CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208194Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approval, pending an acceptable recommendation from the Office of Study Integrity and Surveillance (OSIS) of the bioequivalence clinical site inspections

NDA 208194
Review #1

Drug Name/Dosage Form	Bendamustine hydrochloride injection
Strength	100 mg/4 mL (25 mg/mL)
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Eagle Pharmaceutical, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000	02/13/2015
0002	03/03/2015
0004	03/18/2015
0005	04/02/2015
0015	06/25/2015
0017	07/09/2015
0018	07/14/2015
0019	08/11/2015
0020	09/01/2015
0021	09/14/2015

QUALITY ASSSSMENT

Bendeka (bendamustine hydrochloride) injection
Eagle Pharmaceuticals, Inc.

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION	REVIEW RECOMMENDATION
Drug Substance	Nina Ni	Branch II/DNDP1/ONDP	Approval
Drug Product	Nina Ni	Branch II/DNDP1/ONDP	Approval
Process	Vidya Pai	Branch VII/DPAIII/OPF	Approval
Microbiology	Vinayak Pawar	MABI/DMA/OPF	Approval
Facility	Zhong Li	IABI/DIA/OPF	Approval
Biopharmaceutics	Jing Li	BBI/DB/ONDP	Approval pending an acceptable OSIS recommendation
Business Process Manager	Rabiya Laiq	Branch1/DRBPMI/OPRO	NA
Application Technical Lead	Janice Brown	Branch II/DNDP1/ONDP	Approval pending an acceptable OSIS recommendation
Laboratory (OTR)	N/A	N/A	N/A
ORA Lead	Paul Perdue Jr.	MDTP/DMPTPO/OMPTP	See facility review recommendation
Environmental Assessment (EA)	Janice Brown	Branch II/DNDP1/ONDP	Categorical exclusion accepted

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Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	05/06/2014	Reviewed by Joyce Crich
	III			N/A	N/A	Adequate information provided in the NDA
	III			N/A	N/A	Adequate information provided in the NDA
	III			N/A	N/A	Adequate information provided in the NDA

Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	205580	(b) (4)

3. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

Executive Summary

I. Recommendations

NDA 208194, Bendamustine hydrochloride injection is recommended for approval from a product quality perspective, pending an acceptable recommendation from the Office of Study Integrity and Surveillance (OSIS) of the bioequivalence clinical site inspections.

Include the following statement 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.

A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues: Not applicable.

2. Action letter language, related to critical issues such as expiration date: Refer to section I above.

3. Benefit/Risk Considerations

The risks associated with product quality have been described and adequately controlled to assure the quality of the drug product and consistent clinical performance. Based on the data provided, the quality of the bendamustine hydrochloride injection drug substance and drug product is considered acceptable. Pending an approval recommendation of the bioequivalence clinical site inspections from the Office of Study Integrity and Surveillance (OSIS) there are no unresolved quality issues which might have a negative impact on the risk benefit of this product.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Quality Assessments

NDA 208194 for bendamustine hydrochloride injection (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), and over a shorter time period (10 minutes) as well as providing three options for admixtures, including a new 5% dextrose diluent option for a sodium-free dosing regimen.

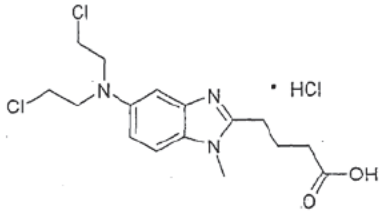
Eagle received tentative approval for NDA 205580 for bendamustine hydrochloride injection on July 2, 2014. NDA 205580 provides for the administration of bendamustine (b) (4).

A. Drug Substance [Bendamustine hydrochloride] Quality Summary

Bendamustine hydrochloride is a (b) (4) 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 leads to cell death. The applicant referenced the CMC information for bendamustine hydrochloride to DMF No. (b) (4). DMF No. (b) (4) was reviewed and found adequate.

1. Chemical Name or IUPAC Name/Structure

The chemical name of bendamustine hydrochloride is 1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1 methyl, mono hydrochloride. Bendamustine hydrochloride has the following structure:



Molecular formula $C_{16}H_{21}C_{12}N_3O_2 \cdot HCl$
Molecular Weight 394.7 (b) (4) g/mol

2. Properties/CQAs Relevant to Drug Product Quality

Bendamustine hydrochloride is a (b) (4) A significant feature of bendamustine hydrochloride is its relatively poor solubility and susceptibility of hydrolysis in aqueous conditions.

3. List of starting materials

(b) (4)

B. Drug Product [Bendamustine hydrochloride Injection] Quality Summary

1. Strength

100 mg/4 mL (25 mg/mL)

2. Description/Commercial Image

Bendeka (bendamustine hydrochloride) injection is supplied as a sterile, clear, colorless to yellow ready-to-dilute solution in a multi-use clear glass vial.

Bendeka is intended for intravenous infusion only after dilution with either of the following:

- 0.9% Sodium Chloride Injection, USP (normal saline); or
- 2.5% Dextrose/0.45% Sodium Chloride Injection, USP; or
- 5% Dextrose Injection, USP.

3. Summary of Product Design

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

The formulation contains excipients chosen to minimize potential stability issues. Bendamustine is susceptible to hydrolysis and undergoes rapid degradation (b) (4) [redacted] Polyethylene glycol 400 (PEG 400) was selected as the vehicle (b) (4) [redacted] propylene glycol (PG), (b) (4) [redacted]

Monothioglycerol is present at a concentration of 5 mg/mL (b) (4) [redacted] The level of degradants is dependent upon the acidity level of the PEG 400. (b) (4) [redacted] was able to minimize the formation of impurities, particularly the (b) (4) impurities, in bendamustine hydrochloride injection formulation. (b) (4) [redacted]

(b) (4)

[redacted]

4. List of Excipients

Each milliliter of Bendeka (bendamustine hydrochloride) injection contains 25 mg of bendamustine hydrochloride, 0.1 mL of propylene glycol, USP, 5 mg of monothioglycerol, NF (b) (4) polyethylene glycol (PEG) 400, NF. Sodium hydroxide may have been used to adjust the acidity of PEG 400.

The excipients monothioglycerol, propylene glycol, polyethylene glycol 400 and sodium hydroxide which are inactive ingredients present in many FDA approved intravenous injection drug products. The levels, in terms of concentration in the drug product and the admixture of excipients are below the levels used in currently approved parenteral drug products and do not require qualification.

5. Process Selection (Unit Operations Summary)

(b) (4)

[redacted]

(b) (4)

7. Expiration Date & Storage Conditions

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

Bendamustine hydrochloride is a multi-use vial. Although it does not contain any antimicrobial preservative, bendamustine hydrochloride 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 - 8°C or 36 - 46°F). Each vial is not recommended for more than a total of six (6) dose withdrawals.

The in-use stability for the 50 mL diluted product in 0.9% Sodium Chloride and 0.45% Sodium Chloride/2.5% Dextrose admixture solutions is 6 hours at room temperature and

24 hours at refrigerated conditions.

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.

8. List of co-packaged components

There are no co-packaged components supplied with the drug product.

9. Facility Review

There are no significant, outstanding manufacturing risks and the Office of Process and Facilities recommended approval of the NDA submission. Based on firm inspectional history and district file review, the manufacturing facilities as listed below for NDA 208194 are acceptable.

Drug Substance Facilities

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

Drug Product Facilities

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

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Bendeka
Non Proprietary Name of the Drug Product	bendamustine hydrochloride injection
Non Proprietary Name of the Drug Substance	bendamustine hydrochloride
Proposed Indication(s) including Intended Patient Population	• Chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established. • Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.
Duration of Treatment	Treatment continues until disease progression or unacceptable toxicity.
Maximum Daily Dose	For CLL: 100 mg/m^2 infused intravenously over 10 minutes on Days 1

	and 2 of a 28-day cycle, up to 6 cycles For NHL: 120 mg/m^2 infused intravenously over 10 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles
Alternative Methods of Administration	None

D. Biopharmaceutics Considerations

1. BCS Classification:
   - Drug Substance: Not established
   - Drug Product: Not established

2. Biowaivers/Biostudies
   - Biowaiver Requests: N/A
   - PK studies: A bioequivalence study comparing Eagle's product and Treanda®, the reference product, is reviewed.

Based on FDA recommendations given 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 Division of Biopharmaceutics recommends APPROVAL of NDA 208194 for Bendamustine Hydrochloride Capsules, 25 mg/mL.

E. Novel Approaches: None

F. Any Special Product Quality Labeling Recommendations:

BENDEKA (bendamustine hydrochloride) Injection should be stored refrigerated at 2° to 8°C (36° to 46°F). Retain in original carton until time of use to protect 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.*"

G. Process/Facility Quality Summary (see Attachment A)

H. Life Cycle Knowledge Information (see Attachment B)

Digitally signed by Janice T. Brown -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300101685, cn=Janice T. Brown -A
Date: 2015.11.05 13:24:01 -05'00'

ASSESSMENT OF THE BIOPHARMACEUTICS INFORMATION

33. Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?

Not Applicable. The drug product is a solution for intravenous infusion and dissolution testing is not needed.

34. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

The same formulation used throughout development is the intended commercial product. No bridging is therefore needed. The Biopharmaceutics review will focus on the Bioequivalence study comparing the Applicant's product and Treanda®, the listed drug.

The Applicant has developed a sterile solution of bendamustine hydrochloride (BDM HCl) for intravenous administration for the treatment of chronic lymphocytic leukemia (CLL) and indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen. The comparison between the proposed drug product and the LD, Treanda, in terms of physical properties and dosing regimen are summarized in the table below:

Table 34-1: Comparison of Eagle BDM HCl vs Treanda®

	Vial	Physical form	Amount	Volume	Infusion volume	Infusion time
Eagle BDM HCl	Multi-dose	Ready-to-dilute solution	100 mg	4 mL	50 mL	10 min
Treanda®	Single-dose	Lyophilized powder	25 mg 100 mg		500 mL	30 min for CLL, 60 min for NHL

The Applicant conducted an open-label, randomized, crossover (3-period, partially replicated) phase 1 study **(# EGL-BDM-C-1301)** to demonstrate the bioequivalence of the drug product to the listed drug. The safety and tolerability profile of the two drug products were also assessed.

BIOEQUIVALENCE STUDY EGL-BDM-C-1301

Study Title:

Phase 1, open-label, crossover, randomized, bioequivalence study to evaluate two formulations of Bendamustine (BDM) Hydrochloride (HCl) administered to cancer patients.

Objectives

- To demonstrate the bioequivalence (BE) of between Eagle's BDM HCl (Test product) and Teva's BDM HCl (Reference product).
- To Evaluate the infusion-related safety and tolerability profile of Eagle BDM.
- To characterize additional BDM pharmacokinetic (PK) parameters of Eagle-BDM (T) and Teva-BDM (R), as well as PK parameters for the metabolite, gamma-hydroxy-bendamustine (M3)

Design

Open-label, randomized, partially replicated crossover (3-period, TRR, RTR, or RRT).

Population: Cancer patients with 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.

Study Products:

- Test: Eagle-BDM, 120[1] mg/m^2, 50 mL given by IV infusion over 10 min.
- Reference: Teva-BDM, 120 mg/m^2, 500 mL admixture given by IV infusion over 60 min.

Sample size: Sixty (60) patients received all 3 doses of BDM. The sample size was calculated based on an interim analysis[2] which showed that BDM is a highly variable drug (within subject CV% of BDM was 41.987%), and 80% of power.

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;

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[1] In view of the shorter infusion time for Eagle-BDM resulting in a higher C_{max} and possibly impacting safety, the FDA requested that the highest approved BDM dose (120 mg/m^2) be evaluated in this study.

[2] FDA has agreed on the interim analysis, which was planned for the first 12 patients (4 patients from each treatment sequence) completed randomized treatments, in order to estimate the within patient variability of Teva-BDM, estimate the ratio of geometric means, adjust study sample size to maintain the study power of ≥80%, and review the safety assessment. (IND116448 Office of Clinical Pharmacology Review, 03/20/2014)

- 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.

Treatment Schedule and Sampling Time:

Table 34-2 Treatment Schedule and Sampling Time

Dosing #	Drug product	Dosing Time	Day # since initial dose	Sampling Time
#1	Depending on randomization	Cycle* 1, day 1	1	Predose on day 1 (Dose 1) till 8 hours after the end of administration on day 2 (Dose 2)
#2		Cycle 1, day 2	1	
#3		Cycle 2, day 1	29	Predose till 24 hours after Dose 3
#4	EAGLE-BDM	Cycle 2, day 2	30	No PK sampling

Note: * one treatment cycle is 28-day

Washout Period: 24 hours between the 1st and 2nd doses, which was justified by a short plasma elimination T½ of approximately 40 minutes

Blood Sampling: 15 to 30 minutes before infusion of Study Treatment; half-way through the nominal infusion period; immediately after completion of the infusion (within 1 minute); 5, 15, 30, and 45 minutes post infusion; and 1, 1.5, 2, 3, 4, 5, and 8 hours post infusion. Additional PK blood samples were taken 24 hours from the start of infusion for Dose 1 and Dose 3 (Day 1 of both cycles).

Bioanalytical Method and Validation

Plasma BDM concentration was measured. Plasma concentrations of M3 (a minor active metabolite) were also measured but not analyzed for BE determination.

Table 34-3 Bioanalytical Method and Validation

Matrix	Plasma	
Sample Volume Required, Storage Conditions, Extraction Procedure	Five (5) mL blood samples were drawn from a peripheral vein in the opposite arm/side from the site of administration. Stored at -10 to -30 °C and -60 to -80 °C. Supported-liquid extraction	
Concentration Range	10.0 to 10000 ng/mL for BDM, and 1.00 to 1000 ng/mL for M3	
Analytical Methodology	Supported liquid extraction/ LC-MS	
Detection	Tandem mass spectrometry	
Regression Type	Weighted ($1/X^2$) quadratic regression	
Coefficient of Determination	>0.99	
Between-Batch Accuracy	standards QCs	N/A Range of ±15.0% bias (±20.0% at LLOQ) of the nominal concentration

Between-Batch CV	standards QCs	N/A NMT (b) (4) % at LLOQ)
Within-Batch	Accuracy CV	Range of ±15.0% bias (±20.0% at LLOQ) of the nominal concentration NMT (b) (4) % at LLOQ)
Recovery	BDM BDM- internal standard M3 M3- Internal standard	78.3% 79.8% 85.3% 90.9%
Stability in human plasma	Room temp Freeze/thaw Long term Wet ice	1 hour (RT), 2 hours (wet ice) 5 cycles (-10 to -30 °C); 4 cycles (-60 to -80 °C) 30days (-10 ~ -30 °C); 198 days (-60 ~ -80 °C) 8 hours
Solution Stability	at room temp -10 to -30 °C	6 hours 35 days
Reference Solution Stability	at room temp -10 to -30 °C	6 hours 35 days
LLOQ (Accuracy / CV)		10.0 ng/mL for BDM, 1.00 ng/mL for M3
Processed Stability	2 to 8 °C	96 hours
Dilution Integrity (v:v sample-blank)		1:10

The Bioanalytical method was performed acceptably, and the method was appropriately validated.

Pharmacokinetic Parameters and Statistical Analysis

BE analysis: The BDM PK parameters for Eagle-BDM and Teva-BDM (AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, and $T_{½}$) were generated from the actual plasma concentration-time data using non-compartmental analysis for the above-mentioned 4 sub-. A statistical analysis was performed in the 2 Primary PKE sub-populations (n=60 [FDA requested primary] and n=44 [Eagle proposed primary]), as well as for the 2 secondary sensitivity populations (n=57 [FDA requested primary] and n=38 [Eagle proposed primary]) to determine whether Eagle-BDM was bioequivalent to Teva-BDM on the basis of total BDM exposures, AUC_{0-t} and $AUC_{0-\infty}$. It was decided on the internal meeting for IND116448 held on 01/15/2013 that similarity in AUC is sufficient for concluding bioequivalence because C_{max} (and T_{max}) will be different due to the differences in concentration and administration duration between the formulations.[3]
Both the unscaled and the reference-scaled average BE approaches were used in the analyses of the data. Per the Applicant, the within-subject variability (S_{WR}) of the drug is more than 30%; the reference-scaled BE analysis was therefore relied upon to determine bioequivalence.

Safety Assessment

[3] IND116448 Memorandum of Meeting Minutes. 01/16/2013

Eagle-BDM administered IV to cancer patients appeared to be safe and well tolerated in this study. The most common TEAEs reported for patients treated with either Eagle-BDM or Teva-BDM were either known treatment effects of BDM HCl or expected from the underlying disease condition.
The higher Cmax values observed with the "short-infusion" Eagle-BDM product administered in this study produce a similar safety profile as the currently marketed Teva-BDM formulation and thus the PK safety link has been established. Refer to the Clinical Safety review for additional details.

Results

Bioequivalence: The mean PK profiles in semi-logarithmic scale comparing Eagle and Teva BDM are presented below for the FDA requested primary population (n=60) and the Eagle proposed secondary population (n=38) respectively.

Figure 34-1 Primary PKE Population (FDA recommended) Mean BDM (±SD) Plasma Concentration-Time Comparative Profiles (0-8 Hours Truncated) Following a Single-Dose Infusion of Eagle-BDM (10 Minute Infusion) and Teva BDM (60 Minute Infusion) in "End of Life" Cancer Patients (Linear Scale/ N=60)

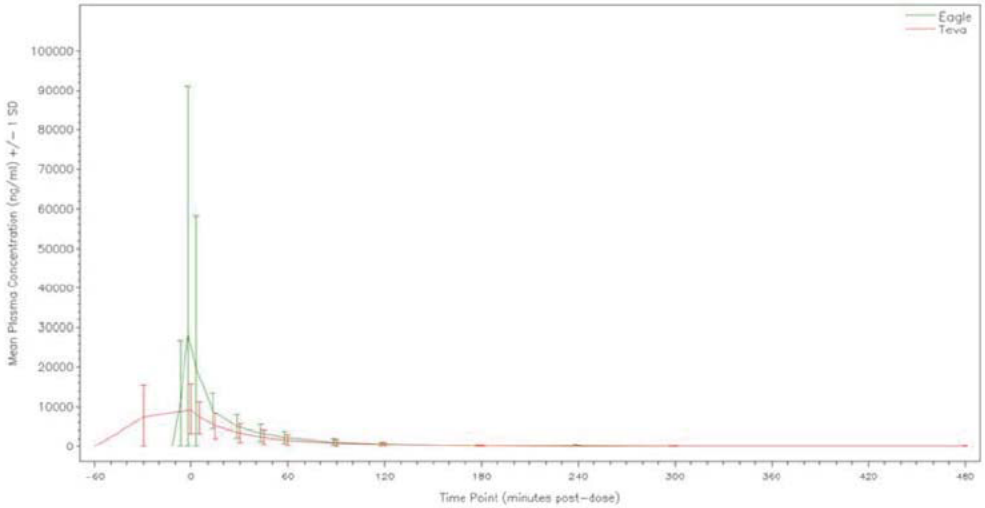
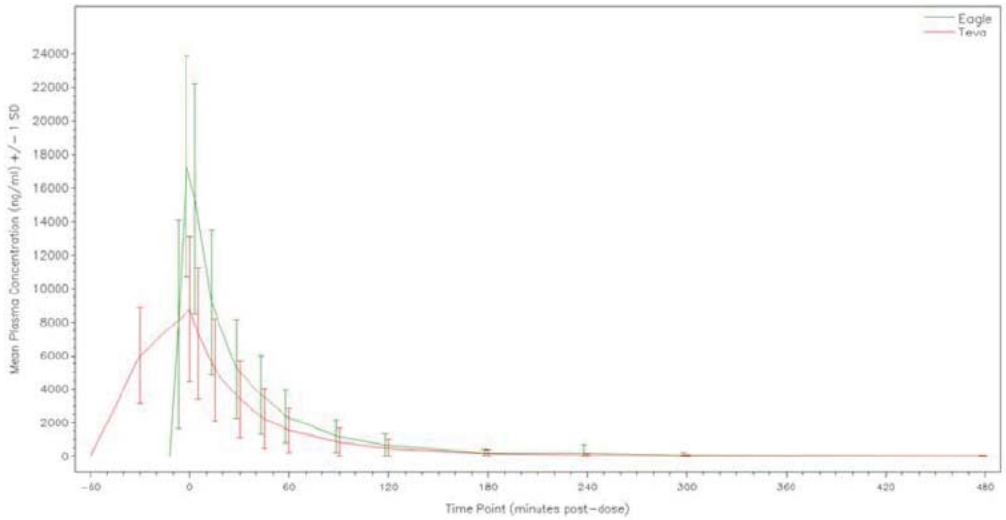


Figure 34-2 Secondary Sensitivity PKE Population (Eagle Proposed per SAP) Mean BDM (±SD) Plasma Concentration- Time Comparative Profiles (0-8 Hours Truncated) Following a Single-Dose Infusion of Eagle-BDM (10 Minute Infusion) and Teva BDM (60 Minute Infusion) in "End of Life" Cancer Patients (Linear Scale/ N=38)



As expected, Eagle-BDM Cmax values are approximately 250% higher than that of Teva-BDM. The total BDM exposure is nearly identical. The descriptive summary of the PK parameters can be found in Table 12 and Table 13 of the clinical study report (page 100-101).

Bioequivalence was determined based on comparison of the AUCs (AUC_{0-t} & $AUC_{0-\infty}$) between the Test product and the Listed Drug. The results are presented in the table below. Four (4) populations were evaluated using both reference scaled approach and the average BE approach. The results support bioequivalence.

Table 34-4. Primary PKE Population Bioequivalence (FDA Requested and Eagle Proposed) and Secondary Sensitivity PKE Population (FDA Requested and Eagle Proposed) ANOVA Analysis Results for Eagle-BDM and Teva-BDM in "End-of-Life" Cancer Patients

BDM AUC_{0-t} (ng.h/mL)	**FDA Requested**		**Eagle Proposed**
PKE Population	**Primary PKE (N=60)**	**Secondary Sensitivity PKE (N=57)**	(b) (4)
Eagle-BDM (Test)[a]	9546.49	9855.58	
Teva-BDM (Reference)[a]	9450.25	9618.32	
Test/Reference[a]	**1.01**	**1.02**	
90% Confidence Interval	**0.914 – 1.114**	**0.925 – 1.135**	
Upper Critical Bound	-0.09	-0.09	
S_{WR}	0.392	0.391	
S^2_{WR}	0.154	0.153	
BE Method	RSABE	RSABE	
BE Result	**Passed**	**Passed**	
BDM $AUC_{0-\infty}$ (ng.h/mL)	**FDA Requested**		**Eagle Proposed**

PKE Population	Primary PKE (N=60)	Secondary Sensitivity PKE (N=57)	Primary PKE (N=44)	Secondary Sensitivity PKE (N=38)
Eagle-BDM (Test)[a]	9547.23	9884.32	8879.02	9173.01
Teva-BDM (Reference)[a]	9464.6	9632.81	8943.95	9062.77
Test/Reference[a]	**1.01**	**1.03**	**0.99**	**1.02**
90% Confidence Interval	**0.915 -1.115**	**0.926 -1.137**	**0.888 – 1.112**	**0.899 – 1.146**
Upper Critical Bound	-0.09	-0.09	-0.08	-0.09
S_{WR}	0.391	0.391	0.383	0.402
S^2_{WR}	0.153	0.153	0.147	0.162
BE Method	RSABE	RSABE	RSABE	RSABE
BE Result	**Passed**	**Passed**	**Passed**	**Passed**

[a] Geometric Means Values

PK parameters by-sex comparison was conducted on the Eagle proposed secondary population (n=38). The results indicated that females appeared to have higher C_{max} and AUC than males, and the difference between female and male AUCs were higher for Teva-BDM than Eagle-BDM (18% vs 11%). The applicant indicated the differences are not clinically significant and there is no sex impact.

Reviewer's Assessment:

The objective of Study EGL-BDM-C-1301 was to demonstrate that the EAGLE-BDM product given over a 10 min infusion interval is bioequivalent to the reference product (Teva-BDM) given over 60 min, and they have similar safety profiles (see Clinical safety review in DARRTS). Based on FDA recommendations given 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).

The study design is acceptable. The RSABE method is deemed appropriate to assess BE by FDA for highly-variable drugs such as BDM HCl. 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.

This Biopharmaceutics Reviewer analyzed the provided raw PK data on the FDA recommended primary and secondary PKE populations only using the NCA, ABE, and RSABE tools of Phoenix Winnonlin 6.4. The results are summarized in the Table below. The results confirm that the drug product is highly variable (cv%=39%), and the proposed drug product is bioequivalent to the reference product by RSABE as well as ABE analysis.

		FDA recommended primary PKE (n=60)		FDA recommended secondary PKE (n=57)	
		AUC_{last}	AUC_{inf}	AUC_{last}	AUC_{inf}
ABE	Ratio (%)	104.92	105.17	106.67	106.94
	90% CI lower	94.74	94.95	95.98	96.19
	90% CI upper	116.18	116.50	118.56	118.89
RSABE	sWR	0.387	0.387	0.388	0.388
	Point Estimate	1.0479	1.0504	1.0667	1.0694
	Critical bound	-0.0832	-0.0825	-0.0780	-0.0771
	Conclusion	**PASS**	**PASS**	**PASS**	**PASS**

In addition to the parent drug BDM, the applicant also measured the metabolite M3 in the BE study but did not analyze the data. This is acceptable. According to Guidance for Industry *Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs-General Considerations (March 2014)*, measurement of the active ingredient, rather than metabolites is generally recommended. For this particular drug product, the parent drug BDM is in much higher quantity and the cytotoxic activity is primarily due to BDM, therefore BE evaluation was based on the parent drug BDM.

The applicant's conclusion of no gender effect is consistent with the labeling of Treanda.

The safety profiles of the two products are similar, despite the higher Cmax achieved by the Eagle-BDM product.

OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

Reviewer's Assessment and Signature:

From a Biopharmaceutics perspective, NDA 208-194 is recommended for **APPROVAL.**

Jing Li, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Supervisor Comments and Concurrence:
I concur with Dr. Li's review and approval recommendation for NDA 208194.

Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

35. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment:

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE – Non-sterile

P DRUG PRODUCT

(b) (4)

(b) (4)

The product is labeled multi-dose with maximum of 2 doses available in each vial.

P.1 Description of the Composition of the Drug Product

- Description of drug product – Bendamustine hydrochloride injection is a sterile non-aqueous solution that is intended for infusion after dilution in an IV solution. As stated in the Remarks Section, Drug product composition – The Batch Formula is presented in Table 1 (copied from Table 3.2.P.1-1)

Table 1. Composition of Bendamustine HCl Injection, 25 mg/mL

Ingredient	Quality Standard	Amount per Vial (mg)	Concentration	Function
Bendamustine HCl*	In-House	100 mg	25 mg/mL	Active Ingredient
Monothioglycerol	NF	20 mg	5 mg/mL	(b) (4)
Propylene Glycol	USP	0.4 mL	0.1 mL/mL	
Polyethylene Glycol 400 (PEG 400)§	NF		(b) (4	

(b) (4)

(b) (4)

- Description of container closure system – The container closure system used for the drug product consist of a 5 mL USP Type I molded glass vial ((b) (4) rubber stopper (DMF (b) (4) flip off seal. The secondary packaging for the vials is a single vial carton. The CCI information in DMFs (b) (4) was found adequate.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

(b) (4)

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Reviewer's Assessment: The product does not contain any materials sourced from animals.

38. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response: This can be adopted from the QbR-QOS and Module 3 provided from the firm.

Reviewer's Assessment: N/A

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: The applicant meets the regulatory expectations for validating the process used for sterilization of the containers, closures and manufacturing equipment. The applicant has also met regulatory expectations with regard to the test method, acceptance criteria and verification of the suitability of use of the bacterial endotoxins test that will be performed on the drug product prior to its release.

Vinayak Pawar, Ph.D.
October 14, 2015

Supervisor Comments and Concurrence:
I concur
Erika Pfeiler, Ph.D.
October, 14, 2015

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

39. Is the applicant's claim for categorical exclusion acceptable?

40. Is the applicant's Environmental Assessment adequate for approval of the application?

Reviewer's Assessment:

The applicant has requested a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR, part 25, §25.31(a) for bendamustine hydrochloride injection. This NDA submission meets the requirements of a categorical exclusion under 21 CFR §25.31(a) since it will not increase the use of the drug. To the best of Eagle's knowledge, no extraordinary circumstances exist in regards to these actions. The applicant's request for a categorical exclusion is accepted.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL ANALYSIS

Reviewer's Assessment and Signature:

The cited categorical exclusion at 21 CFR 25.31(a) is appropriate for the submitted application, and a statement of no extraordinary circumstances has been submitted. The claim of categorical exclusion is acceptable.

Janice Brown, M.S.
November 5, 2015

Supervisor Comments and Concurrence:
I concur that the claim of categorical exclusion is acceptable.

Olen Stephens, Ph.D.
November 5, 2015

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

BENDEKA™ (bendamustine hydrochloride) Injection, for intravenous use.
Initial U.S. Approval: 2008
Injection: 100 mg/4 mL (25 mg/mL) in a multiple-dose vial (3).

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	BENDEKA™ (bendamustine hydrochloride) Injection	Adequate.
Dosage form, route of administration	Injection for intravenous use	Adequate.
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	100 mg/4 mL (25 mg/mL)	Adequate.

Conclusion: This section is adequate.

(b) "Full Prescribing Information" Section

 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

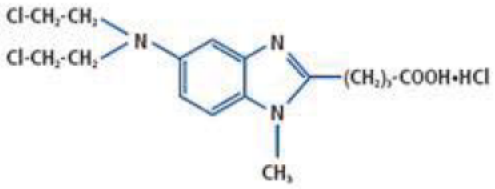
Injection: 100 mg/4 mL (25 mg/mL) as a clear and colorless to yellow ready-to-dilute solution in a multiple-dose vial.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Injection is provided	Adequate.
Strengths: in metric system	25 mg/mL is provided	Adequate.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	"as a clear and colorless to yellow ready-to-dilute solution in a multiple-dose vial" is provided.	Adequate.

Conclusion: This section is adequate.

#11: Description (21CFR 201.57(c)(12))

BENDEKA (bendamustine hydrochloride) Injection is an alkylating agent. The chemical name of bendamustine hydrochloride is 1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1 methyl-, monohydrochloride. Its empirical molecular formula is C16H21Cl2N3O2 · HCl, and the molecular weight is 394.7. Bendamustine hydrochloride contains a mechlorethamine group and a benzimidazole heterocyclic ring with a butyric acid substituent, and has the following structural formula:



BENDEKA (bendamustine hydrochloride) Injection is supplied as a sterile, clear, and colorless to yellow ready-to-dilute solution in a multiple-dose clear glass vial. Each milliliter (b) (4) contains 25 mg of bendamustine hydrochloride, 0.1 mL of propylene glycol, USP, 5 mg of monothioglycerol, NF, (b) (4) polyethylene glycol 400, NF. Sodium hydroxide may have been used to adjust the acidity of polyethylene glycol PEG 400.

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Bendamustine hydrochloride is provided	Adequate.
Dosage form and route of administration	Bendamustine hydrochloride injection is intended for intravenous infusion only after dilution is provided	Adequate.
Active moiety expression of strength with equivalence statement for salt (if applicable)	N/A	N/A
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Provided	Adequate.
Statement of being sterile (if applicable)	Provided	Adequate.
Pharmacological/ therapeutic class	Provided as an alkylating agent	Adequate.
Chemical name, structural formula, molecular weight	Provided	Adequate.
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa,	N/A	N/A

solubility, or pH)		

Conclusion: This section is adequate.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16.1 Safe Handling and Disposal

BENDEKA (bendamustine hydrochloride) Injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.1 Care should be exercised in the handling and preparation of solutions prepared from BENDEKA (bendamustine hydrochloride) Injection. The use of gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If a solution of BENDEKA (bendamustine hydrochloride) Injection contacts the skin, wash the skin immediately and thoroughly with soap and water. If BENDEKA (bendamustine hydrochloride) Injection contacts the mucous membranes, flush thoroughly with water.

16.2 How Supplied

BENDEKA (bendamustine hydrochloride) Injection is supplied in individual cartons of 5 mL clear multiple-dose vials containing 100 mg of bendamustine hydrochloride as a clear, and colorless to yellow ready-to-dilute solution.

- NDC 63459-348-04, 100 mg/4 mL (25 mg/mL)

16.3 Storage

BENDEKA (bendamustine hydrochloride) Injection should be stored in refrigerator, 2° to 8°C (36° to 46°F). Retain in original carton until time of use to protect from light.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	25 mg/mL is provided	Adequate.
Available units (e.g., bottles of 100 tablets)	Supplied in individual carton is provided	Adequate.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	"as a clear, colorless to yellow ready-to-dilute solution" is provided	Adequate.
Special handling (e.g., protect from light, do not freeze)	"Retain in original package until time of use to protect from light" is provided	Adequate.
Storage conditions	"Bendamustine hydrochloride should be stored between 2° to 8°C (36° to 46°F)" is provided	Adequate.

Manufacturer/distributor name listed at the end of PI, following Section #17

Distributed By:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Provided	Adequate.

Conclusion: This section is adequate.

2. Labels

1) Immediate Container Label

(b) (4)

QUALITY ASSSSMENT

Bendeka (bendamustine hydrochloride) injection
Eagle Pharmaceuticals, Inc.

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	BENDEKA (bendamustine HCl) Injection is provided	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	25 mg/mL is provided	Adequate
Route of administration 21.CFR 201.100(b)(3))	For intravenous infusion only is provided	Adequate
Net contents* (21 CFR 201.51(a))	100 mg/4 mL is provided	Adequate
Name of all inactive ingredients (Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Both inactive ingredients and quantitative information are only provided in the carton label, not provided in the immediate container label since the label is too small	Adequate
Lot number per 21 CFR 201.18	Space for lot number is not allocated	Inadequate
Expiration date per 21 CFR 201.17	Space for expiration date is not allocated	Inadequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Rx only statement is provided	Adequate
Storage condition (not required)	Storage condition is provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC number is provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)***	Bar code is provided	Adequate
Name of manufacturer/distributor (21 CFR 201.1)	Provided	Adequate
Others	Special handling is provided to protect from light Need to change ""multi-use vial" to "multi-dose vial"	Inadequate

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: A final review and recommendation will be made by CDTL in the CDTL review.

2) Cartons

(b) (4)

QUALITY ASSSSMENT

Bendeka (bendamustine hydrochloride) injection
Eagle Pharmaceuticals, Inc.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	BENDEKA (bendamustine HCl) Injection is provided	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	100 mg/4 mL, 25 mg/mL is provided	Adequate
Net contents (21 CFR 201.51(a))	Bendamustine HCl injection is supplied in individual carton is provided in the package insert Need to change ""multi-use vial" to "multi-dose vial"	Inadequate
Lot number per 21 CFR 201.18	Space for lot number is allocated	Adequate
Expiration date per 21 CFR 201.17	Space for expiration date is allocated	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	Both inactive ingredients and quantitative information are provided However, the following correction needs to be made: Each mL contains 25 mg bendamustine hydrochloride, 0.1 mL propylene glycol, USP, 5 mg monothioglycerol, NF in polyethylene glycol 400, NF. Sodium hydroxide, NF to adjust pH of polyethylene glycol 400.	Inadequate
Sterility Information (if applicable)	Sterile is provided	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	Rx only is provided	Adequate
Storage Conditions	Storage condition is provided	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC number is provided	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Bar code is provided	Adequate
Name of manufacturer/distributor	Name of manufacturer/distributor is provided	Adequate
"See package insert for dosage information" (21 CFR 201.55)	See package insert for dosage information is provided	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	Not required for Rx	Adequate

Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	For intravenous infusion only is provided	Adequate

Conclusion: A final review and recommendation will be made by CDTL in the CDTL review.

II. List of Deficiencies To Be Communicated

A. Drug Substance: None
B. Drug Product: None
C. Process/Facility: None
D. Biopharmaceutics: None
E. Microbiology: None
F. Label/Labeling

The following container/carton labeling comments were sent to the applicant:

Carton label

1. Change from: [redacted (b) (4)]

   To: Each mL contains 25 mg bendamustine hydrochloride, 0.1 mL propylene glycol, USP, 5 mg monothioglycerol, NF in [redacted (b) (4)] polyethylene glycol 400, NF. [redacted (b) (4)] Sodium hydroxide, NF to adjust pH of polyethylene glycol 400.

2. Change [redacted (b) (4)] to "multi-dose vial".

Vial label

3. Change [redacted (b) (4)] to "multi-dose vial".
4. Allocate a space for lot number.
5. Allocate a space for an expiration date.

Evaluation: The acceptability of the final PI and container/carton labeling will be addressed by CDTL in the CDTL review.

III. Attachments

A. Facility

OVERALL RECOMMENDATION:				
DRUG SUBSTANCE				
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**INITIAL RISK IDENTIFICATION**	**FINAL RECOMMENDATION**
Responsible for the manufacture, control, packaging, QC release and stability testing of the drug substance.	(b) (4)	(b) (4)	Low	Acceptable Based on District Recommendation
Responsible for (b) (4) testing of the drug substance	(b) (4)	(b) (4)	Low	Acceptable Based on Profile
DRUG PRODUCT				
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**INITIAL RISK IDENTIFICATION**	**FINAL RECOMMENDATION**
Responsible for testing and release of raw materials (drug substance and excipients); Drug product manufacturing, testing, release, and stability testing.	(b) (4)	(b) (4)	Low	Acceptable Based on District Recommendation
Responsible for performing admixture and stability testing on the drug product	(b) (4)	(b) (4)	Low	Acceptable Based on Profile

B. Lifecycle Knowledge Management

Drug Product

From Initial Risk Identification		Review Assessment		
Attribute/ CQA	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations / Comments****
Sterility	H	Adequate controls in place	Acceptable	
Endotoxin (b) (4)	M	Adequate controls in place	Acceptable	
Assay (API), stability	L		Acceptable	
Assay (preservative)	NA	The drug product is self-preserving	Acceptable	
Assay (anti-oxidant)	H	The drug product is stable under the storage condition during shelf life Development study shows that (b) (4) mg/mL of monochloroethyl bendamustine is adequate to (b) (4) during compounding and filling	Acceptable	
Uniformity of Dose (Fill Volume/ Deliverable volume)	L		Acceptable	
Osmolality	M	Drug product will be diluted with either normal (b) (4) prior to IV administration	Acceptable	
pH- (High)	M	Non aqueous vehicle of PG and PEG400 are used in the drug product	Acceptable	
pH- (Low)	L		Acceptable	
Particulate matter (non aggregate for solution only)	M	Adequate controls in place	Acceptable	
Leachable extractables	L		Acceptable	
Appearance (Color/turbidity)	L		Acceptable	

*Risk ranking applies to product attribute/CQA
**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

IV. Administrative

A. Reviewer's Signature: Refer to discipline specific reviews in the IQA.

B. Endorsement Block

Reviewer Name/Date: See signed discipline specific reviews in IQA
Secondary Reviewer Name/Date: See signed discipline specific reviews in IQA
Project Manager Name/Date: Rabiya Laiq, 03-Nov-2015