CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216078Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	December 13, 2022
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 216078
Product Name and Strength:	Bendamustine Hydrochloride, Injection, 100 mg/4 mL (25 mg/mL)
Applicant/Sponsor Name:	Baxter Healthcare Corporation (Baxter)
TTT ID #:	2022-2747-1
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on December 8, 2022 for Bendamustine Hydrochloride. We reviewed the revised container labels and carton labeling for Bendamustine Hydrochloride (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] The Applicant communicated on December 2, 2022 that they have already printed materials in advance to ensure timely availability of the product to patients due to extensive supply chain lead times. As such, they commit to implement the proposed revisions to include the degree sign after the first temperature the storage statement on the container labels and carton labeling post approval.

2 CONCLUSION

The Applicant has accepted our proposed revisions for the container labels and carton labeling and commits to implement them post approval. The difference in the revised container labels and carton labeling is a degree sign after the first temperature in the storage statement . As

[a] Iverson, N. Label and Labeling Review for Bendamustine Hydrochloride (NDA 216078). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 NOV 30. TTT ID No.: 2022-2747.

there was no change to any other content on the labels and labeling we find this proposal acceptable.

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/s/

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HINA S MEHTA
12/13/2022 02:14:53 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	November 30, 2022
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 216078
Product Name and Strength:	Bendamustine Hydrochloride, Injection, 100 mg/4 mL (25 mg/mL)
Applicant/Sponsor Name:	Baxter Healthcare Corporation (Baxter)
TTT ID #:	2022-2747
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

As part of the approval process of the 505(b)(2) NDA class I resubmission for Bendamustine Hydrochloride Injection, we reviewed the proposed Bendamustine Hydrochloride container labels, flip cap label, ferrule label, carton labeling, and Prescribing Information (PI) for areas of vulnerability that may lead to medication errors. DMEPA had made recommendations during previous label and labeling reviews.[a,b]

1.1 REGULATORY HISTORY

NDA 216078 relies upon the listed drug Belrapzo (bendamustine hydrochloride) which was approved under NDA 205580 on May 15, 2018. Celerity Pharmaceutical, LLC originally submitted NDA 216078 on September 14, 2021 and received tentative approval on July 14, 2022, due to patent protection of the listed drug, Belrapzo. The ownership of this NDA has been transferred to Baxter on September 13, 2022. Baxter submitted a request for final approval of Bendamustine Hydrochloride Injection on October 31, 2022.

[a] Iverson, N. Label and Labeling Review for Bendamustine Hydrochloride (NDA 216078). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 MAR 14. OSE RCM No.: 2021-1805.
[b] Iverson, N. Label and Labeling Review for Bendamustine Hydrochloride (NDA 216078). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 APR 11. OSE RCM No.: 2021-1805-1.

2 CONCLUSION

We performed a risk assessment of the container labels, flip cap label, ferrule label, carton labeling, and PI labeling for Bendamustine Hydrochloride Injection to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. We find the proposed flip cap label and ferrule label acceptable from a medication error perspective. However, we have identified an area of the proposed PI, container labels, and carton labeling that could be revised to improve clarity and readability of important information. We note the how supplied information and storage information lacks clarity, which may confuse the user and inadvertently lead to medication errors. We provide a recommendations for the Division in Section 3 and for Baxter in Section 4 to address these deficiencies.

3 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 2 (DHM 2)

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

A. Prescribing Information
   1. How Supplied/Storage and Handling
      i. We recommend revising the statement, "Bendamustine Hydrochloride injection is supplied in individual cartons of 6 mL clear multiple-dose vials containing 100 mg of bendamustine hydrochloride as a clear and colorless to yellow (b) (4) solution." to "Bendamustine Hydrochloride injection is supplied in individual cartons of 6 mL clear multiple-dose vials containing 100 mg of bendamustine hydrochloride as a clear and colorless to yellow solution.".
      ii. We recommend revising the storage statement to include the degree sign after the first temperature for added clarity to appear as, "Store Bendamustine Hydrochloride Injection in refrigerator, 2° to 8 °C (36° to 46 °F)."

4 RECOMMENDATIONS FOR BAXTER HEALTHCARE CORPORATION (BAXTER)

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

A. General Comments (Container labels & Carton Labeling)
   1. We recommend revising the storage statement to include the degree sign after the first temperature for added clarity to appear as, "Store in refrigerator, 2° to 8 °C (36° to 46 °F)."

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11/30/2022 06:49:23 PM

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

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

Memorandum

Date: 11/30/2022

To: Patty Garvey, Regulatory Project Manager
Division of Hematological Malignancies II (DHM2)

From: Louiza Bako, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for BENDAMUSTINE HYDROCHLORIDE injection, for intravenous use

NDA: 216078

Background:
In response to DHM2's consult request dated November 21, 2022, OPDP has reviewed the proposed Prescribing Information (PI), and carton and container labeling for the original NDA resubmission for BENDAMUSTINE HYDROCHLORIDE injection, for intravenous use.

PI:
OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on November 18, 2022, and we do not have any comments at this time.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on October 31, 2022, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Louiza Bako at (301) 796-3970 or Louiza.Bako@fda.hhs.gov.

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LOUIZA N BAKO
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: 05/12/22

To: Wanda Nguyen, PharmD, Senior Regulatory Health Project Manager, Division of Hematological Malignancies II (DHM2)

From: Jennifer Chen, PharmD, MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for BENDAMUSTINE HYDROCHLORIDE injection, for intravenous use

NDA: 216078

In response to DHM2's consult request dated November 16, 2021, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for BENDAMUSTINE HYDROCHLORIDE injection, for intravenous use.

Labeling: OPDP's comments on the proposed PI are based on the draft labeling received by electronic mail from DHM2 (Wanda Nguyen) on May 11, 2022, and we have no additional comments at this time.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 4, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Jennifer Chen at (301) 796-9398 or Jennifer.Chen@fda.hhs.gov.

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JENNIFER W CHEN
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	May 11, 2022
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 216078
Product Name and Strength:	Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL)
Applicant/Sponsor Name:	Celerity Pharmaceuticals, LLC
OSE RCM #:	2021-1805-2
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels, flip cap label, ferrule label, and carton labeling received on May 4, 2022 for Bendamustine HCl. We reviewed the revised container labels, flip cap label, ferrule label, and carton labeling for Bendamustine HCl (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Iverson, N. Label and Labeling Review for Bendamustine HCl (NDA 216078). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 APR 11. RCM No.: 2021-1805-1.

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NICOLE F IVERSON
05/11/2022 03:48:31 PM

HINA S MEHTA
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Office of Oncologic Diseases Associate Director for Labeling Review of the Prescribing Information

Product Title	**Bendamustine Hydrochloride Injection**
Applicant	Celerity Pharmaceuticals LLC
Application/Supplement Number	NDA 216078
Type of Application/Submission[1]	505(b)(2) NDA
Is Proposed Labeling in "Old" Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Proposed Indication(s)	• 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.
Approved Indication(s)	N/A
Date FDA Received Application	September 14, 2021
Review Classification (Priority/Standard)	Standard
Action Goal Date	July 14, 2022
Review Date	May 11, 2022
Reviewer	Elizabeth Everhart, MSN, RN, ACNP

This Associate Director for Labeling (ADL) review provides recommendations on the content and format of the United States Prescribing Information (USPI) to help ensure that the USPI:

- Is compliant with Physician Labeling Rule (PLR) [including the Pregnancy and Lactation Labeling Rule (PLLR)] requirements,[2]
- Is consistent with labeling guidance recommendations[3] and with CDER labeling policies, as appropriate,
- Conveys the essential scientific information needed for safe and effective use of the drug,
- Is clinically meaningful and scientifically accurate,
- Is a useful communication tool for health care practitioners, and
- Is consistent with other USPI with the same active moiety, drug class, or similar indication, as appropriate

[1] Examples include: Original Biologics License Application (BLA), New Molecular Entity (NME) NDA, Original NDA, NDA Efficacy Supplement, 505(b)(2) New Drug Application (NDA), New Chemical Entity (NCE) NDA, NDA Prior Approval Labeling Supplement, NDA CBE-0 Labeling Supplement

[2] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR 201.56(a) and (e) and 201.80.

[3] See *Prescription Drug Labeling Resources* website for PLR labeling guidances. When final, guidances represent the FDA's current thinking on a topic. Applicants can use an alternative approach if it satisfies statutory and regulatory requirements.

The Applicant submitted a 505(b)(2) NDA for Bendamustine Hydrochloride Injection; Belrapzo (bendamustine hydrochloride injection) NDA 205580 is the listed drug for this NDA.

The USPI submitted by the Applicant was compared to the approved USPI for the listed drug, Belrapzo. Edits were made to the title of this product since it does not have a proposed proprietary name. Throughout the USPI, when referring to this product, the product title was changed to Bendamustine Hydrochloride Injection; when referring to the listed drug, the product was referred to as bendamustine hydrochloride.

Additional updates to the USPI were made to align with recent updates to the listed drug's label and with current labeling practices including the addition of a salt equivalency statement as per the Guidance for Industry: Naming of Products Containing Salt Drug Substances. Please see the attached label with tracked changes and edits/comments for further information.

Per 21 CFR 201.57 (d)(8), the Highlights (HL) of the USPI should not exceed ½ page; the HL for this USPI exceeds ½ page and a waiver for this requirement is acceptable.

At the completion of labeling negotiations, the USPI is acceptable from the ADL standpoint. Because of marketing exclusivity of the listed drug, this application will receive a tentative approval; the revision date at the end of the Highlights will remain as X/XXXX until this product receives full approval. See the USPI attached to the approval letter for final agreed upon labeling.

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Attachment: Revised labeling with track changes edits and bubble comments explaining the revisions.

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ELIZABETH E EVERHART
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	April 11, 2022
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 216078
Product Name and Strength:	Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL)
Applicant/Sponsor Name:	Celerity Pharmaceuticals, LLC
OSE RCM #:	2021-1805-1
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels, flip cap label, ferrule label, and carton labeling received on April 1, 2022 for Bendamustine HCl. We reviewed the revised container labels, flip cap label, ferrule label, and carton labeling for Bendamustine HCl (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised upper container label, sublabel, flip cap label, ferrule label and carton labeling are acceptable from a medication error perspective. However, the revised RS upper label is unacceptable from a medication error perspective. We note in the response to our information request received on April 1, 2022, the Applicant stated they revised the statement, (b) (4) to "See Prescribing Information" on the RS upper container label, however the statement (b) (4) has not been revised on the RS upper container label submitted.

3 RECOMMENDATIONS FOR CELERITY PHARMACEUTICALS, LLC

[a] Iverson, N. Label and Labeling Review for Bendamustine HCl (NDA 216078). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 MAR 14. RCM No.: 2021-1805.

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

A. Container label

1. We note in your response to our information request received on April 1, 2022, that you have revised the statement, [redacted] (b) (4) to "See Prescribing Information" on the RS upper container label, however the statement [redacted] (b) (4) has not been revised on the RS upper container label submitted. Therefore, we recommend revising the statement, [redacted] (b) (4) to "See Prescribing Information" on the RS upper container label.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	March 14, 2022
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 216078
Product Name, Dosage Form, and Strength:	Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Celerity Pharmaceuticals, LLC
FDA Received Date:	September 14, 2021 and March 10, 2022
OSE RCM #:	2021-1805
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the approval process of the 505(b)(2) NDA for Bendamustine HCl Injection, we reviewed the proposed Bendamustine HCl Prescribing Information, container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Celerity Pharmaceuticals, LLC, submitted Bendamustine Hydrochloride (NDA 216078) on September 14, 2021, a 505(b)(2) application which relies upon the listed drug, Belrapzo (bendamustine Hydrochloride) Injection under NDA 205580. Belrapzo (bendamustine hydrochloride) Injection is currently marketed as 100 mg/4 mL (25 mg/mL) multiple-dose vial. The proposed product will be available in the same presentation as the reference product.

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 Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note the proposed Bendamustine Hydrochloride Injection product has the same active ingredient, strength (100 mg/4 mL) in a multiple-dose vial, dosage form (injection), route of administration (intravenous), dosing regimen, diluents, administration time (30 minutes or 60

minutes), and resulting concentration (0.05 mg/mL to 0.7 mg/mL) as the reference listed drug, Belrapzo. We note there are several Bendamustine Hydrochloride products currently marketed (See Appendix A for product characteristics comparison of the listed drug Belrapzo (NDA 205580), Bendeka (NDA 208194), Treanda (NDA 022249), and the proposed Bendamustine Hydrochloride product (NDA 216078)).

We performed a risk assessment of the proposed PI, container labels, and carton labeling for Bendamustine HCl to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. We identified areas of the proposed PI, container labels, and carton labeling that could be revised to improve clarity and readability of important information. For the Division, we note the PI uses incorrect nomenclature for the diluent and lacks clarity on the package type term. For the Applicant, we note the format of the expiration date is inconsistent with our recommend format, lack of clarity of the package type term, and lack of prominence of the storage information. In addition, container labels and carton labeling contain terminology inconsistent with the PI. These factors may confuse the user and inadvertently lead to medication errors. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed container labels, carton labeling, and PI that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for Celerity Pharmaceuticals, LLC to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 2 (DHM 2)

A. Prescribing Information

1. Dosage and Administration Section
    a. Section 2.3 Preparation for Intravenous Administration
        i. We note in the title of Table A in Section 2.3 that the word (b) (4) is used instead of “Sodium Chloride Injection”. Additionally, we note the dextrose diluent is referred to as (b) (4) and not “Dextrose Injection, USP”. We recommend revising the title of Table A to read “Volume (mL) of bendamustine hydrochloride injection required for dilution into 500 mL of 0.9% Sodium Chloride Injection, USP, or 0.45% Sodium Chloride/2.5% Dextrose Injection, USP for a given dose (mg/m2) and Body Surface Area (m2)”.

ii. We recommend revising the statement, “Bendamustine HCl injection is a [redacted] to “Bendamustine HCl injection is a hazardous drug.” to be consistent with current labeling practices for hazardous drugs.

iii. The final concentration calculated should consider all dose reduction scenarios and body surface areas shown in Table A (e.g., the final concentration for an individual with a BSA of 1 m^2 being administered a 25mg/m^2 dose due to dose reductions will be 0.05 mg/mL in a 500 mL infusion bag). Therefore, we recommend revising the concentration from, “0.2-0.7 mg/dL” to “0.05 mg/mL to 0.7 mg/mL” to be consistent with Table A.

2. Dosage Forms and Strengths

   a. We recommend revising the statement “Injection: 100 mg/4 mL (25 mg/mL) as a clear and colorless to yellow [redacted] solution in a multiple-dose vial.” to “Injection: 100 mg/4 mL (25 mg/mL) as a clear and colorless to yellow solution in a multiple-dose vial.”.

3. Clinical Pharmacology

   a. Section 12.3 Pharmacokinetics

      i. The route of administration is abbreviated as “IV”. Presenting the route of administration as an abbreviation may lead to misinterpretation of the correct route of administration. We recommend revising all instances of “IV” to “Intravenous”.

4. How Supplied/Storage and Handling Section

   a. Section 16.1 Safe Handling and Disposal

      i. We recommend revising the statement, “Bendamustine HCl injection is a [redacted] drug.” to “Bendamustine HCl injection is a hazardous drug.” to be consistent with current labeling practices for hazardous drugs.

   b. Section 16.2 How Supplied

      i. We recommend revising the statement, “Bendamustine HCl injection [redacted] is supplied in individual cartons of 6 mL clear multiple-dose vials containing 100 mg of bendamustine hydrochloride as a clear, and colorless to yellow [redacted] solution.” to “Bendamustine HCl injection [redacted] is supplied in individual cartons of

6 mL clear multiple-dose vials containing 100 mg of bendamustine hydrochloride as a clear, and colorless to yellow solution.".

4.2 RECOMMENDATIONS FOR CELERITY PHARMACEUTICALS, LLC

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

A. General Comments (Container labels & Carton Labeling)

1. As currently presented, the format for the expiration date is not defined. We are unable to assess the proposed expiration date format from a medication safety perspective. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a forward slash or a hyphen be used to separate the portions of the expiration date.
2. Bold the statement, "Store in refrigerator, 2° to 8°C (36° to 46°F)." We recommend this to increase prominence of this important information and minimize the risk of the storage information being overlooked.
3. As currently presented, the container label and carton labeling defines the package type as (b) (4) We note based on the proposed PI for Bendamustine Hydrochloride that the package type for the vial will be "multiple-dose vial". We recommend revising the package type on the proposed container label and carton labeling to read "multiple-dose vial".

B. Container Labels

1. As currently presented, the side panel of the container label contains the statement "See prescribing information for dosage (b) (4) To ensure consistency with the terminology in the Prescribing Information, we recommend revising the statement to read, "Dosage: See Prescribing Information."
2. The linear barcode is presented in a horizontal position on the container label. Barcodes placed in a horizontal position may not scan due to container

curvature. The bending of barcodes around a curved surface affects how light reflects off them, and, if it is distorted in such a way, scanners cannot capture the entire barcode. We recommend reorienting the linear barcode on the container label to a vertical position to improve the scannability of the barcode.

3. We note the RS upper label and sublabel on the container label have the statement, [redacted]". We recommend revising the statement, to "See Prescribing Information" to be consistent with the Prescribing Information.

4. We note the placement of a Pharmacode data matrix barcode on the side panel of the container label. Please indicate where the end user will be directed to upon scanning this barcode.

C. Carton Labeling

1. We note the statement [redacted] presented on the side panel of the proposed carton labeling. We recommend revising this statement to read "Hazardous Agent" for consistency with the prescribing information.
2. As currently presented, the side panel of the carton labeling contains the statement [redacted]: See prescribing information [redacted] To ensure consistency with the terminology in the Prescribing Information, we recommend revising the statement to read, "Dosage: See Prescribing Information."
3. We note on the side panel of the carton labeling states, "[redacted]". We recommend revising this statement to read "See Prescribing Information for details".

4. The net quantity statement does not appear on the principal display panel of the carton labeling. Failure to include the net quantity statement on the principal display panel may result in confusion regarding the contents of the carton. We recommend relocating and revising the statement, [redacted] to include the net quantity statement as, "One 4 mL multiple-dose vial" at the bottom of the principal display panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bendamustine HCl received on September 14, 2021 from Celerity Pharmaceuticals, LLC, and the listed drug (LD).

Table 2. Relevant Product Information for Bendamustine HCl and the Listed Drug				
Product Name	Bendamustine HCl (NDA 216078)	Belrapzo[a] (NDA 205580)	Bendeka[b] (NDA 208194)	Treanda[c] NDA 022249)
Initial Approval Date	N/A	May 15, 2018	December 7, 2015	March 20, 2008
Active Ingredient	Bendamustine hydrochloride			
Indication	An alkylating drug indicated for treatment of patients with: • 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.			
Route of Administration	Intravenous infusion			
Dosage Form	Injection			Injection and For Injection
Strength	100 mg/4 mL (25 mg/mL) in a multiple dose vial			Injection: 45 mg/0.5 mL or 180 mg/2 mL (90

[a] Belrapzo [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 OCT 30. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/205580s006lbl.pdf.

[b] Bendeka [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 NOV 08. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208194s020lbl.pdf

[c] Treanda [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2021 JUN 10. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022249s025lbl.pdf

				mg/mL) in a single-dose vial. For Injection: 25 mg or 100 mg lyophilized powder in a single-dose vial for reconstitution.
Dose and Frequency	For CLL: • 100 mg/m^2 infused intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles. For NHL: • 120 mg/m^2 infused intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles.			
Preparation	Injection: Dilute with 500 mL infusion bag of 0.9% Sodium Chloride Injection, USP; or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. The resulting final concentration of Bendamustine hydrochloride in the infusion bag should be	Injection: Dilute with 500 mL infusion bag of 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP Resulting final concentration of bendamustine HCl in the infusion bag should be within 0.05 mg/mL to 0.7 mg/mL	Injection: Dilute with 50 mL infusion bag of 0.9% Sodium Chloride Injection, USP; or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP; or 5% Dextrose Injection, USP. Resulting final concentration of bendamustine	Injection: Dilute with 500 mL infusion bag of 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP For injection: Reconstitute with SWFI 25 mg TREANDA for Injection vial: Add 5 mL of only

	within 0.05 mg/mL to 0.7 mg/mL[d].		hydrochloride in the infusion bag should be within 0.49 mg/mL to 5.6 mg/mL	Sterile Water for Injection, USP. 100 mg TREANDA for Injection vial: Add 20 mL of only Sterile Water for Injection, USP Dilute with 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP
How Supplied	Bendamustine HCl injection (bendamustine hydrochloride) is supplied in individual cartons of 6 mL clear multiple-dose vials containing 100 mg of bendamustine hydrochloride as a clear, and colorless to	Belrapzo (bendamustine hydrochloride) 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.	Store BENDEKA (bendamustine hydrochloride) injection in refrigerator, 2°-8°C (36°-46°F). Retain in original carton until time of use to protect from light.	Injection: Store TREANDA Injection in refrigerator 2°C to 8°C (36°F to 46°F). Retain in original package until time of use to protect from light. For Injection: TREANDA for Injection may be stored up to 25°C (77°F) with

[d] We note final concentration has been changed to 0.05 mg/mL to 0.7 mg/mL to align with the reference listed drug, Belrapzo.

	yellow ready-to-dilute solution.			excursions permitted up to 30°C (86°F) (see USP Controlled Room Temperature). Retain in original package until time of use to protect from light.
Storage	Store bendamustine HCl injection (bendamustine hydrochloride) in refrigerator, 2 to 8°C (36 to 46°F). Retain in original carton until time of use to protect from light.	Store Belrapzo (bendamustine hydrochloride) in refrigerator, 2 to 8°C (36 to 46°F). Retain in original carton until time of use to protect from light.	Store BENDEKA (bendamustine hydrochloride) injection in refrigerator, 2°-8°C (36°-46°F). Retain in original carton until time of use to protect from light.	Injection: Store TREANDA Injection in refrigerator 2°C to 8°C (36°F to 46°F). Retain in original package until time of use to protect from light. For Injection: TREANDA for Injection may be stored up to 25°C (77°F) with excursions permitted up to 30°C (86°F) (see USP Controlled Room Temperature). Retain in original package until time of use to

				protect from light.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Bendamustine HCl labels and labeling submitted by Celerity Pharmaceuticals, LLC.

- Container labels received on March 10, 2022
- Flip cap label received on March 10, 2022
- Ferrule label received on March 10, 2022
- Carton labeling received on March 10, 2022
- Prescribing Information (Image not shown) received on September 14, 2021, available from \\CDSESUB1\evsprod\nda216078\0001\m1\us\pi-draft-labeling-text-original-draft-v1.pdf

G.2 Label and Labeling Images

Container labels

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

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

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