CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208194Orig1s000

SUMMARY REVIEW

M E M O R A N D U M

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

Date: July 8, 2016

From: Andrew Dmytrijuk M.D.
Medical Officer
Division of Hematology Products

Subject: Correction to Division of Hematology Products (DHP) Clinical Review for Bendeka by Dr. Andrew Dmytrijuk, Final Signature Date November 19, 2015

Re: NDA 208194 Bendeka® (Bendamustine Hydrochloride Injection) 100mg/4 mL (25mg/mL)

This memorandum is intended to note and correct a typographical error and clarify a sentence in the Division of Hematology Products (DHP) Clinical Review of NDA 208194 Bendeka® (Bendamustine Hydrochloride Injection) 100mg/4 mL (25mg/mL) by Dr. Andrew Dmytrijuk (final signature date November 19, 2015).

On page 6 under section 1.2 Risk Benefit Assessment, third paragraph, the third sentence which begins, "Bendeka offers patients a more rapid…" has a typographical error. This sentence should be replaced by the following: "Bendeka offers patients a more rapid intravenous infusion of bendamustine hydrochloride (10 minutes for Bendeka compared to 60 minutes for Treanda). Bendeka does not contain DMA and is compatible with closed system transfer devices (CSTDs), adaptors, and syringes containing polycarbonate or acrylonitrile-butadiene-styrene (ABS)."

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

/s/

ANDREW DMYTRIJUK
07/08/2016

KATHY M ROBIE SUH
07/08/2016

THIS CORRECTED DIVISION DIRECTOR'S REVIEW SUPERCEDES THE DIVISION DIRECTOR'S REVIEW DATED 12/02/2015

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Edvardas Kaminskas, M.D.
Subject	Deputy Division Director Summary Review
NDA# **Supplement #**	208194
Applicant Name	Eagle Pharmaceuticals, Inc.
Date of Submission	02/13/2015
PDUFA Goal Date	12/13/2015
Proprietary Name / **Established (USAN) Name**	Bendeka™ Bendamustine hydrochloride
Dosage Forms / Strength	Injection, 100 mg/4 mL (25 mg/mL)
Proposed Indications	For treatment of patients with • chronic lymphocytic leukemia • Indolent B-cell non-Hodgkin Lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.
Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Andrew Dmytrijuk, M.D./Kathy Robie Suh, M.D., Ph.D.
Pharmacology Toxicology Review	Michael L. Manning, Ph.D./Christopher M. Sheth, Ph.D.
CMC Review/Biopharmaceutics Review/Product Quality Microbiology Review	Nina Ni, Ph.D./Vidya Pai, Ph.D./Vinyak Pawar, Ph.D./ Zhong Li, Ph.D./Jing Li, Ph.D./Janice Brown, M.S./Paul Perdue, Jr., Ph.D.
OPDP	Nisha Patel, Pharm.D./Kathleen Davis, Pharm.D.
OSIS/DNDBE	Hansong Chen, Ph.D.,Pharm.D./Charles R. Bonpace, Pharm.D.
CDTL Review	Janice Brown, M.S.
OSE/OMEPRM/DMEPA	Michelle Rutledge, Pharm.D./Yelena Maslov/ Pharm.D. Todd Bridges, R.Ph.

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
OMEPRM=Office of Medication Error Prevention and Risk Management
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Divisiion of Risk Management
OSIS=Office of Study Integrity and Surveillance
DNDBE=Division of New Drug Bioequivalence Evaluation
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

Bendamustine 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 Applicant is relying upon information in the public domain, i.e. labeling for the approved bendamustine HCl product (Treanda® for injection) and published studies about bendamustine HCl, to support the safety and efficacy of the proposed product. The proposed drug product is a ready-to-dilute solution, whereas the listed drug product, Treanda (bendamustine) for injection, is a lyophilized powder that requires reconstitution. The proposed drug product Bendeka™ (bendamustine hydrochloride) Injection is self-preserving and is intended for multiple doses.

2. Background

The Applicant (Eagle Pharmaceuticals, Inc.) received Tentative Approval for the companion NDA 205580 Bendamustine HCl Injection [redacted] (b) (4) on July 2, 2014 for [redacted] (b) (4) indolent B-cell NHL only, as requested by the Applicant. The application could not be granted final approval until all exclusivities expired. The last exclusivity expiration date for the CLL indication was [redacted] (b) (4) and the last exclusivity expiration date for the NHL indication is [redacted] (b) (4).

The Applicant was granted on July 2, 2014 orphan drug designation of bendamustine for 50 mL admixture for *"treatment of follicular lymphoma, treatment of small lymphocytic lymphoma, treatment of lymphoplasmacytic lymphoma, treatment of splenic marginal cell lymphoma, treatment of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoma tissue (MALT), and treatment of nodal marginal zone lymphoma (collectively indolent B-cell non-Hodgkin's lymphoma)".* Also on July 2, 2014, the Applicant was granted orphan drug designation of bendamustine for 50 mL admixture for "*treatment of chronic lymphocytic leukemia".*

On May 11, 2015 Cephalon, Inc. informed the Agency of Waiver of Orphan Drug Exclusivity for Eagle NDA 208194. The letter states "Pursuant to 21 CFR § 316.31(a)(3), Cephalon, Inc. hereby consents to FDA's final approval of NDA 208194, submitted by Eagle Pharmaceuticals, Inc. on February 13, 2015, notwithstanding the orphan drug and pediatric exclusivities applicable to NDA 022249 and NDA 022303 for TREANDA (bendamustine hydrochloride) currently held by or granted to Cephalon."

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

3. CMC/Device

Drug Substance: The CMC information for the drug substance was provided in DMF No. (b) (4) from (b) (4) DMF (b) (4) was reviewed and found adequate to support the manufacture of the drug product as a solution dosage form by Joyce Crich, Ph.D. on 05/06/2014. There is no new quality update provided in the DMF since the last review. The submitted NDA included minor drug substance updates and the drug substance reviewer Dr. Nina Ni, Ph.D. found the information adequate to support NDA 208194.

Drug Product: Bendeka (bendamustine HCl) injection is a ready-to-dilute non-aqueous solution 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 undergoes rapid degradation (b) (4) consists of polyethylene glycol 400 (PEG 400), propylene glycol, and monothioglycerol. 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° – 8°C (36° - 46°F), protected from light. The drug product reviewer recommended approval of the NDA.

Process Review – Drug Product: The drug product manufacturing process was reviewed and found acceptable. The process reviewer recommended approval of the NDA.

Biopharmaceutics Review – below under Clinical Pharmacology.

Facilities Review and Inspection: The Office of Process and Facilities found the facilities acceptable and concluded that there are no significant outstanding manufacturing risks.

Microbiology Review: 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 microbiology section of the NDA was reviewed and found acceptable.

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months, when stored in refrigerator at 2° – 8°C (36° - 46°F), protected from light. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The Applicant did not submit any new nonclinical studies since the previous NDA submission (NDA 205580). Pharmacology/Toxicology had no concerns with the nonclinical findings and the excipients used for Eagle's Bendamustine HCl Injection. The nonclinical reviewer recommended approval of the NDA for Bendamustine HCl Injection administered as a 50 mL admixture over an infusion time of 10 minutes, for the proposed indications.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

There was no Clinical Pharmacology review for this NDA. The submitted bioequivalence study was reviewed by the Office of Product Quality Biopharmaceutics team.

The bioequivalence study was an open-label, cross-over, randomized bioequivalence study designed to evaluate Eagle's Bendamustine HCl Injection (BDM) administered to patients with a histological diagnosis of cancer (solid tumors and hematologic malignancies excluding chronic lymphocytic leukemia) who had progressed or relapsed on standard therapy, or for whom no curative or standard therapy was appropriate. The primary objective was to demonstrate that Eagle-BDM formulation is bioequivalent to the currently marketed Teva-BDM (listed drug) with respect to total bendamustine exposure (AUC). The maximum peak plasma concentration (C_{max}) for Eagle-BDM is higher than for Teva-BDM due to a 6-fold longer administration of Teva-BDM (10 minutes versus 60 minutes).

The study was carried out over two 28-day treatment cycles, in which subjects were randomized into 3 groups. Group 1 received 1 dose of Eagle-BDM followed by 1 dose of Teva-BDM in the 1st cycle, and Teva-BDM followed by Eagle-BDM in the 2nd cycle. Group 2 received 1 dose of Teva-BDM followed by 1 dose of Eagle-BDM in the 1st cycle, and Teva-BDM followed by Eagle-BDM in the 2nd cycle. Group 3 received 1 dose of Teva-BDM followed by 1 dose of Teva-BDM in the 1st cycle, and Eagle-BDM followed by Eagle-BDM in the 2nd cycle. PK analyses were performed after doses 1, 2, and 3. Safety data were obtained throughout the 2 cycles.

The biopharmaceutics review concluded that "the Eagle-BDM is bioequivalent to Teva-BDM for BDM AUC_{0-t} and $AUC_{0-\infty}$ for the two PKE populations (FDA requested [n=60] and Eagle proposed [n=44]), as well as for the two 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." 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 C_{max} achieved by the Eagle-BDM product. No biopharmaceutical issues that would preclude

were identified and the biopharmaceutics reviewer found the information adequate to support the approval of NDA 208194.

I concur with the conclusions reached by the biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A.

7. Clinical/Statistical-Efficacy

There were no clinical data submitted aside from the bioequivalence study described above. No clinical issues that preclude approval were found and the clinical reviewer found the information adequate to support the approval of NDA 208194. There was no Statistical review for this NDA.

8. Safety

The clinical reviewer 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 were similar for Bendeka infusion over 10 minutes compared to Treanda infusion over 60 minutes. Review of safety in the bioequivalence study 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."

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) The clinical review stated, "In NDA 208194, there were no reported adverse reactions of phlebitis or hemolysis. 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".

9. Advisory Committee Meeting

This application was not presented at an Advisory Committee meeting.

10. Pediatrics

Bendamustine 50mL admixture was granted Orphan Designation for both indications (see above in Background) and is not subject to PREA.

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.

11. Other Relevant Regulatory Issues

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

- **Exclusivity or patent issues**: The following exclusivities are listed in the Orange Book:

Exclusivity Data

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

The holder of the exclusivities, Cephalon, Inc., "consents to FDA's final approval of NDA 208194, submitted by Eagle Pharmaceuticals, Inc. on February 13, 2015, notwithstanding the orphan drug and pediatric exclusivities applicable to NDA 022249 and NDA 022303 for TREANDA (bendamustine hydrochloride) currently held by or granted to Cephalon."

- **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
  - 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 on (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 study data from the four clinical sites were found to be acceptable by the OSIS/DGDBE review team.

- **Other discipline consults**: None

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

There are no other unresolved relevant regulatory issues.

12. Labeling

- **Proprietary name:** DMEPA review of the proprietary name, Bendeka, concluded that it was acceptable.

- **Division of Medication Error Prevention and Analysis (DMEPA):** Labeling recommendations included an increase the font size, reduction of the size of company logo, bolding important information and including a re-sealable peel-back label for the container carton label.

- **Office of Prescription Drug Promotion (OPDP)**: OPDP did not have any labeling comments to the draft prescribing information.

- **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.

In summary: Final labeling was found acceptable for all the review disciplines and it was agreed upon by the Applicant.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment: The indications for Bendeka are the same as that for Treanda and patients will be treated with the same total drug dose as using Treanda. There are no new active ingredients, no new indications, no change in the route of administration and no significant differences in the safety profiles of Bendeka compared to Treanda, even though Bendeka is more rapidly infused compared to Treanda. The risk benefit assessment favors the approval of the Bendeka formulation for the same indications as that of the Treanda formulation. Bendeka is compatible with closed system transfer devices, adaptors, and syringes containing polycarbonate or acrylonitrile-butadiene-styrene.

- Recommendation for Postmarketing Risk Management Activities
  None.

- Recommendation for other Postmarketing Study Commitments
  None.

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

/s/

EDVARDAS KAMINSKAS
07/08/2016

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Edvardas Kaminskas, M.D.
Subject	Deputy Division Director Summary Review
NDA# **Supplement #**	208194 01
Applicant Name	Eagle Pharmaceuticals, Inc.
Date of Submission	02/13/2015
PDUFA Goal Date	12/13/2015
Proprietary Name / **Established (USAN) Name**	Bendeka Bendamustine hydrochloride
Dosage Forms / Strength	Injection, 100 mg/4 mL (25 mg/mL)
Proposed Indications	For treatment of patients with • chronic lymphocytic leukemia • Indolent B-cell non-Hodgkin Lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.
Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Andrew Dmytrijuk, M.D./Kathy Robie Suh, M.D., Ph.D.
Pharmacology Toxicology Review	Michael L. Manning, Ph.D./Christopher M. Sheth, Ph.D.
CMC Review/Biopharmaceutics Review/Product Quality Microbiology Review	Nina Ni, Ph.D./Vidya Pai, Ph.D./Vinyak Pawar, Ph.D./ Zhong Li, Ph.D./Jing Li, Ph.D./Janice Brown, M.S./Paul Perdue, Jr., Ph.D.
OPDP	Nisha Patel, Pharm.D./Kathleen Davis, Pharm.D.
OSIS/DNDBE	Hansong Chen, Ph.D.,Pharm.D./Charles R. Bonpace, Pharm.D.
CDTL Review	Janice Brown, M.S.
OSE/OMEPRM/DMEPA	Michelle Rutledge, Pharm.D./Yelena Maslov/ Pharm.D. Todd Bridges, R.Ph.

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
OMEPRM=Office of Medication Error Prevention and Risk Management
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Divisiion of Risk Management
OSIS=Office of Study Integrity and Surveillance
DNDBE=Division of New Drug Bioequivalence Evaluation
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

Bendamustine 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 Applicant is relying upon information in the public domain, i.e. labeling for the approved bendamustine HCl product (Treanda® for injection) and published studies about bendamustine HCl, to support the safety and efficacy of the proposed product. The proposed drug product is a ready-to-dilute solution, whereas the listed drug product, Treanda (bendamustine) for injection, is a lyophilized powder that requires reconstitution. The proposed drug product Bendeka™ (bendamustine hydrochloride) Injection is self-preserving and is intended for multiple doses.

2. Background

The Applicant 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, as requested by the Applicant. The application could not be granted final approval until all exclusivities expired. The last exclusivity expiration date for the CLL indication was (b) (4) and the last exclusivity expiration date for the NHL indication is (b) (4).

The Applicant was granted on July 2, 2014 orphan drug designation of bendamustine for 50 mL admixture for *"treatment of follicular lymphoma, treatment of small lymphocytic lymphoma, treatment of lymphoplasmacytic lymphoma, treatment of splenic marginal cell lymphoma, treatment of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoma tissue (MALT), and treatment of nodal marginal zone lymphoma (collectively indolent B-cell non-Hodgkin's lymphoma)"*. Also on July 2, 2014, the Applicant was granted orphan drug designation of bendamustine for 50 mL admixture for "*treatment of chronic lymphocytic leukemia"*.

On May 11, 2015 Cephalon, Inc. informed the Agency of Waiver of Orphan Drug Exclusivity for Eagle NDA 208194. The letter states "Pursuant to 21 CFR § 316.31(a)(3), Cephalon, Inc. hereby consents to FDA's final approval of NDA 208194, submitted by Eagle Pharmaceuticals, Inc. on February 13, 2015, notwithstanding the orphan drug and pediatric

exclusivities applicable to NDA 022249 and NDA 022303 for TREANDA (bendamustine hydrochloride) currently held by or granted to Cephalon."

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

3. CMC/Device

Drug Substance: The CMC information for the drug substance was provided in DMF No. (b) (4) from (b) (4) DMF (b) (4) was reviewed and found adequate to support the manufacture of the drug product as a solution dosage form by Joyce Crich, Ph.D. on 05/06/2014. There is no new quality update provided in the DMF since the last review. The submitted NDA included minor drug substance updates and the drug substance reviewer Dr. Nina Ni, Ph.D. found the information adequate to support NDA 208194.

Drug Product: Bendeka (bendamustine HCl) injection is a ready-to –dilute non-aqueous solution 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 undergoes rapid degradation (b) (4) consists of polyethylene glycol 400 (PEG 400), propylene glycol, and monothioglycerol. 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° – 8°C (36° -46°F), protected from light. The drug product reviewer recommended approval of the NDA.

Process Review – Drug Product: The drug product manufacturing process was reviewed and found acceptable. The process reviewer recommended approval of the NDA.

Biopharmaceutics Review – below under Clinical Pharmacology.

Facilities Review and Inspection: The Office of Process and Facilities found the facilities acceptable and concluded that there are no significant outstanding manufacturing risks.

Microbiology Review: 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 microbiology section of the NDA was reviewed and found acceptable.

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months, when stored in refrigerator at 2° – 8°C (36° -46°F), protected from light. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The Applicant did not submit any new nonclinical studies since the previous NDA submission (NDA 205580). Pharmacology/Toxicology had no concerns with the nonclinical findings and the excipients used for Eagle's Bendamustine HCl Injection. The nonclinical reviewer recommended approval of the NDA for Bendamustine HCl Injection administered as a 50 mL admixture over an infusion time of 10 minutes, for the proposed indications.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

There was no Clinical Pharmacology review for this NDA. The submitted bioequivalence study was reviewed by the Office of Product Quality Biopharmaceutics team.

The bioequivalence study was an open-label, cross-over, randomized bioequivalence study designed to evaluate Eagle's Bendamustine HCl Injection (BDM) administered to patients with a histological diagnosis of cancer (solid tumors and hematologic malignancies excluding chronic lymphocytic leukemia) who had progressed or relapsed on standard therapy, or for whom no curative or standard therapy was appropriate. The primary objective was to demonstrate that Eagle-BDM formulation is bioequivalent to the currently marketed Teva-BDM (listed drug) with respect to total bendamustine exposure (AUC). The maximum peak plasma concentration (C_{max}) for Eagle-BDM is higher than for Teva-BDM due to a 6-fold longer administration of Teva-BDM (10 minutes versus 60 minutes).

The study was carried out over two 28-day treatment cycles, in which subjects were randomized into 3 groups. Group 1 received 1 dose of Eagle-BDM followed by 1 dose of Teva-BDM in the 1st cycle, and Teva-BDM followed by Eagle-BDM in the 2nd cycle. Group 2 received 1 dose of Teva-BDM followed by 1 dose of Eagle-BDM in the 1st cycle, and Teva-BDM followed by Eagle-BDM in the 2nd cycle. Group 3 received 1 dose of Teva-BDM followed by 1 dose of Teva-BDM in the 1st cycle, and Eagle-BDM followed by Eagle-BDM in the 2nd cycle. PK analyses were performed after doses 1, 2, and 3. Safety data were obtained throughout the 2 cycles.

The biopharmaceutics review concluded that "the Eagle-BDM is bioequivalent to Teva-BDM for BDM AUC_{0-t} and $AUC_{0-\infty}$ for the two PKE populations (FDA requested [n=60] and Eagle proposed [n=44]), as well as for the two 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." 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 C_{max} achieved by the Eagle-BDM product. No biopharmaceutical issues that would preclude were identified and the biopharmaceutics reviewer found the information adequate to support the approval of NDA 208194.

I concur with the conclusions reached by the biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A.

7. Clinical/Statistical-Efficacy

There were no clinical data submitted aside from the bioequivalence study described above. No clinical issues that preclude approval were found and the clinical reviewer found the information adequate to support the approval of NDA 208194. There was no Statistical review for this NDA.

8. Safety

The clinical reviewer 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 were similar for Bendeka infusion over 10 minutes compared to Treanda infusion over 60 minutes. Review of safety in the bioequivalence study 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."

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) The clinical review stated, "In NDA 208194, there were no reported adverse reactions of phlebitis or hemolysis. 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".

9. Advisory Committee Meeting

This application was not presented at an Advisory Committee meeting.

10. Pediatrics

Bendamustine 50mL admixture was granted Orphan Designation for both indications (see above in Background) and is not subject to PREA.

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.

11. Other Relevant Regulatory Issues

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

- **Exclusivity or patent issues**: The following exclusivities are listed in the Orange Book:

Exclusivity Data

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

The holder of the exclusivities, Cephalon, Inc., "consents to FDA's final approval of NDA 208194, submitted by Eagle Pharmaceuticals, Inc. on February 13, 2015, notwithstanding the orphan drug and pediatric exclusivities applicable to NDA 022249 and NDA 022303 for TREANDA (bendamustine hydrochloride) currently held by or granted to Cephalon."

- **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
  - 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 on (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 study data from the four clinical sites were found to be acceptable by the OSIS/DGDBE review team.

- **Other discipline consults**: None

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

"There are no other unresolved relevant regulatory issues"

12. Labeling

- **Proprietary name:** The DMEPA review of the proprietary name, Bendeka, was found acceptable.

- **Division of Medication Error Prevention and Analysis (DMEPA):** Labeling recommendations included an increase the font size, reduction of the size of company logo, bolding important information and including a re-sealable peel-back label for the container carton label.

- **Office of Prescription Drug Promotion (OPDP)**: OPDP did not have any labeling comments to the draft prescribing information.

- **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.

In summary: Final labeling was found acceptable for all the review disciplines and it was agreed upon by the Applicant.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment: The indications for Bendeka are the same as that for Treanda and patients will be treated with the same total drug dose as that for Treanda. There are no new active ingredients, no new indications, no change in the route of administration and no significant differences in the safety profiles of Bendeka compared to Treanda even though Bendeka is more rapidly infused compared to Treanda. 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 and does contain DMA which is compatible with closed system transfer devices, adaptors, and syringes containing polycarbonate or acrylonitrile-butadiene-styrene.

- Recommendation for Postmarketing Risk Management Activities
  None.

- Recommendation for other Postmarketing Study Commitments
  None.

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

/s/

EDVARDAS KAMINSKAS
12/02/2015