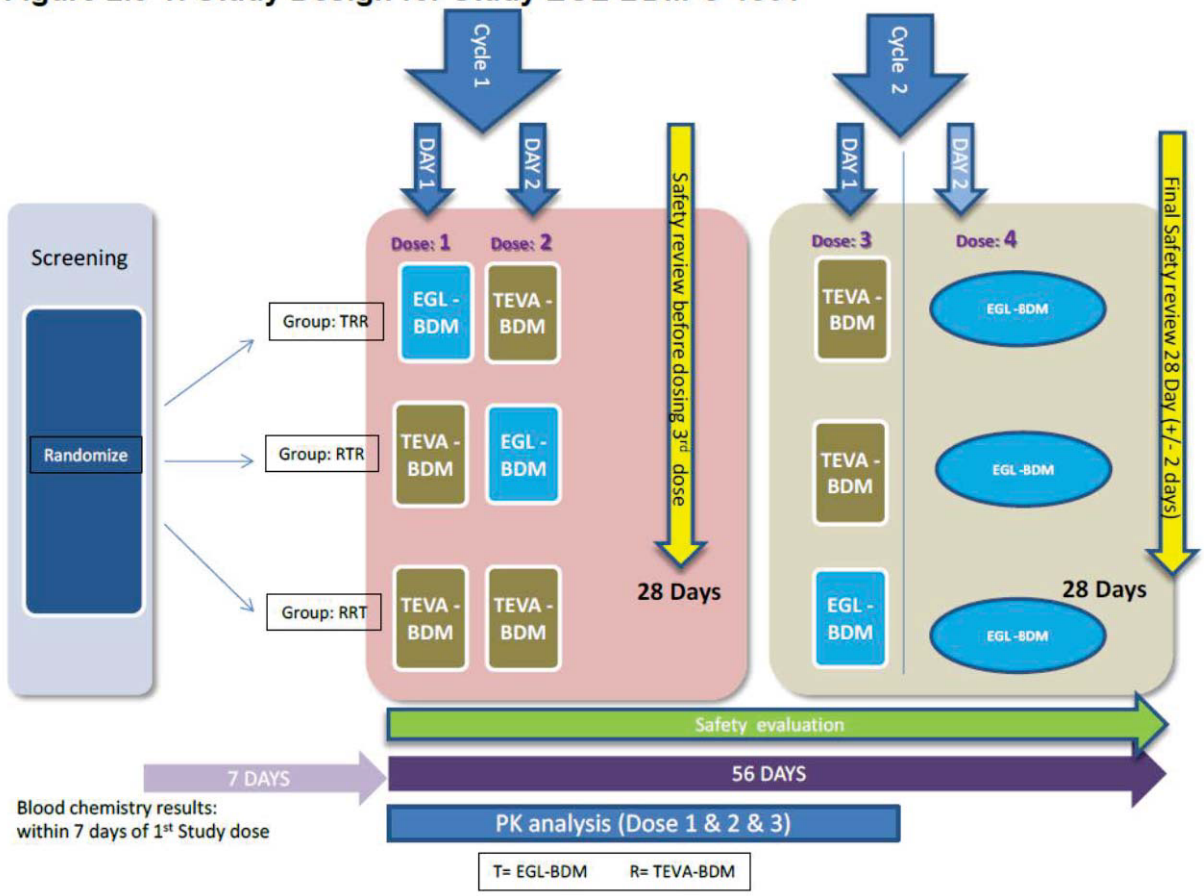
Clinical Pharmacology: The bioequivalence study was reviewed by the OPQ biopharmaceutics team, therefore, there is no Clinical Pharmacology review for this NDA.

Biopharmaceutics: The applicant conducted a Phase 1, open-label, crossover, randomized, bioequivalence study (# EGL-BDM-C-1301) to evaluate Eagle's Bendamustine (BDM) Hydrochloride (HCl) injection and Treanda for injection (Teva- BDM) administered to patients with a histologically confirmed diagnosis of cancer (solid tumors and hematologic malignancies excluding chronic lymphocytic leukemia [CLL]) who had progressed or relapsed on standard therapy, or for whom no curative or standard therapy was appropriate. The primary objective of Study EGL-BDM-C-1301 was to demonstrate that the Eagle-BDM formulation is bioequivalent to the currently marketed Teva- BDM with respect to total bendamustine systemic exposure (AUC). The maximum peak plasma concentration (Cmax) value for Eagle-BDM is higher than Teva-BDM due to the 6-fold increase in administration rate for the Eagle-BDM (10 minutes versus 60 minutes).

The reference product (Teva-BDM; 120 mg/m2) was replicated across 2 periods and the test product (Eagle-BDM; 120 mg/m2) was administered once over the 2 treatment cycles for PK evaluation (allowing for 3 treatments per patient) to determine whether the two BDM HCl formulations were bioequivalent: (1) Eagle-BDM was given IV over 10 minutes, and (2) Teva-BDM was given IV over 60 minutes (see figure 2.5.1 for the study design reproduced below).

A total of 102 patients were screened, of which 83 were randomized into 3 study cohorts based on treatment sequences. Of the 83 patients randomized into a treatment sequence, two patients were not dosed; therefore, a total of 81 patients received at least one dose of study drug. Of these 81 patients, 60 patients completed all 3 study treatment doses.

Figure 2.5-1: Study Design for Study EGL-BDM-C-1301



According to the biopharmaceutics review, four (4) PK Evaluable (PKE) sub-populations were evaluated:

- FDA-requested population for primary BE analysis: n=60, who received 3 doses of BDM, which included 22 patients who completed 3 doses but had major infusion-related deviations or PK sample collection deviations;
- FDA-requested population for secondary BE sensitivity analysis: n=57, who received 3 doses of BDM, but excluding the 2 patients with major PK sample collection deviations and 1 patient with a major infusion-related deviation;
- Eagle original proposed population for primary BE analysis: n=44, who received 3 doses of BDM without deviations, plus 6 patients with PK sampling deviation but used for interim analysis;
- Eagle original proposed population for secondary BE sensitivity analysis: n=38, who received 3 doses of BDM without deviations.

The biopharmaceutics review concluded, "Study EGL-BDM-C-1301 demonstrated that the EAGLE-bendamustine (Eagle-BDM) product given over a 10 minutes infusion interval is bioequivalent to the reference product (Teva-BDM) given over 60 minutes. The results showed the Eagle-BDM is bioequivalent to Teva-BDM for BDM AUC_{0-t} and $AUC_{0-\infty}$ for the 2 Primary PKE populations (FDA requested [n=60] and Eagle proposed [n=44]), as well as for

the 2 Secondary Sensitivity populations (FDA requested [n=57] and Eagle proposed [n=38]), respectively, by using the RSABE method as well as the unscaled- ABE method.

Based on FDA recommendations in a meeting held on 1/15/2013, BE was based only on the AUCs for BDM, because the proposed product was intentionally formulated to exhibit different Cmax and Tmax compared to the Listed Drug (due to the difference in concentration and duration of administration). Bioequivalence was determined based on comparison of the bendamustine AUCs (AUC_{0-t} & $AUC_{0-\infty}$) between the Test product and the Listed Drug."

The biopharmaceutics reviewer concluded that the safety profiles of the two products are similar based on the clinical safety review in DARRTs, despite the higher Cmax achieved by the Eagle-BDM product. No biopharmaceutics issues which preclude approval were identified and the biopharmaceutics reviewer found the information adequate to support the approval of NDA 208194 (refer to the biopharmaceutics section of the integrated quality assessment signed by Jing Li, Ph.D.).

6. Clinical Microbiology

No Clinical Microbiology review was required for this NDA.

7. Clinical/Statistical- Efficacy

The clinical recommendation for the approval of Bendeka is based on the safety and efficacy of the marketed bendamustine (Treanda) lyophilized powder for injection product (NDA 22249), supportive safety and efficacy information from the marketed bendamustine (Treanda) products and the available Bendeka supportive safety information from the bioequivalence study EGL-BDM-C-1301.

According to the clinical review, "From a clinical perspective NDA 208194 should be granted approval for the following indications which are the same indications as the reference drug.

- Bendamustine hydrochloride is an alkylating drug indicated for 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."

No clinical issues which preclude approval were found and the clinical reviewer found the information adequate to support the approval of NDA 208194 for the proposed indications (see review by Andrew Dmytrijuk M.D., final signature November 19, 2015).

No Statistical Review was done for this NDA.

8. Safety

The clinical review concluded that "From a clinical perspective the pharmacokinetic results, the proportion of patients with adverse events and severity of adverse events in the bioequivalence study EGL-BDM-C-1301 were similar for Bendeka infusion over 10 minutes compared to Treanda infusion over 60 minutes.

Review of safety in study EGL-BDM-C-1301 supporting the Bendeka application NDA 208194 does not raise new or additional safety concerns for the Bendeka formulation and faster infusion rate compared to the marketed Treanda lyophilized powder product. This study was conducted in patients with a histologically confirmed diagnosis of any malignant disease for which no curative or standard therapy is appropriate. Most patients 38/81 (47%) in this study had stage IV solid tumor malignancies at the time of enrollment in which disease progression and a high mortality rate is expected. In this study 6 patients died. All 6 patients had stage IV disease and a poor prognosis (AJCC Cancer Staging Handbook, 2002). There was no clear difference between Bendeka and Treanda in the proportion of patients with CTCAE grade $\geq$ 3 AEs or SAEs. Exclusion of patients with CLL from study EGL-BDM-1301-C is acceptable, as is also stated in the Reviewer Comment for section 5 in this review, because the recommended dose of Treanda for patients with CLL is lower than the recommended dose of Treanda for patients with indolent NHL which would make it difficult to compare pharmacokinetic results for patients with CLL to those with solid tumor malignancies or NHL."

The increased osmolality of the proposed drug product once diluted into either 0.9% Sodium Chloride Injection, USP or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP (b) (4) 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. 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. I agree with Dr. George's assessment of the potential for these adverse reactions and his conclusion. In NDA 208194, there were no reported adverse reactions of phlebitis or hemolysis. Skin adverse events were generally reported infrequently and were considered to be to be of mild severity. There were two patients who developed adverse skin reactions (mild macular rash and mild urticaria) during the study drug administration or within 1 hour after the end of study drug administration. The faster infusion rate of Bendeka, i.e., 10 minutes, compared to the infusion rate of Treanda, i.e., 60 minutes, does not appear to increase the risk for hemolysis, phlebitis, or infusion site reactions. Also, the current proposed Warnings and Precautions section

labeling for Bendeka is the same as that of Treanda and states that there is a potential risk for skin reactions including SJS and TEN and extravasation." The clinical team leader agrees with Dr. Dmytrijuk' s conclusion.

9. Advisory Committee Meeting

There was no Advisory Committee meeting held for this application.

10. Pediatrics

The labeling for the listed drug contains information in the Pediatric Use section based upon a study conducted by the listed drug applicant. Information from the study regarding pediatric experience was placed into the label based on safety concerns that could arise should the product be used off label in pediatric patients. Consequently, this information was retained in the label for the new Eagle bendamustine product.

Also, as noted in the Clinical Review, on July 2, 2014 Office of Orphan Products granted orphan drug designation to Eagle's Bendamustine HCl 50 mL admixture. Therefore, PREA requirements do not apply.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)**: No issues were identified.

- **Exclusivity or patent issues of concern**: The following exclusivities are listed in the orange book:

Exclusivity Data

Application Number	Product Number	Exclusivity Code	Exclusivity Expiration (b) (4)
N022249	001	ODE	
N022249	001	PED	
N022249	001	ODE	
N022249	001	PED	

- **Financial disclosures**: In accordance with 21 CFR 54.4, the applicant submitted the required financial disclosure requirement and certification.

- **Other GCP issues**: None

- **Office of Study Integrity and Surveillance (OSIS) Audits:** FDA Office of Scientific Investigations performed inspections of the following clinical sites:

- Oncology Institute of Hope and Innovation, Long Beach, CA
- Innovative Clinical Research Institute, Whittier, CA
- Evergreen Hematology & Oncology, Spokane, WA
- Greenville Hospital System University Medical Center, Greenville, SC
- Cancer Center of Kansas, Wichita, KS
- (b) (4)

The inspection of the (b) (4) site where analytical testing in support of the bioequivalence study was conducted from (b) (4). A 1-item Form FDA 483 was issued at the conclusion of the inspection. OSIS concluded that this observation does not affect the data integrity of the study.

The status of the remaining clinical sites are pending.

- **Other discipline consults**: None

- **Any other outstanding regulatory issues**: None

12. Labeling

General: Final labeling was found acceptable for all the review disciplines.

- **Proprietary name:** Bendeka. The DMEPA review of the proprietary name, Bendeka, was found acceptable (see review by Michelle Rutledge, PharmD on June 15, 2015).

- **Division of Medication Error Prevention and Analysis *(DMEPA):*** Labeling recommendations were provided by the (DMEPA). Recommendations included the removal of trailing zeros after the decimal point in Section 2.3 - Preparation for Intravenous Administration in the full prescribing information. The review also recommendation to increase the font size, reduce size of company logo, bolding important information and including a resealable peel-back label for the container carton label (see review by Michelle Rutledge, PharmD on September 16, 2015).

- **Office of Prescription Drug Promotion (OPDP)**: OPDP did not have any labeling comments to the draft prescribing information (see review by Nisha Patel on August 12, 2015).

- **Prescribing Information**: The wording of the labeling in the PLR format has been reviewed and comments from all disciplines (including DMEPA) were conveyed to the applicant.

- **Carton and Immediate container label**: The drug product and DMEPA reviewers made suggested edits to the carton and immediate container label. All revisions were accepted by the applicant.

- **Patient labeling/Medication guide***:* This is not required for this product.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**: Approval

- **Risk Benefit Assessment**

According to the clinical review, "Overall, the risk benefit assessment favors the approval of the Bendeka formulation for the same indications as that of the Treanda formulation. Bendeka offers patients a more rapid intravenous infusion of bendamustine hydrochloride (10 minutes for Bendeka compared to 60 minutes for Treanda) and does contain DMA which is compatible with closed system transfer devices (CSTDs), adaptors, and syringes containing polycarbonate or acrylonitrile-butadiene-styrene (ABS). Overall the proportion of patients with adverse events and severity of adverse events were similar for Bendeka infusion over 10 minutes compared to Treanda infusion over 60 minutes in study EGL-BDM-C-1301."

The clinical reviewers for (b) (4) 208194 (b) (4) concluded that 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. Additionally, In NDA 208194 there were no reported adverse reactions of phlebitis or hemolysis.

A bioequivalence study (EGL-BDM-C-1301) demonstrated the bioequivalence of Eagle bendamustine product given over a 10 minutes infusion interval compared to the listed drug Treanda (bendamustine hydrochloride) for injection given over 60 minutes. The safety profile of Eagle's bendamustine drug product is consistent with known effects of bendamustine.

Nonclinical and clinical studies performed with Eagle's BDM HCl Injection demonstrated an acceptable safety and tolerability profile, with no increased toxicity risk compared to the existing Treanda formulation.

The drug product reviewer determined that the lack of compatibility data was acceptable based on a risk assessment. The PG and monothioglycerol are present in the drug product at very low concentrations ((b) (4)%, respectively). (b) (4) PEG 400 is very hydrophilic and is present at no more than (b) (4)% in the admixture solutions. Thus, both formulation and admixtures are considered low risk in terms of extraction power. The contact time for admixture solutions in the infusion bags is considered short which is no more than 6 hours at room temperature or no more than 24 hours at refrigerator. The total infusion time is only 10 minutes. Therefore, as a summary, the drug product is considered compatible with the

proposed infusion bags as well as all the other commercially available transfer devices, including adaptor, syringe, filter, and tubing."

Pharmacology/Toxicology has no concerns with the nonclinical findings and the excipients used for Eagle's bendamustine HCl injection at the defined levels. The Applicant has satisfactorily responded to the identified CMC and biopharmaceutics deficiencies, and the application has received an overall acceptable recommendation from the Office of Compliance.

- **Recommendation for Postmarketing Risk and Management Activities**

No post-marketing risk evaluation and mitigation strategy (REMS) is recommended for the Bendeka formulation.

- **Recommendation for other Postmarketing Study Commitments**

No Postmarketing Requirements (PMRs) or Postmarketing Commitments (PMCs) for this NDA submission are recommended.

On July 2, 2014 Office of Orphan Products granted orphan drug designation to Eagle's Bendamustine HCl 50 mL admixture. Therefore, PREA requirements do not apply.

- **Recommended Comments to Applicant**

None.