CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 208194/S-003

Name: Bendeka™ (bendamustine hydrochloride) Injection, 100 mg/4 mL (25 mg/mL).

Sponsor: Eagle Pharmaceuticals, Inc.

Approval Date: September 23, 2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 208194/S-003

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 208194/S-003

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208194/S-003

APPROVAL LETTER

Eagle Pharmaceuticals, Inc.
Attention: Foma Rashkovsky
Vice President, Regulator Affairs
50 Tice Boulevard, Suite 315
Woodcliff Lake, NJ 07677

Dear Mr. Rashkovsky:

Please refer to your Supplemental New Drug Application (sNDA) dated August 3, 2016, received August 3, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Bendeka (bendamustine hydrochloride) Parenteral 100 mg/4mL (25mg/mL).

This "Prior Approval" supplemental new drug application proposes the following change(s): Conduct the in-house (b) (4) test for release of the drug substance annually on the first batch received and adopt results from the vendor's CoA on the other subsequent batches for the year.

We have completed our review of this supplemental new drug application. This supplement is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153.

Sincerely,

{See appended electronic signature page}

Anamitro Banerjee, Ph.D.
Branch Chief, Branch II (Acting)
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Anamitro Banerjee

Digitally signed by Anamitro Banerjee
Date: 9/23/2016 06:09:04PM
GUID: 5075764700003844b7bc89632228509f
Comments: The changes proposed in the NDA 208194/S-003 is acceptable. This supplement may be approved.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 208194/S-003

CHEMISTRY REVIEWS

Office of New Drug Products
Division of New Drug Products I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number:** NDA 208194 / S-003

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
0051	S-003	08/03/2016	08/03/2016	08/09/2016	11/08/2016	08/15/2016
0052	Amendment	09/06/2016	09/06/2016	NA	NA	09/07/2016

3. **Proposed Changes**: Eagle proposed stopping the current in-house (b) (4) testing for release of the drug substance and adopting the result from the vendor's Certificate of Analysis (CoA).

4. **Review #**: 1

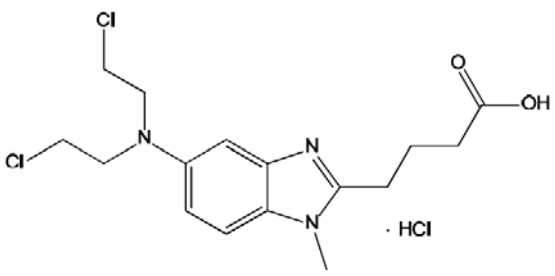
5. **Clinical Review Division**: DHP

6. **Name and Address of Applicant**:
Eagle Pharmaceuticals
50 Tice Blvd., Suite 315
Woodcliff Lake, NJ 07677
Phone: 201-326-5300

7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Bendeka (bendamustine hydrochloride) injection	Injection	100 mg/4 mL (25 mg/mL)	IV infusion	Rx	N/A

8. **Chemical Name and Structure of Drug Substance**:

	USAN: Bendamustine Hydrochloride Chemical Name: 1H-benzimidazole-2-butanoic acid, 5- [bis(2-chloroethyl)amino]-methyl-, monohydrochloride, or 4-{ 5-[Bis(2-chloroethyl)amino]-1-methyl-1 H-benzimidazol-2-yl} butanoic acid hydrochloride Molecular Formula: $C_{16}H_{21}Cl_2N_3O_2 \cdot HCl$ MW: 394.72 (salt form) MW: 358.26 (free base)

9. **Indication**: For the treatment of Chronic Lymphocytic Leukemia (CLL) and Indolent B-Cell non- Hodgkin Lymphoma (NHL)
10. **Supporting/Relating Documents**: NDA 208194 original submission

11. **Consults**: None

12. **Executive Summary**:

The applicant has submitted this manufacturing supplement to propose stopping the current in-house (b) (4) testing for release of the drug substance and adopt the result from the vendor's Certificate of Analysis (CoA).

The applicant has conducted an evaluation of (b) (4) test results obtained by (b) (4) (drug substance vendor) and (b) (4) (drug product manufacturer). Based on the review of results from multiple batches of bendamustine hydrochloride and the fact that (b) (4) is used as a (b) (4), the applicant determined that the (b) (4) testing performed by the vendor, (b) (4) is adequate to monitor and control (b) (4) levels in the drug substance. There is no need for the additional confirmatory (b) (4) testing currently performed by the drug product manufacturer, (b) (4) for incoming drug substance lots. The test will remain as a release test on the (b) (4) CoA and the (b) (4) level will continue to be reviewed by (b) (4) and Eagle QA prior to batch release and recorded on the (b) (4) CoA.

13. **Conclusions & Recommendations**:

This manufacturing supplement is recommended for approval.

14. **Comments/Deficiencies to be Conveyed to Applicant**: None

15. **Primary Reviewer**:

Nina Ni, Ph.D., CMC reviewer, Branch II, Division of New Drug Products I, Office of New Drug Products, Office of Pharmaceutical Quality (OPQ)

Nina Ni, Ph.D. 09/07/2016

16. **Secondary Reviewer**:

Anamitro Banerjee, Ph.D., Acting Branch Chief, Branch II, Division of New Drug Products I, Office of New Drug Products, Office of Pharmaceutical Quality (OPQ)

Anamitro Banerjee, Ph.D.
September 08, 2016

CMC Assessment

I. Background Information

Bendeka (bendamustine hydrochloride) injection was approved for the treatment of Chronic Lymphocytic Leukemia (CLL) and Indolent B-Cell non- Hodgkin Lymphoma (NHL) on 12/07/2015.

In the original NDA, the drug substance manufacturer, (b) (4) performs (b) (4) testing by (b) (4) MS as part of routine batch release requirements. The drug product manufacturer, (b) (4), performs (b) (4) testing by (b) (4) MS as part of incoming drug substance release testing. Both sites use a specification of Not More Than (b) (4).

II. Proposed Changes

In this manufacturing supplement, the applicant determined that the (b) (4) testing performed by the vendor, (b) (4) is adequate to monitor and control (b) (4) levels in the drug substance. There is no need for the additional confirmatory (b) (4) testing currently performed by the drug product manufacturer, (b) (4) for incoming drug substance lots. The test will remain as a release test on the (b) (4) CoA and the (b) (4) level will continue to be reviewed by (b) (4) and Eagle QA prior to batch release and recorded on the (b) (4) CoA. The following data are provided by the applicant to support the proposed change:

Table 3-1: Comparison of (b) (4) Results

No.	Lot No.	(b) (4)	(b) (4)	(b) (4)
1	15001BR26E			
2	15002FR26E			
3	15003GR26E			
4	15004GR26E			
5	15005PR26E			
6	15007GR26E			
7	15008GR26E			
8	15009HR26E			
9	15011IR26E			
10	15012IR26E			
11	15013IR26E			

Conclusion: Adequate.

The drug product manufacturer, (b) (4) has conducted (b) (4) test for total 11 batches of drug substance manufactured by (b) (4) using (b) (4) MS. The data show that all drug substance batches met the specification for (b) (4) and the data are comparable between two testing sites. It is noted that (b) (4) is used as a (b) (4) bendamustine HCl drug substance. (b) (4) levels should not increase or decrease during shipping or storage.

Based on the data, Eagle determined that the (b) (4) testing performed by the vendor, (b) (4) is adequate to monitor and control (b) (4) levels in the drug substance. Therefore, the drug product manufacturer, (b) (4) will not conduct in-house release testing for (b) (4) when they release the drug substance. Instead, the testing result for (b) (4) from (b) (4) CoA will be adapted into the (b) (4) CoA.

Based on:

- 21CFR211.84(d)(2): Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.
- ICH Q7 7.31 Good manufacturing practice guide for active pharmaceutical ingredients: Full analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a full analysis should be performed at appropriate intervals and compared with the Certificates of Analysis.

The applicant's proposal does not comply with either ICH Q7 or 21CFR 211.84 (d)(2) since the reliability of CoA should be checked at regular intervals. The following information request was conveyed to the applicant on 08/30/2016:

- You have proposed to adopt testing result for (b) (4) from the vendor's CoA to your CoA to release drug substance for in-house use. However, as per 21CFR211.84(d)(2) and ICH Q7 7.31, a full analysis should be performed at appropriate intervals and compared with certificates of analysis when a reduced in-house testing approach is adopted to release in-coming material. Therefore, provide your plan to periodically verify the (b) (4) test in-house by your drug product manufacturer.

The applicant has agreed to conduct the in-house (b) (4) test for release of the drug substance annually on the first batch received and adopting results from the vendor's CoA on the other subsequent batches for the year in the Amendment 0052, dated 09/06/2016, which deems acceptable. The applicant has also updated both drug product specification and analytical procedure accordingly.

Nina
Ni

Digitally signed by Nina Ni
Date: 9/08/2016 10:38:36AM
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Anamitro
Banerjee

Digitally signed by Anamitro Banerjee
Date: 9/08/2016 10:40:26AM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 208194/S-003

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Laiq, Rabiya

From: Laiq, Rabiya
Sent: Tuesday, August 30, 2016 12:42 PM
To: 'Foma Rashkovsky'
Subject: FDA Information Request NDA 208194-003- Please Respond by September 6, 2016

Importance: High

Dear Mr. Rashkovsky:

We have received your supplemental New Drug Application (sNDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 208194

SUPPLEMENT NUMBER: 003

PRODUCT NAME: Bendeka (bendamustine hydrochloride) Parenteral 100 mg/4mL (25mg/mL)

DATE OF SUBMISSION: August 3, 2016

Our CMC team has the following information request:

1. **You have proposed to adopt testing result for (b) (4) from the vendor's CoA to your CoA to release drug substance for in-house use. However, as per 21CFR211.84(d)(2) and ICH Q7 7.31, a full analysis should be performed at appropriate intervals and compared with certificates of analysis when a reduced in-house testing approach is adopted to release in-coming material. Therefore, provide your plan to periodically verify the (b) (4) test in-house by your drug product manufacturer.**

Kindly confirm receipt of this email.

Please respond via email followed by a formal response to through the FDA gateway.

Thank you,
Rabiya

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (240) 402-6153
Email: rabiya.laiq@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

Rabiya Laiq -S

Digitally signed by Rabiya Laiq -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Laiq -S, 0.9.2342.19200300.100.1.1=2001555007
Date: 2016.08.30 12:53:34 -04'00'

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208194/S-003

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Eagle Pharmaceuticals, Inc.
Attention: Foma Rashkovsky
Vice President, Regulator Affairs
50 Tice Boulevard, Suite 315
Woodcliff Lake, NJ 07677

Dear Mr. Rashkovsky:

We have received your supplemental New Drug Application (sNDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 208194

SUPPLEMENT NUMBER: 003

PRODUCT NAME: Bendeka (bendamustine hydrochloride) Parenteral 100 mg/4mL (25mg/mL)

DATE OF SUBMISSION: August 3, 2016

DATE OF RECEIPT: August 3, 2016

This supplemental application proposes the following change(s): providing a proposed revision to the (b) (4) (drug product manufacturer) specification and analytical procedure for the drug substance, Bendamustine Hydrochloride.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 30, 2016, in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be **December 3, 2016**.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology and Oncology Products, OHOP
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at (240) 402-6153 or email me at rabiyalaiq@fda.hhs.gov.

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Rabiya Laiq -S

Digitally signed by Rabiya Laiq -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Rabiya Laiq -S, 0.9.2342.19200300.100.1.1=2001555007
Date: 2016.08.16 17:59:26 -04'00'