

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205580Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: March 30, 2018
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 205580
Product Name and Strength: Bendamustine Hydrochloride Injection, 100 mg/4 mL (25 mg/mL)
Applicant/Sponsor Name: Eagle Pharmaceuticals
FDA Received Date: March 20, 2018
OSE RCM #: 2018-283-1
DMEPA Safety Evaluator: Nicole Garrison, PharmD, BCPS
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Hematology Products (DHP) requested that we review the revised container labels and carton labeling for Bendamustine Hydrochloride (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a We note per email response; the Applicant intends to market the product with the established name, bendamustine hydrochloride for now^b.

2 CONCLUSION

The revised container labels and carton labeling are acceptable from a medication error perspective.

^a Garrison N. Label and Labeling Review for Bendamustine Hydrochloride (NDA 205580). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAR 13. RCM No.: 2018-283.

^b Information Request Response received on March 30, 2018.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MARCH 20, 2018

Container labels



3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

NICOLE B GARRISON
03/30/2018

HINA S MEHTA
03/30/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: March 13, 2018

Requesting Office or Division: Division of Hematology Products (DHP)

Application Type and Number: NDA 205580

Product Name and Strength: Belrapzo (bendamustine hydrochloride) Injection, 100 mg/4 mL (25 mg/mL)

Applicant/Sponsor Name: Eagle Pharmaceuticals

FDA Received Date: January 31, 2018 and February 9, 2018

OSE RCM #: 2018-283

DMEPA Safety Evaluator: Nicole Garrison, PharmD, BCPS

DMEPA Team Leader: Hina Mehta, PharmD

DMEPA Associate Director (Acting): Mishale Mistry, PharmD, MPH

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the proposed container label, carton labeling, and Prescribing Information (PI) for Bendamustine Injection (NDA 205580) for areas of vulnerability that may lead to medication errors (Appendix A). DHP requested this review as a part of their evaluation of the 505(b)(2) NDA class I resubmission for Bendamustine Injection. DMEPA provided recommendations during a previous label and labeling review.^{a,b}

1.1 REGULATORY HISTORY

^a Gao. T. Label, Labeling and Packaging Review for Bendamustine (NDA 205580). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 DEC 24. RCM No.: 2013-1791.

^b Gao. T. Label, Labeling Review Memo for Bendamustine (NDA 205580). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 APR 09. RCM No.: 2013-1791.

Eagle Pharmaceuticals submitted Bendamustine Injection (NDA 205580) on September 6, 2013, a 505(b)(2) application which relies upon the listed drug, Treanda (bendamustine hydrochloride) for Injection under NDA 022249. Treanda is currently marketed in the following dosage forms and strengths: For injection 25 mg per vial and 100 per vial, and Injection 45 mg/0.5 mL (90 mg/mL) and 180 mg/2 mL (90 mg/mL). The proposed product will be available in an injection dosage form with a strength of 100 mg/4 mL (25 mg/mL). The application received a Tentative Approval letter on July 2, 2014 due to patent protection of the listed drug, Treanda.

On December 7, 2015, the Applicant received marketing approval for Bendeka (bendamustine hydrochloride) Injection 100 mg/4 mL (25 mg/mL) for infusion in a 50-mL admixture, under NDA 208194.

Eagle Pharmaceuticals submitted a request for final approval of Bendamustine Injection (NDA 205580) on January 31, 2018.

2 OVERALL ASSESSMENT

We note that Bendeka is the same formulation, dosage form (injection) and uses the same container closure system (multiple-dose vial) as the proposed Bendamustine Hydrochloride Injection. However, there are differences in the required diluent as both products can be diluted in Sodium 0.9% Chloride Injection and 2.5% Dextrose/0.45% Sodium Chloride Injection; however, Bendeka can also be diluted in 5% Dextrose whereas the proposed Bendamustine Hydrochloride Injection cannot. Furthermore, Bendeka requires a diluent volume of 50 mL, with a resulting final concentration of bendamustine hydrochloride in the infusion bag within 1.85 mg/mL – 5.6 mg/mL. The proposed Bendamustine Hydrochloride product requires a diluent volume of 500 mL, with a resulting final concentration of bendamustine hydrochloride in the infusion bag within 0.2 mg/mL– 0.7 mg/mL. The administration time of Bendeka is 10 minutes whereas the proposed Bendamustine hydrochloride product has an administration time of 30 or 60 minutes. Finally, the storage time following dilute also differs (6 hours vs. 3 hours) between Bendeka and Bendamustine Hydrochloride, respectively. See Appendix A for product characteristics comparison of the listed drug Treanda (NDA 022249), Bendeka (NDA 208194), and the proposed Bendamustine hydrochloride injection product (NDA 205580).

From a medication error perspective, the introduction of Bendamustine Hydrochloride diluted in a larger volume (500 mL) with a lower resulting final concentration than the currently approved, Bendeka, may result in preparation errors if the labeling is overlooked or does not sufficiently indicate the proper diluent, required volume for infusion, and final resulting concentration. Therefore, it is important to ensure that labels and labeling contain warning statements regarding further dilution and include prominent concentration information.

The proposed PI, label, and labeling can be improved to increase readability and prominence of proper preparation of the product as well as ensuring that peel-back labels does not get detached. Additionally, we note that the labels and labeling contain both term (b) (4)

and “multiple-dose”, we defer to the Office of Pharmaceutical Quality (OPQ) for determination of the appropriate package type and to maintain consistency of terms on labels and labeling.

3 CONCLUSION & RECOMMENDATIONS

We determined that the proposed PI, container label and carton labeling is vulnerable to confusion that can lead to medication errors. We provide recommendations for the Division in Section 3.1 and for the Applicant in Section 3.2 to be implemented prior to approval of NDA 205580.

3.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Highlights and Full Prescribing Information
 - a. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise those abbreviations, symbols, and dose designations as follows:
 - i. Replace the symbols “≤” and “≥” with their intended meanings to prevent misinterpretation and confusion.
2. Highlights of Prescribing Information
 - a. General Dosing Considerations
 - i. Consider removing storage information as this information is contained in Section 2.3 *Preparation for Intravenous Administration*.
3. Section 2.3 Preparation for Intravenous Administration
 - a. Intravenous Infusion
 - i. Bold the statement, “... 500 mL infusion bag”. We recommend this revision to increase prominence of this important information and to mitigate the risk of preparation errors.
 - ii. Bold the statement, “The resulting final concentration of bendamustine HCl in the infusion bag should be within 0.2-0.7 mg/mL.” We recommend this revision to increase prominence of this important information and to mitigate the risk of preparation errors.
 - iii. In Table A, underline the statement in the heading, “dilution into 500 mL”. We recommend this revision to increase prominence of this important information and to mitigate the risk of preparation errors.

3.2 RECOMMENDATIONS FOR EAGLE PHARMACEUTICALS

We recommend the following be implemented prior to approval of this NDA:

A. Container label

1. Please indicate where the required lot number and expiration date will appear as required per 21 CFR 610.60.
2. Revise the statement, (b) (4) to “See prescribing information for dosing and dilution information.”
3. As the peel-back labels contain important information regarding the preparation of the product, we are concerned that the peel-back labels may become detached from the product container under actual use. Therefore, we recommend that the peel-back label are resealable, able to withstand repeated openings and closings without detaching itself from the product container, and able to withstand moisture without detaching from the product container.^c
4. On the principal display panel (PDP), revise the cautionary statement, “(b) (4)” to the following:
“Must dilute required dose in a 500 mL admixture prior to administration”.
 We recommend this revision using bold, red font to bring prominence to this important information and to mitigate the risk of preparation errors and confusion with other formulations of Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL), which are diluted in a 50 mL admixture prior to administration with a resulting higher concentration.
5. On the peel-back label, include the diluent solutions (e.g. Sodium 0.9% Chloride Injection and 2.5% Dextrose/0.45% Sodium Chloride Injection) that can be used to prepare a 500 mL infusion bag of Bendamustine HCl. For example:
 “Aseptically withdraw the volume needed for the required dose based on **25 mg/mL** concentration as per Table A (see package insert) and immediately transfer to a **500 mL infusion bag** of **Sodium 0.9% Chloride Injection or 2.5% Dextrose/0.45% Sodium Chloride Injection**. We recommend this revision in bold, red font to bring prominence to this important information.

B. Ferrule label

1. You did not submit a copy of the ferrule label with the resubmission. If you intend to have a ferrule label we ask that you resubmit it to the Agency. If you intend to have a ferrule label, please ensure the cautionary statement ‘Dilute Before Using’ also appears on the ferrule in addition to the cap overseal in accordance with United States Pharmacopeia (USP) General Chapter <7> Labeling standard. We recommend this to minimize the risk of a medication error where the drug is administered undiluted, because this is a multi-dose vial and the cap overseal is often discarded during the pharmacy dispensing process.

C. Carton labeling

1. See A.2 and A.4 and revise the carton labeling accordingly.
2. On the PDP, revise the cautionary statement, (b) (4) to the following:

^c Label Process Series LPS2011-04, Guidance for Designing Peel-Back and Multi-Component Labels of Domestic Class Pest Control Products [Internet]. Ottawa (Ontario): Health Canada Pest Management Regulatory Agency. 2011 [cited 2013 Nov 6]. Available from <http://www.hc-sc.gc.ca/cps-spc/pubs/pest/pol-guide/lps2011-04/index-eng.php#a5>.

“Must dilute required dose in a 500 mL infusion bag of Sodium 0.9% Chloride Injection or 2.5% Dextrose/0.45% Sodium Chloride Injection prior to administration”.

We recommend this revision using bold, red font to bring prominence to this important information.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Belrapzo received on January 31, 2018 and February 9, 2018 from Eagle Pharmaceuticals, in comparison to Treanda and Bendeka.

| Table 2. Relevant Product Information for Belrapzo, Bendeka and Treanda | | | |
|--|--|---|--|
| Product Name | Belrapzo (NDA 205580) | Treanda (NDA 022249) | Bendeka (NDA 208194) |
| Initial Approval Date | Conditionally approved on July 2, 2014 | March 20, 2008 | December 7, 2015 |
| Active Ingredient | Bendamustine Hydrochloride | | |
| Indication | For the 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. | | |
| Route of Administration | Continuous intravenous infusion | | |
| Dosage Form | Injection | Injection and For Injection | Injection |
| Strength | 100 mg/4 mL (25 mg/mL) in a multiple-dose vial | Injection (in a single-dose vial) 45 mg/0.5 mL 180 mg/2 mL (90 mg/mL) For Injection (lyophilized powder in a single-dose vial for reconstitution) 25 mg per vial 100 mg per vial | 100 mg/4 mL (25 mg/mL) in a multiple-dose vial |
| Dose and Frequency | CLL: The recommended dose is 100 mg/m ² administered intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles. NHL: The recommended dose is 120 mg/m ² administered intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles. | | |
| Preparation | Injection: | Injection: | <u>Injection:</u> |

| | | | |
|----------------|--|--|---|
| | <p>Dilute with <u>500 mL infusion bag</u> of 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP</p> <p>Resulting final concentration of bendamustine HCL in the infusion bag should be within 0.2 mg/mL– 0.7 mg/mL</p> | <p>Dilute with <u>500 mL infusion bag</u> of 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP</p> <p>For injection: <u>Reconstitute with SWFI</u> 25 mg TREANDA for Injection vial: Add 5 mL of only Sterile Water for Injection, USP. 100 mg TREANDA for Injection vial: Add 20 mL of only Sterile Water for Injection, USP</p> <p><u>Dilute with</u> 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP</p> | <p>Dilute with <u>50 mL infusion bag</u> of 0.9% Sodium Chloride Injection, USP; or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP; or 5% Dextrose Injection, USP.</p> <p>Resulting final concentration of bendamustine hydrochloride in the infusion bag should be within 1.85 mg/mL – 5.6 mg/mL</p> |
| Storage | <p>Bendamustine HCL Injection 100 mg/4 mL (25 mg/mL) should be stored between 2° and 8°C (36° to 46°F). Retain in original package until time of use to protect from light.</p> <p>After first use, the ^{(b) (4)} vial should be stored in original carton at 2 °C to 8 °C,</p> | <p>Treanda Injection must be stored refrigerated between 2-8°C (36-46°F). Retain in original package until time of use to protect from light.</p> <p>Treanda for Injection may be stored up to 25°C (77°F) with excursions permitted up to 30°C (86°F) (see</p> | <p>Store Bendeka in refrigerator, 2°-8°C (36° to 46°F). Retain in original package until time of use to protect from light.</p> |

| | | | |
|--|-----------------------------------|---|--|
| | and then discarded after 28 days. | USP Controlled Room Temperature). Retain in original package until time of use to protect from light. | |
|--|-----------------------------------|---|--|

APPENDIX B. IMAGES OF LABEL AND LABELING RECEIVED ON FEBRUARY 9, 2018

Container labels



(b) (4)

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Carton labeling

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

/s/

NICOLE B GARRISON
03/13/2018

HINA S MEHTA
03/13/2018

MISHALE P MISTRY
03/13/2018

LABEL AND LABELING REVIEW - MEMO

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: April 9, 2014
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 205580
Product Name and Strength: Bendamustine Hydrochloride for Injection,
100 mg/4 mL (25 mg/mL)
Product Type: Single Ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Eagle Pharmaceuticals, Inc.
Submission Date: March 31, 2014
OSE RCM #: 2013-1791
DMEPA Primary Reviewer: Tingting Gao, PharmD
DMEPA Team Leader: Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the revised container label and carton labeling for Bendamustine hydrochloride for Injection, NDA 205580, submitted by Eagle Pharmaceuticals, Inc. on February 28, 2014 for areas of vulnerability that could lead to medication errors. DMEPA previously reviewed the proposed labels and labeling under OSE Review # 2013-1791 dated December 24, 2013 for NDA 205580.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

| Table 1. Materials Considered for this Label and Labeling Review | |
|--|--|
| Material Reviewed | Appendix Section (for Methods and Results) |
| Product Information/Prescribing Information | A |
| FDA Adverse Event Reporting System (FAERS) | B – N/A |
| Previous DMEPA Reviews | C |
| Human Factors Study (if applicable) | D – N/A |
| ISMP Newsletters | E – N/A |
| Other (if applicable) | F – N/A |
| Container Label, Carton Labeling, and Instructions for Use or Medication Guide (if applicable) | G |

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the revised labels and labeling submitted by the Applicant on February 28, 2014 and compared the revised labels and labeling against the recommendations contained in OSE Review #2013-2126 dated November 6, 2013. We identified the following areas of vulnerability to error in the container label and carton labeling:

- The “hydrochloride” part of the established name is in a different font size and does not appear to be part of the drug name.
- The barcode appears to be a (b) (4) instead of a linear barcode. This is not in accordance with 21 CFR 201.25(c) and 2004 FDA Barcode Rule.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed container label, carton and insert labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product to mitigate any confusion. DMEPA provides the following comments for consideration by the review Division prior to the approval of this NDA.

4.1 COMMENTS TO THE APPLICANT

A. All container labels and carton labeling

- a. The “Hydrochloride” part of the established name is in a different font size and does not appear to be part of the drug name. Revise the drug name so that the entire drug name, “Bendamustine hydrochloride” is presented in the same font size and boldness.

B. Container label

- a. The barcode on the vial label appears to be a (b) (4) [REDACTED] instead of a linear barcode. Revise this barcode to a linear barcode that contains, at a minimum, the appropriate National Drug Code (NDC) number in accordance with 21 CFR 201.25(c).

C. Ferrule Label

- a. Ensure the cautionary statement “Dilute Before Using” also appears on the ferrule in addition to the cap overseal in accordance with United States Pharmacopeia (USP) General Chapter <1> Injections labeling standard. We recommend this to minimize the risk of a medication error where the drug is administered undiluted, because this is a multi-dose vial and the cap overseal is often discarded during the pharmacy dispensing process.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for bendamustine hydrochloride that Egel Pharmaceuticals, Inc. submitted on September 6, 2013.

| | 505(b)(2) Bendamustine HCl Injection (100 mg/4 mL (25 mg/mL) | RLD Treanda® (bendamustine hydrochloride) for Injection |
|--------------------------------|---|---|
| Active ingredient | Bendamustine Hydrochloride | |
| Indication of Use | <ul style="list-style-type: none"> Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. | <ul style="list-style-type: none"> Chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established.¹ Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. |
| Route of Administration | Continuous intravenous infusion | |
| Dosage Form | Concentrated solution for dilution (ready-to-dilute solution) | Injection, powder for reconstitution |
| Strength | 100 mg/4 mL (25 mg/mL) | 25 mg/vial, 100 mg/vial |
| Dose and Frequency | NHL: 120 mg/m ² infused intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles. | CLL: 100 mg/m ² infused intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles. NHL: 120 mg/m ² infused |

¹ The CLL indication is not included in the Applicant's proposed prescribing information because it is covered by an Orphan Drug Exclusivity (ODE) that expires on September 20, 2015 (with PED extension). Therefore, this indication must be excluded from the proposed labeling until the expiration of the associated ODE and its associated PED extension.

| | 505(b)(2) Bendamustine HCl Injection (100 mg/4 mL (25 mg/mL) | RLD Treanda® (bendamustine hydrochloride) for Injection |
|--|--|--|
| | | intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles. |
| How Supplied | <ul style="list-style-type: none"> 100 mg/4 mL (25 mg/mL) in 5 mL (b) (4) vial | <ul style="list-style-type: none"> 25 mg in 8 mL single-use vial 100 mg in 20 mL single-use vial |
| Storage | <p>Store at 2° to 8°C (36° to 46°F). Retain in original package until time of use to protect from light. Partially used vials are stable for up to 28 days when stored in its original carton at 2-8°C (36-46°F).</p> | <p>Stored up to 25°C (77°F) with excursions permitted up to 30°C (86°F)</p> <p>Protect from light.</p> <p>Discard unused portion.</p> |
| Container and Closure System | (b) (4) vial in an individual carton | Amber single-use vial in an individual carton |
| Instructions for reconstitution | Not applicable | <p>Instructions for reconstitution:</p> <p><u>25 mg/vial:</u> Add 5 mL Sterile Water for Injection</p> <p><u>100 mg/vial:</u> Add 20 mL Sterile Water for Injection</p> <p>Concentration after reconstitution: 5 mg/mL</p> |
| Instructions for dilution | <p>Aseptically withdraw the volume needed (see Table 1) for the required dose (based on 25 mg/mL concentration)</p> <p>and immediately transfer to a 500 mL infusion bag of 0.9% NaCl or 2.5% Dextrose/0.45% NaCl</p> | <p>Aseptically withdraw the volume needed for the required dose (based on 5 mg/mL concentration)</p> |

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive on April 7, 2014 using the terms, bendamustine to identify reviews previously performed by DMEPA.

C.2 Results

DMEPA had previously reviewed bendamustine Labels and Labeling under the following OSE Reviews:

- OSE Review #2013-1791 dated December 24, 2013

We looked at all reviews to ensure all our recommendations were implemented.

APPENDIX G. CONTAINER LABEL, CARTON LABELING, INSTRUCTIONS FOR USE, MEDICATION GUIDE

G.1 List of Label and Labeling Reviewed

We reviewed the following bendamustine labels and labeling submitted by Eagle Pharmaceuticals, Inc. on March 31, 2014.

- Container label
- Carton labeling

G.2 Label and Labeling Images

Container Labels



(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

TINGTING N GAO
04/09/2014

YELENA L MASLOV
04/10/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: March 17, 2014

To: Laura Wall – Regulatory Project Manager
Division of Hematology Products (DHP)

From: Richard Lyght, Pharm.D. – Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Karen Rulli, Ph.D, Team Leader, OPDP

Subject: OPDP comments on draft Prescribing Information (PI) for bendamustine hydrochloride injection for intravenous infusion

This consult is in response to DHP's October 10, 2013 request for OPDP review of the draft bendamustine hydrochloride Prescribing Information. OPDP comments are based on the proposed draft marked-up labeling revised by the review division and received by OPDP on March 12, 2014

OPDP appreciates the opportunity to provide comments. If you have any questions, please contact Richard Lyght at 301-796-2874 or at richard.lyght@fda.hhs.gov.

| Section | Statement from draft | Comment |
|------------------------------------|--|--|
| Highlights--Warnings & Precautions | | In the Highlights, consider changing "Anaphylaxis and Infusion Reactions" to "Infusion Reactions and Anaphylaxis" to be consistent with 5.3 of the FPI |
| 12.1 Mechanism of Action | The bifunctional covalent linkage can lead to cell death via several pathways | The term "via several pathways" is vague and overly promotional. This phrase could be used to overstate the efficacy of bendamustine associated with its MOA compared to |

| | | |
|--|--|---|
| | | <p>other drugs. Please consider revising this statement to either delete "via several pathways" or to include the actual pathways.</p> |
| <p>16.1 Safe Handling and Disposal</p> | <p>(b) (4) care should be exercised in the handling and preparation of solutions prepared from bendamustine hydrochloride Injection</p> | <p>The phrase (b) (4) could be used promotionally to minimize the risks associated with bendamustine. Please consider deleting this statement</p> |

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

/s/

RICHARD A LYGHT
03/19/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: December 24, 2013

Reviewer: Tingting Gao, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Yelena Maslov, PharmD
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Bendamustine Hydrochloride for Injection,
100 mg/4 mL (25 mg/mL)

Application Type/Number: NDA 205580

Applicant: Eagle Pharmaceuticals, Inc.

OSE RCM #: 2013-1791

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

| | | |
|-----|---|---|
| 1 | Introduction | 1 |
| 1.1 | Regulatory History | 1 |
| 1.2 | Product Information | 1 |
| 2 | Methods and Materials Reviewed | 3 |
| 2.1 | Selection of Medication Error Cases..... | 3 |
| 2.2 | Labels and Labeling | 3 |
| 2.3 | Previously Completed Reviews | 3 |
| 3 | Integrated Summary of Medication Error Risk Assessment..... | 4 |
| 4 | Conclusions | 4 |
| 5 | Recommendations | 4 |
| 5.1 | Comments to the Division..... | 4 |
| 5.2 | Comments to the Applicant..... | 5 |
| | Appendices..... | 7 |
| | Appendix A. Database Descriptions | 7 |
| | Appendix B: Bendamustine HCl Injection Container Label..... | 8 |
| | Appendix C: Bendamustine HCl Injection Carton Label..... | 9 |
| | Appendix D: Bendamustine HCl Injection Ferrule Label..... | 9 |

1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Bendamustine Hydrochloride Injection, NDA 205580, for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

This NDA is a 505(b)(2) application. The Reference Listed Drug (RLD), Treanda (bendamustine hydrochloride) for Injection, was approved on March 20, 2008 under NDA 022249, and is marketed as 25 mg per vial and 100 mg per vial. No other bendamustine products are available on the market.

The Applicant proposes introducing a new dosage formation for Bendamustine Hydrochloride Injection, 100 mg/4 mL (25 mg/mL) in a (b) (4) vial.

1.2 PRODUCT INFORMATION

The Applicant provided the following product information in the draft insert labeling for the proposed Bendamustine Hydrochloride Injection, submitted on September 6, 2013.

| | 505(b)(2) Bendamustine HCl Injection (100 mg/4 mL (25 mg/mL)) | RLD Treanda® (bendamustine hydrochloride) for Injection |
|--------------------------------|---|--|
| Active ingredient | Bendamustine Hydrochloride | |
| Indication of Use | <ul style="list-style-type: none">• Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. | <ul style="list-style-type: none">• Chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established.¹• Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. |
| Route of Administration | Continuous intravenous infusion | |

¹ The CLL indication is not included in the Applicant's proposed prescribing information because it is covered by an Orphan Drug Exclusivity (ODE) that expires on September 20, 2015 (with PED extension). Therefore, this indication must be excluded from the proposed labeling until the expiration of the associated ODE and its associated PED extension.

| | 505(b)(2) Bendamustine HCl Injection (100 mg/4 mL (25 mg/mL)) | RLD Treanda® (bendamustine hydrochloride) for Injection |
|--|--|--|
| Dosage Form | Concentrated solution for dilution (ready-to-dilute solution) | Injection, powder for reconstitution |
| Strength | 100 mg/4 mL (25 mg/mL) | 25 mg/vial, 100 mg/vial |
| Dose and Frequency | NHL: 120 mg/m ² infused intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles. | CLL: 100 mg/m ² infused intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles. NHL: 120 mg/m ² infused intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles. |
| How Supplied | <ul style="list-style-type: none"> • 100 mg/4 mL (25 mg/mL) in 5 mL (b) (4) vial | <ul style="list-style-type: none"> • 25 mg in 8 mL single-use vial • 100 mg in 20 mL single-use vial |
| Storage | Store at 2° to 8°C (36° to 46°F). Retain in original package until time of use to protect from light. Partially used vials are stable for up to 28 days when stored in its original carton at 2-8°C (36- 46°F). | Stored up to 25°C (77°F) with excursions permitted up to 30°C (86°F) Protect from light. Discard unused portion. |
| Container and Closure System | (b) (4) vial in an individual carton | Amber single-use vial in an individual carton |
| Instructions for reconstitution | Not applicable | Instructions for reconstitution: <u>25 mg/vial:</u> Add 5 mL Sterile Water for Injection <u>100 mg/vial:</u> Add 20 mL Sterile Water for Injection Concentration after reconstitution: 5 mg/mL |
| Instructions for dilution | Aseptically withdraw the volume needed (see Table 1) for the required dose (based on 25 mg/mL concentration) and immediately transfer to a 500 mL infusion bag of 0.9% NaCl or 2.5% Dextrose/0.45% NaCl | Aseptically withdraw the volume needed for the required dose (based on 5 mg/mL concentration) |

2 METHODS AND MATERIALS REVIEWED

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database from the date of the last DMEPA search using the strategy listed in Table 1. See Appendix A for a description of the FAERS database.

| Table 1: FAERS Search Strategy | |
|---------------------------------------|--|
| Date | September 15, 2013 to November 1, 2013 |
| Drug Names | Bendamustine (active ingredient) Bendamustine Hydrochloride (active ingredient) |
| MedDRA Search Strategy | Medication Errors HLGT Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT |

The FAERS database search identified 2 cases. Each case was reviewed for relevancy and duplication. After individual review, no cases were included in the final analysis because they did not involve wrong technique errors.

2.2 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,² along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Drug Container Labels submitted July 1, 2013 (Appendix B)
- Carton Labeling submitted July 1, 2013 (Appendix C)
- Vial Ferrule Label submitted July 1, 2013 (Appendix D)
- Insert Labeling submitted July 1, 2013 (no image)
- Failure Mode and Effects Analysis (FMEA) – Label Comprehension Study submitted July 1, 2013 (no image)

2.3 PREVIOUSLY COMPLETED REVIEWS

We evaluated the following DMEPA reviews for Treanda to help us evaluate whether the introduction of the new strength may potentiate additional medication errors related to the use of bendamustine or help mitigate the errors:

- 2013-694 Treanda LQ (Bendamustine) Label, Labeling and Packaging Review
- 2013-694-1 Treanda (Bendamustine) Injection Label and Labeling Memorandum
- 2013-1501 Treanda (Bendamustine) Citizens Petition Consult 27June13

² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- [REDACTED] (b) (4)

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT

The proposed Bendamustine Hydrochloride Injection has one difference from the currently marketed Treanda.

Currently, Treanda for Injection is available as a lyophilized powder for reconstitution with a strength of 25 mg per vial and 100 mg per vial. Treanda for Injection is also now approved as a higher concentrated liquid formation with a strength of 45 mg/0.5 mL (90 mg/mL) and 180 mg/2 mL (90 mg/mL). The higher concentration Treanda is not yet available on the market.

The proposed Bendamustine Hydrochloride Injection is proposed to be marketed as a new strength of 100 mg/4 mL (25 mg/mL). From a medication error perspective, the introduction of a new strength may result in wrong dose errors if the labeling is overlooked or does not sufficiently indicate that this concentration must be diluted prior to administration, or if one formulation is mistakenly used in place of another formulation. Therefore, we recommend improving the labels and labeling to minimize product selection errors between the lyophilized powder and different liquid concentrations of Bendamustine Hydrochloride.

Our evaluation of the proposed Bendamustine Hydrochloride Injection [REDACTED] (b) (4) indicates that this is not the most concentrated bendamustine product available on the market.

Additionally, we also considered whether the proposed dosage form, for injection [REDACTED] (b) (4), was an approved CDER dosage form. Per our previous conversation with the Office of New Drug Quality Assessment (ONDQA), we found out the appropriate dosage form for this product is “injection”. Therefore, we recommend removing the statement [REDACTED] (b) (4) in the proposed labels and labeling for bendamustine hydrochloride injection.

4 CONCLUSIONS

DMEPA concludes that the proposed container label, carton and insert labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product to mitigate any confusion. DMEPA provides the following comments for consideration by the review Division prior to the approval of this NDA.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

5.1 COMMENTS TO THE DIVISION

Based on this review, DMEPA provides the following comments for consideration by the review division prior to the approval of this NDA:

- A. Highlights of Prescribing Information and Dosage & Administration, Full Prescribing Information
- a. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise the those abbreviations, symbols, and dose designations as follows:
 - i. Revise the "≥" and "≤" symbols to read "greater than or equal to" and "less than or equal to".
 - ii. Remove trailing zeros after the decimal point (e.g. 1.0, 2.0) in Table A in Section 2.3 Preparation for Intravenous Administration.
 - b. Remove the statement (b) (4) since it is not an acceptable dosage form.

5.2 COMMENTS TO THE APPLICANT

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. Container Label

- a. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore it is an important safety feature that should be part of the label whenever possible. Your product has not been provided an exception, therefore we request you add the product barcode to each individual vial as required per 21 CFR 201.25(b)(1)(ii).
- b. There is a possibility that the peel-back labels may become detached from the product container under normal use. Therefore, we recommend that the peel-back label should be resealable, able to withstand repeated openings and closings without detaching itself from the product container, and able to withstand moisture without detaching from the product container.³
- c. Remove the statement (b) (4) since it is not an acceptable dosage form.

B. Ferrule and cap overseal label

³ Label Process Series LPS2011-04, Guidance for Designing Peel-Back and Multi-Component Labels of Domestic Class Pest Control Products [Internet]. Ottawa (Ontario): Health Canada Pest Management Regulatory Agency. 2011 [cited 2013 Nov 6]. Available from <http://www.hc-sc.gc.ca/cps-spc/pubs/pest/pol-guide/lps2011-04/index-eng.php#a5>.

- a. Our review of the Failure Mode Effect Analysis conducted by Drug Safety Institute indicates that the proposed bendamustine ferrule and cap overseas label contains the statement (b) (4). This statement may not prevent medication error if the healthcare practitioner does not know that 25 mg/mL is a concentrated strength of bendamustine. We recommend revising the statement “(b) (4)” to “Dilute Before Using” as suggested by the United States Pharmacopeia (USP) General Chapter <1> Injections labeling standard.

If you have further questions or need clarifications, please contact Sonny Saini, project manager, at 301-796-0532.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

APPENDIX B: Bendamustine HCl Injection Container Label

(b) (4)



1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

TINGTING N GAO
12/24/2013

YELENA L MASLOV
12/26/2013