# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208194Orig1s000

# MICROBIOLOGY/VIROLOGY REVIEW(S)

# Product Quality Microbiology Review

**September 27, 2015**

**NDA:** 208194

**Drug Product Name**
**Proprietary:** N/A
**Non-proprietary:** bendamustine hydrochloride, 100 mg/4mL

**Review Number:** 1

**Dates of Submission(s) Covered by this Review**

| Submit | Received | Review Request | Assigned to Reviewer |
|---|---|---|---|
| February 12, 2015 | February 13, 2015 | February 23, 2015 | February 25, 2015 |

**Submission History (for 2nd Reviews or higher) – N/A**

**Applicant/Sponsor**
**Name:** Eagle Pharmaceuticals
**Address:** 50 Tice Blvd., Woodcliff Lake, NJ 07677
**Representative:** Foma Rashkovsky, Vice President of RA
**Telephone:** (210)-326-5309

**Name of Reviewer:** Vinayak B. Pawar, Ph.D.

**Conclusion:** Recommend Approval.

# Product Quality Microbiology Data Sheet

**A. 1. TYPE OF SUBMISSION:** Original NDA

**2. SUBMISSION PROVIDES FOR:** Bendamustine HCl, 100 mg/4 ML

**3. MANUFACTURING SITE:** [redacted] (b) (4)

**4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 100 mg/4 mL Solution for IV infusion. Multi-dose vial for either a single dose 100 mg/m$^2$ or [redacted] (b) (4) 50 mg/m$^2$ doses on Days 1 & 2 of the cycle.

**5. METHOD(S) OF STERILIZATION:** [redacted] (b) (4)

**6. PHARMACOLOGICAL CATEGORY:** Treatment of Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma

**B. SUPPORTING/RELATED DOCUMENTS:**
DMF [redacted] (b) (4), Microbiology Review #25 - August 20, 2013
NDA 205580, Product Quality Review - May 14, 2014.

**C. REMARKS:** In accordance with Section 505(b) (2), this submission provides for a review of original NDA 208194 for the drug Bendamustine HCl, 100 mg/4 ML. The sponsor requests for Priority Review Designation. The sponsor references prior finding of safety and effectiveness for TREANDA (bendamustine HCl for injection) under NDA 22249, which requires reconstitution and dilution prior to administration. This is an electronic submission.
The [redacted] (b) (4) drug product submitted in the NDA 205580 by the same applicant.

[redacted] (b) (4)

**filename:** 208194R1.doc

# Executive Summary

## I. Recommendations

### A. Recommendation on Approvability - Recommend Approval.

### B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

## II. Summary of Microbiology Assessments

### A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –

(b) (4)

visually inspected and the finished goods are quarantined for labeling and packing and finally stored.

### B. Brief Description of Microbiology Deficiencies - None

### C. Contains Potential Precedent Decision(s) - ☐ Yes ☒ No

## III. Product Quality Microbiology Risk Assessment

### A. Initial Product Quality Microbiology Risk Assessment

| CQA | Risk Factor | Prob. of Occ. (O) | Modifier for O[3, 4, 5] | Severity of Effect (S) | Detect. (D) | Risk Priority Number[6] (RPN) | Additional Review Emphasis based on Risk (in addition to normal review process) |
|---|---|---|---|---|---|---|---|
| Ster. | (b) (4) | 10 | | 5 | 5 | | Simulations and interventions conducted during media fills, Environmental monitoring |
| Endo | | 4 | | 4 | 4 | | |

(b) (4)

3 = Anti-Microbial Formulation (e.g., meets USP <51>), modifies O (-1) [less emphasis on in process hold times]

4 = Post-Constitution/-Dilution Hold Times in Labeling, modifies O (+1) [emphasize Labeling instructions for administration, dosing, storage conditions, and specified diluents. Microbial challenge studies supporting label recon/dilution/storage instructions if >4 hr RT or >24 hr refrig.]
5 = Components derived from animal sources, modifies O (+1) [emphasize Component bioburden, TSE/BSE-free documentation (TS and AP), viral inactivation studies (AP), bioburden reduction processes.]
6 = RPN = O (after modification when applicable) ×S×D
RPN <50 = Low Risk; RPN 50-120 = Moderate Risk; RPN >120 = High Risk

**B. Final Risk Assessment** - Low

## IV. Administrative

**A. Reviewer's Signature** _____
Vinayak B. Pawar, Ph.D., Sr. Review Microbiologist, OPQ/DMA

**B. Endorsement Block –** _____
Erika A. Pfeiler, Ph.D., ATL, Branch I (Acting), OPQ/DMA

**C. CC Block**
N/A

# 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

***Note*: *The proposed 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 (b) (4) | NF | | (b) (4) | |
| | NF | | | (b) (4) |

(b) (4)

10 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

this batch. The change or deterioration in the distributed drug product shall be reported, as required under 21 CFR 314.81 (b) (1) (ii).

- Container Closure Integrity – N/A
- Sterility/Endotoxin – Tested at 12, 24, 30 and 36 months.

**P.8.3 Stability Data** – See Review Section P.8.1.

**ADEQUATE**

**REVIEWER COMMENT –** The applicant meets the regulatory expectations with regard to the design of the stability program to support the drug product's microbiological quality throughout its shelf life.

## 2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

**PACKAGE INSERT**

Drug product is intended for dilution in lower volumes of 0.9% sodium chloride for injection USP or 2.5% dextrose/0.45% sodium chloride for injection USP or additional diluent 5% Dextrose Injection (b) (4) Dosage and administration instructions state that the multi-dose product (per dosing instructions: to be used at Day 1 and Day 2) should be used within 24 hours when held under refrigeration or 3 hours when stored at room temperature (these times include administration time). The drug product has antimicrobial properties. Package insert states that in-use vials should be discarded after 28 days. Labeling meetings are ongoing.

**ADEQUATE**

**REVIEWER COMMENT –** The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling.

## 3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

None

Digitally signed by Vinayak B. Pawar -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300151299, cn=Vinayak B. Pawar -A
Date: 2015.10.06 02:08:25 -04'00'

Erika A. Pfeiler -S

Digitally signed by Erika A. Pfeiler -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000396533, cn=Erika A. Pfeiler -S
Date: 2015.10.06 07:12:00 -04'00'