

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212209Orig1s000

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 1, 2022
Requesting Office or Division: Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number: NDA 212209
Product Name and Strength: Vivimusta (bendamustine hydrochloride injection), 100 mg/4 mL (25 mg/mL)
Applicant/Sponsor Name: Slayback Pharma LLC (Slayback)
TTT ID #: 2022-524-1
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 November 30, 2022 for Vivimusta. We reviewed the revised container labels and carton labeling for Vivimusta (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 November 29, 2022 that they have already manufactured, packaged and serialized (b) (4) drug product batches ((b) (4) vials) in preparation for commercial launch. As such, they requested to launch their product with the original labeling submitted on March 11, 2022 and March 14, 2022, until they print the (b) (4) production batch effective February 15, 2023.

Additionally, we note the Applicant will conduct a clinical assessment within the oncology clinics and provide promotional labeling of the infusion profile which includes the 20 minute infusion time and 250 mL diluent volume after marketing approval. We defer to clinical team on the acceptability of the promotional labeling communication.

^a Iverson, N. Label and Labeling Review for Vivimusta (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 NOV 22. TTT ID No.: 2022-524.

2 CONCLUSION

The Applicant will need to launch their product with the already printed container labels and carton labeling submitted on March 11, 2022 and March 14, 2022 since they manufactured, packaged and serialized (b) (4) drug product batches (b) (4) vials) in preparation for commercial launch. The revised container labels and carton labeling received on November 30, 2022 will begin to be utilized once the (b) (4) batches are printed on February 15, 2023. The difference in the revised container labels and carton labeling is increased prominence of the dilution volume (250 mL). As there was no change to any other content on the labels and labeling we find this proposal acceptable.

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/s/

NICOLE F IVERSON
12/01/2022 01:44:30 PM

HINA S MEHTA
12/01/2022 03:48:12 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 22, 2022
Requesting Office or Division: Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number: NDA 212209
Product Name and Strength: Vivimusta (bendamustine hydrochloride injection), 100 mg/4 mL (25 mg/mL)
Applicant/Sponsor Name: Slayback Pharma LLC (Slayback)
TTT ID #: 2022-524
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 Vivimusta (bendamustine hydrochloride injection), we reviewed the proposed Vivimusta container labels, ferrule label, cap overseal 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,c,d,e,f,g,h}

1.1 REGULATORY HISTORY

NDA 212209 relies upon the listed drug Belrapzo (bendamustine hydrochloride) which was approved under NDA 205580 on May 15, 2018. Slayback submitted Bendamustine Hydrochloride Injection on August 31, 2018 and received tentative approval on July 2, 2020, due to patent protection of the (b) (4). Slayback submitted a request for final approval of Bendamustine Hydrochloride Injection on October 7, 2022.

Vivimusta is being proposed to be diluted in 250 mL of 0.9% Sodium Chloride Injection, USP (b) (4) /or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP to a final concentration of (b) (4) mg/mL to 1.36 mg/mL which is different from the listed drug and other marketed bendamustine products.

2 CONCLUSION

We performed a risk assessment of the container labels, ferrule label, cap overseal label, carton labeling, and PI labeling for Vivimusta Injection to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. We find the proposed ferrule label, cap overseal label, and Prescribing Information acceptable from a medication error perspective. However, we note the diluent volume on the principal display panel of the container label (Face 1) and carton labeling lacks prominence. We recommend bringing prominence to this important information as the diluent volume (250 mL) differs from the diluent volume (500 mL) of the listed drug, Belrapzo. We are concerned that this information may be missed by the intended users, which could inadvertently lead to product preparation errors. We provide a recommendation for the Applicant in Section 3 to address this deficiency.

^a Garrison, N. Label and Labeling Review for Bendamustine Hydrochloride (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 19. RCM No.: 2018-1879.

^b Garrison, N. Label and Labeling Review for Bendamustine Hydrochloride (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 26. RCM No.: 2018-1879-1.

^c Garrison, N. Label and Labeling Review for Bendamustine Hydrochloride (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 24. RCM No.: 2018-1879-2.

^d Iverson, N. Label and Labeling Review for Bendamustine Hydrochloride (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 4. RCM No.: 2018-1879-3.

^e Iverson, N. Label and Labeling Review for Bendamustine Hydrochloride (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 28. RCM No.: 2018-1879-4.

^f Iverson, N. Label and Labeling Review for Bendamustine Hydrochloride (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 26. RCM No.: 2018-1879-5.

^g Kane, D. Label and Labeling Review for Bendamustine Hydrochloride (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 OCT 27. RCM No.: 2018-1879-6.

^h Kane, D. Label and Labeling Review for Bendamustine Hydrochloride (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2022 MAR 15. RCM No.: 2018-1879-7.

3 RECOMMENDATIONS FOR SLAYBACK PHARMA LLC (SLAYBACK)

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

A. Container labels and Carton Labeling

1. The diluent volume (250 mL) lacks prominence on the principal display panel of the container label (Face 1) and carton labeling. We recommend bringing prominence to this important information as the diluent volume (250 mL) differs from the diluent volume (500 mL) of the listed drug, Belrapzo. We are concerned that this information may be missed by the intended users, which could inadvertently lead to product preparation errors. We recommend using different colors, boxing, or some other means to ensure prominence of the diluent volume for the container label and carton labeling.

APPENDIX A. LABELS AND LABELING RECEIVED ON OCTOBER 24, 2022 AND NOVEMBER 17, 2022

- Prescribing Information (Image not shown) received on November 9, 2022, available from <\\CDSESUB1\EVSPROD\nda212209\0047\m1\us\prescribing-information-label-0047.docx>

Container labels



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/s/

NICOLE F IVERSON
11/22/2022 03:39:26 PM

HINA S MEHTA
11/22/2022 03:42:26 PM

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

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

Memorandum

Date: 11/21/2022

To: Patty Garvey, Regulatory Project Manager, 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 VIVIMUSTA (bendamustine hydrochloride injection)

NDA: 212209

Background:

In response to DHM2's consult request dated November 01, 2022, OPDP has reviewed the proposed Prescribing Information (PI), and carton and container labeling for the original NDA submission for VIVIMUSTA (bendamustine hydrochloride injection).

PI:

OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on November 09, 2022, and our comments are provided below.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on November 09, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Louiza Bako at Louiza.Bako@fda.hhs.gov

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/s/

LOUIZA N BAKO
11/21/2022 02:07:51 PM

Office of Oncologic Diseases Associate Director for Labeling Memo of the Prescribing Information

Product Title	Vivimusta (bendamustine hydrochloride injection)
Applicant	Slayback Pharma
Application/Supplement Number	NDA 212209 Class I resubmission
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	June 27, 2022
Review Classification (Priority/Standard)	Standard/Class I resubmission
PDUFA Date	August 27, 2022
Review Date	August 9, 2022
Reviewer	Elizabeth Everhart, MSN, RN, ACNP

This Associate Director for Labeling (ADL) memo provides a brief update to the review of the content and format of the United States Prescribing Information (USPI) of Slayback Pharma’s 505(b)(2) NDA for Bendamustine Hydrochloride Injection. Please refer to the labeling review in DARRTS dated February 25, 2022 for more information.

The Applicant resubmitted a 505(b)(2) NDA for Vivimusta (bendamustine hydrochloride injection). Currently, there is unexpired orphan drug exclusivity for the (b) (4) so this NDA will receive a Tentative Approval (TA) at this time.

When the NDA is eligible for full approval, the Applicant will resubmit the NDA and the USPI for final review. At this time, since the NDA will receive a TA, the revision date will be updated to be displayed as follows: X/XXXX. At the time the NDA receives full approval, the revision date will be updated with the full approval month and year. There are no other changes to the USPI from the TA of March 16, 2022 at this time.

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/s/

ELIZABETH E EVERHART
08/09/2022 11:58:54 AM

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: March 15, 2022
Requesting Office or Division: Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number: NDA 212209
Product Name and Strength: Vivimusta (bendamustine hydrochloride) Injection, 100 mg/4 mL (25 mg/mL)
Applicant/Sponsor Name: Slayback Pharma LLC (Slayback)
OSE RCM #: 2018-1879-7
DMEPA 2 Safety Evaluator: Devin Kane, PharmD
DMEPA 2 Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Slayback Pharma LLC (Slayback) submitted revised vial container labels and carton labeling on February 18, 2022, March 11, 2022, and March 14, 2022 for Vivimusta (bendamustine hydrochloride) injection under NDA 212209. We reviewed the revised vial container labels and carton labeling for Vivimusta (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 and via email on March 11, 2022.^a

2 CONCLUSION

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

^a Kane, D. Label and Labeling Review for bendamustine hydrochloride (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 OCT 27. RCM No.: 2018-1879-6.

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/s/

DEVIN R KANE
03/15/2022 08:52:41 AM

HINA S MEHTA
03/15/2022 09:44:27 AM

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

Product Title	Bendamustine Hydrochloride Injection
Applicant	Slayback
Application/Supplement Number	NDA 212209
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	June 16, 2021
Review Classification (Priority/Standard)	Standard
Action Goal Date	March 16, 2022
Review Date	February 25, 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 recommendations³ 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.

In the Dosage and Administration subsection 2.3 Preparation and Administration, the Applicant provided stability data to support dilution of bendamustine hydrochloride into 250 mL of an appropriate diluent, with a final concentration range of 0.1 to 1.36 mL to align Table 1 with the listed drug.

A new Warning and Precaution (W&P) 5.3 for Progressive multifocal leukoencephalopathy (PML) was added, and an update to W&P 5.8 Other Malignancies was made to align with recent changes to the listed drug. Corresponding edits were made in section 17 Patient Counseling.

Additional updates to the USPI were made to align with current labeling practices including removing the phrase “(b) (4)” and changing “(b) (4)” to “last” in sections 5.10, 8.2, 8.3, and 17.

Near the end this review cycle, the Applicant submitted a proposed proprietary name which is still under review; if it is acceptable, the USPI will be updated with the new proprietary name.

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

At the completion of labeling negotiations, the USPI is acceptable from the ADL standpoint pending a decision about the proprietary name. Because of marketing exclusivity of the (b) (4) this application will receive a Tentative Approval. See the USPI attached to the approval letter for final agreed upon labeling.

APPEARS THIS WAY ON ORIGINAL

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ELIZABETH E EVERHART
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LABEL AND LABELING REVIEW
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:	October 27, 2021
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 212209
Product Name, Dosage Form, and Strength:	Bendamustine Hydrochloride Injection, 100 mg/4 mL (25 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Slayback Pharma LLC (Slayback)
FDA Received Date:	May 15, 2020 and June 16, 2021
OSE RCM #:	2018-1879-6
DMEPA Safety Evaluator:	Devin Kane, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Slayback Pharma LLC (Slayback) submitted a class 2 resubmission for a 505(b)(2) application for Bendamustine Hydrochloride Injection NDA 212209 on June 16, 2021. Bendamustine Hydrochloride Injection is an alkylating drug proposed for treatment of patients with Chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established, 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. We evaluated the proposed Bendamustine Hydrochloride prescribing information (PI), vial container label, carton labeling, and ferrule label for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND OR REGULATORY HISTORY

NDA 212209 relies upon the listed drug Belrapzo (bendamustine hydrochloride) which was approved under NDA 205580 on May 15, 2018. NDA 212209 for Bendamustine Hydrochloride was originally submitted on August 31, 2018 and received tentative approval on July 2, 2020. On August 17, 2020, Slayback submitted a Type C meeting request to propose revisions to the diluent information for the proposed Bendamustine Hydrochloride product. Specifically, Slayback proposed a change in the diluent from (b) (4) mL of 0.9% Sodium Chloride Injection, USP to 250 mL of 0.9% Sodium Chloride Injection, USP and/or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. The change would result in a final concentration change from (b) (4) mg/mL to (b) (4) mg/mL to (b) (4) mg/mL to 1.36 mg/mL and a decrease the infusion time from (b) (4) minutes to 20 minutes. On October 23, 2020, Slayback received written communication from the Agency requiring diluent compatibility (stability) studies for the new dilution concentrations.^a Subsequently, Slayback submitted a class 2 resubmission for Bendamustine Hydrochloride under NDA 212209 on June 16, 2021 which included the requested diluent compatibility (stability) studies to support the proposed dilution concentrations.

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
Previous DMEPA Reviews	B
Human Factors Study	C – N/A

^a Nguyen, W. Meeting Request Written Responses for Bendamustine Hydrochloride (NDA 212209). Silver Spring (MD): FDA, CDER, OOD, DHM2 (US); 2020 OCT 23.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
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 performed a risk assessment of the proposed prescribing information (PI), vial container label, carton labeling, and ferrule label for Bendamustine Hydrochloride to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. We note the proposed prescribing information (PI), vial container label, carton labeling, and ferrule label for Bendamustine Hydrochloride were previously reviewed on February 19, 2019, March 26, 2019, April 24, 2019, May 4, 2020, May 28, 2020, and June 26, 2020 (Appendix B). We note the labels and labeling were revised to include the updated diluent information.

We note a copy of the proposed ferrule label for Bendamustine Hydrochloride was not submitted as part of the resubmission on June 16, 2021. On October 13, 2021 we sent an information request (IR) to Slayback to 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. Per email communication on October 18, 2021 Slayback confirmed that they intend to utilize the ferrule label that was submitted to the Agency on May 15, 2020 and tentatively approved on July 2, 2020.

In addition, we note the final concentration for the reference product was revised to 0.05 mg/mL to 0.7 mg/mL under NDA 205580/S-010. The final concentration for the proposed product in Section 2.3 of the PI is stated as (b)
(4) mg/mL to 1.36 mg/mL. However, based on the lowest dose due to toxicity (25 mg/m²) the final concentration when bendamustine is diluted in 250 mL of diluent is 0.1 mg/mL and with the recommended dose (120 mg/m²) it is 1.36 mg/mL. Bendamustine is being proposed to be diluted in 250 mL of 0.9% Sodium Chloride Injection, USP and/or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP which is different from the reference and other marketed bendamustine products. We note the carton and container are adequately labeled with the required diluent and volume for preparation.

After discussion with the Office of Pharmaceutical Quality we note the stability of the product in the proposed diluent during storage is currently under review. As such we may have additional recommendations for the labels and labelling based on the outcome of the stability information.

Our evaluation of the proposed ferrule label did not identify any areas of vulnerability that may lead to medication errors. Thus, we have no recommendations at this time for the ferrule label. Our evaluation of the proposed PI, vial container label and carton labeling for Bendamustine Hydrochloride identified areas of vulnerability that may lead to medication errors. For the PI, we recommend removing the use of symbols and replacing them with their intended meaning, revising the final concentration of the diluted product, and including the appropriate units after all numeric values. For the proposed vial container label and carton labeling, we recommend revising “(b) (4)” to “Multiple-Dose vial”, and including the net quantity on the principal display panel of the carton labeling. We provide our recommendations below.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed ferrule label did not identify any areas of vulnerability that may lead to medication errors. Thus, we do not have any recommendations at this time for the ferrule label. Our evaluation of the proposed Bendamustine Hydrochloride prescribing information (PI), vial container label and carton labeling identified areas of vulnerability that may lead to medication errors. Below, we have provided recommendations in Section 4.1 for the Division and Section 4.2 for the Applicant. We ask that the Division convey Section 4.2 in its entirety to Slayback Pharma LLC so that recommendations are implemented prior to approval of this NDA.

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

A. Prescribing Information

1. Section 2: Dosage and Administration

- a. We note the use of the symbol “-” used in Section 2.3 to represent the word “to”. We recommend removing the use of the symbol and replacing it with its intended meaning of “to”.
- b. As currently presented, we note there are numeric values presented in Section 2.3 that are not immediately followed by the appropriate units. We recommend including the appropriate units after all numeric values in order to avoid any confusion. Revise “(b) (4) – 1.36 mg/mL” to read “(b) (4) mg/mL to 1.36 mg/mL”.
- c. As currently presented the final concentration of diluted product is not consistent with the doses described in Table 1. We recommend revising the final concentration taking into account the lowest dose described in Table 1.

2. Section 16: How Supplied/Storage and Handling

a. We note in Section 16 under “How Supplied” that the package container type for Bendamustine Hydrochloride is defined as (b) (4). We recommend revising the package type to read “multiple-dose”.

4.2 RECOMMENDATIONS FOR SLAYBACK PHARMA LLC

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

A. Vial Container Label

1. We note the proposed vial container label defines the package type as (b) (4). We recommend revising this language to read “Multiple-Dose Vial”.

B. Carton Labeling

1. We note the proposed carton labeling for Bendamustine Hydrochloride lacks a net quantity statement on the principal display panel (PDP). Per 21 CFR 201.51 the carton labeling should contain a net quantity statement. We recommend revising the statement (b) (4) on the PDP to read “4 mL Multiple-Dose Vial”.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bendamustine Hydrochloride received on June 16, 2021 from Slayback Pharma LLC, and the listed drug (LD).

Table 2. Relevant Product Information for Bendamustine Hydrochloride and the Listed Drug		
Product Name	Bendamustine Hydrochloride	Belrapzo^b (NDA 205580)
Initial Approval Date	N/A	May 15, 2018
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	
Strength	100 mg/4 mL (25 mg/mL) in a multiple dose vial	
Dose and Frequency	(b) (4)	
Preparation	Injection: <u>Dilute with 250 mL infusion bag of</u> 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP	Injection: <u>Dilute with 500 mL infusion bag of</u> 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP

^b Belrapzo [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2021 OCT 13. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/205580s006lbl.pdf

	The resulting final concentration of bendamustine hydrochloride in the infusion bag should be within ^{(b) (4)} mg/mL – 1.36 mg/mL.	Resulting final concentration of bendamustine HCl in the infusion bag should be within 0.05 mg/mL and 0.7 mg/mL.
How Supplied	Bendamustine Hydrochloride Injection is a sterile clear, colorless to yellow solution for intravenous use supplied as individually packaged clear glass multiple-dose vials providing 100 mg bendamustine hydrochloride per 4 mL.	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.
Storage	Store Bendamustine Hydrochloride Injection refrigerated at 2°C to 8°C (36°F 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.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 13, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Bendamustine Hydrochloride and NDA 212209. Our search identified 6 previous reviews^{c,d,e,f,g,h}, and we considered our previous recommendations to see if they are applicable for this current review.

^c Garrison, N. Label and Labeling Review for Bendamustine Hydrochloride (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 19. RCM No.: 2018-1879.

^d Garrison, N. Label and Labeling Review for Bendamustine Hydrochloride (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 26. RCM No.: 2018-1879-1.

^e Garrison, N. Label and Labeling Review for Bendamustine Hydrochloride (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 24. RCM No.: 2018-1879-2.

^f Iverson, N. Label and Labeling Review for Bendamustine Hydrochloride (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 4. RCM No.: 2018-1879-3.

^g Iverson, N. Label and Labeling Review for Bendamustine Hydrochloride (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 28. RCM No.: 2018-1879-4.

^h Iverson, N. Label and Labeling Review for Bendamustine Hydrochloride (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 26. RCM No.: 2018-1879-5.

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,ⁱ along with postmarket medication error data, we reviewed the following Bendamustine Hydrochloride labels and labeling submitted by Slayback Pharma LLC.

- Vial Container Label received on June 16, 2021
- Carton Labeling received on June 16, 2021
- Ferrule Label received on May 15, 2020
- Prescribing Information (Image not shown) received on June 16, 2021, available from <\\CDSESUB1\evsprod\nda212209\0032\m1\us\proposed-prescribing-information.pdf>

G.2 Label and Labeling Images

- Vial Container Label



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

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/s/

DEVIN R KANE
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HINA S MEHTA
10/29/2021 12:27:23 PM

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: June 26, 2020
Requesting Office or Division: Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number: NDA 212209
Product Name and Strength: Bendamustine Hydrochloride Injection, 100 mg/4 mL
Applicant/Sponsor Name: Slayback Pharma LLC
OSE RCM #: 2018-1879-5
DMEPA Safety Evaluator: Nicole Iverson, PharmD, BCPS
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on June 19, 2020 for Bendamustine Hydrochloride Injection. We reviewed the revised carton labeling for Bendamustine Hydrochloride Injection (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

2 CONCLUSION

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

^a Iverson N. Label and Labeling Review for Bendamustine Hydrochloride Injection (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 28. RCM No.: 2018-1879-4.

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NICOLE F IVERSON
06/26/2020 09:05:44 AM

HINA S MEHTA
06/26/2020 04:37:23 PM

OOD Associate Director for Labeling Review

Product Title	BENDAMUSTINE HYDROCHLORIDE injection, for intravenous use
Applicant	Slayback Pharma
Application/Supplement Number	NDA 212209
Type of Application/Submission ¹	Resubmission/Class 2
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) (if applicable)	CLL, NHL
Approved Indication(s) (if applicable)	None
Date FDA Received Application	February 14, 2020
Review Classification (Priority/Standard)	Standard
Action Goal Date	August 14, 2020
Review Date	June 8, 2020
Reviewer	Stacy S Shord, Pharm.D.

Background: The applicant submitted a complete class 2 response to September 16, 2019 action letter. This application is pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Bendamustine Hydrochloride Injection 100mg/4ml (25mg/mL). The Listed Drug product referenced in this application is NDA 205580 (Belrapzo, Eagle Pharmaceuticals). Belrapzo was approved initially on May 15, 2018 and the most recent labeling was approved on October 30, 2019 (Suppl 6).

Labeling Review:

The approved labeling document was reviewed to help ensure that PI:

- Is compliant with Physician Labeling Rule (PLR) and PLLR requirements²
- Is consistent with labeling guidance recommendations³ and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

The labeling document was also reviewed for consistency with the labeling for the listed drug Belrapzo.

A working version (dated May 13, 2020) of the Bendamustine Hydrochloride Injection labeling with my recommended edits and comments (deidentified) and that of other review team members is attached. The labeling recommendations provided in this working version should be considered preliminary and may not represent final recommendations for the Bendamustine Hydrochloride Injection labeling.

Additional labeling comments can be found in the primary labeling review completed on January 31, 2019 by V. Kwitkowski as part of the original submission (August 31, 2018).

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\(e\)](#) and [201.80](#).

³ See [PLR Requirements for PI](#) website for PLR labeling guidances.

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/s/

STACY S SHORD
06/08/2020 01:48:57 PM

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: May 28, 2020
Requesting Office or Division: Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number: NDA 212209
Product Name and Strength: Bendamustine Hydrochloride Injection, 100 mg/4 mL
Applicant/Sponsor Name: Slayback Pharma LLC
OSE RCM #: 2018-1879-4
DMEPA Safety Evaluator: Nicole Iverson, PharmD, BCPS
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels, ferrule label and carton labeling received on May 15, 2020 for Bendamustine Hydrochloride Injection. We reviewed the revised container labels, ferrule label and carton labeling for Bendamustine Hydrochloride Injection (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 container labels and ferrule label are acceptable from a medication error perspective. However, we note carton labeling contains the word, “(b) (4)”, which is inconsistent with terminology recommended in labeling for hazardous drugs.

3 RECOMMENDATIONS FOR SLAYBACK PHARMA LLC

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

A. Carton Labeling

^a Iverson N. Label and Labeling Review for Bendamustine Hydrochloride Injection (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 04. RCM No.: 2018-18793-.

1. Revise the word, “^{(b) (4)}” to “hazardous” on the side panel of the carton labeling to reflect alignment with terminology recommended in labeling for hazardous drugs.

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NICOLE F IVERSON
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HINA S MEHTA
06/02/2020 12:31:27 PM

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

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

Memorandum

Date: May 27, 2020

To: Wanda Nguyen, Regulatory Project Manager
Division of Hematologic Malignancies 2 (DHM2)

Stacy Shord, Associate Director for Labeling, DHM2

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, Team Leader, OPDP

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

NDA: 212209

In response to DHM2's consult request dated April 1, 2020, OPDP has reviewed the proposed product labeling (PI) for the NDA resubmission for BENDAMUSTINE HYDROCHLORIDE injection, for intravenous use.

PI: OPDP's comments on the proposed labeling are based on the draft PI emailed to OPDP on May 13, 2020. We have no comments on the draft PI at this time.

Thank you for your consult. If you have any questions, please contact Nisha Patel at (301) 796-3715 or nisha.patel@fda.hhs.gov.

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

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NISHA PATEL
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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: May 4, 2020
Requesting Office or Division: Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number: NDA 212209
Product Name and Strength: Bendamustine Hydrochloride Injection, 100 mg/4 mL
Applicant/Sponsor Name: Slayback Pharma LLC
OSE RCM #: 2018-1879-3
DMEPA Safety Evaluator: Nicole Iverson, PharmD, BCPS
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

This review evaluates the proposed container labels, carton labeling, and Prescribing Information (PI) for Bendamustine Hydrochloride Injection (NDA 212209) for areas of vulnerability that may lead to medication errors (Appendix A). We reviewed this as part of the evaluation of the 505(b)(2) NDA class 2 re-submission for Bendamustine Hydrochloride Injection. DMEPA provided recommendations during previous label and labeling reviews.^{a,b,c}

1.1 REGULATORY HISTORY

Slayback Pharma LLC, submitted Bendamustine Hydrochloride (NDA 212209) on August 31, 2018, a 505(b)(2) application which relies upon the listed drug, Belrapzo (bendamustine Hydrochloride) Injection under NDA 205580. Belrapzo is currently marketed as 100 mg/4 mL

^a Garrison N. Label and Labeling Review for Bendamustine Hydrochloride Injection (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 19. RCM No.: 2018-1897.

^b Garrison N. Label and Labeling Review for Bendamustine Hydrochloride Injection (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 26. RCM No.: 2018-1897-1.

^c Garrison N. Label and Labeling Review for Bendamustine Hydrochloride Injection (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 24. RCM No.: 2018-1897-2.

(25 mg/mL) multiple-dose vial. The proposed product will be available in the same presentation as the reference product.

The application received a Complete Response (CR) letter on June 17, 2019 due to facility inspection issues. Slayback Pharm LLC submitted a response to the CR letter for Bendamustine Hydrochloride (NDA 212209) on July 23, 2019. Subsequently, the application for Bendamustine Hydrochloride received another CR letter on September 16, 2019 due to facility inspection issues.

Slayback Pharma LLC submitted a response to the second CR letter for Bendamustine Hydrochloride on February 14, 2020.

2 OVERALL ASSESSMENT

We note that Bendamustine Hydrochloride Injection has the same active ingredient, strength (100 mg/4 mL), dosage form (injection), route of administration (intravenous), (b) (4)

(b) (4) as the reference listed drug, Belrapzo. In addition, Bendamustine Hydrochloride Injection has the same storage requirements (store in the original carton until time of use) and is supplied in a multiple dose vial. However, we note the proposed Bendamustine Hydrochloride can only be diluted in 0.9% Sodium Chloride Injection, USP whereas the reference listed drug, Belrapzo can be diluted in 0.9% Sodium Chloride Injection, USP and 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. 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 212209)).

From a medication error perspective, the introduction of Bendamustine Hydrochloride diluted only in 0.9% Sodium Chloride Injection, USP, 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.

We performed a risk assessment of the proposed container labels, carton labeling, and PI to identify deficiencies that may lead to medication errors. The proposed PI and container labels are acceptable from a medication error perspective. The proposed ferrule label and carton labeling can be improved to increase prominence of proper preparation and identification of

the product. We provide recommendations for the Applicant in Section 3.1 to address these deficiencies.

3 CONCLUSION

The proposed PI and container labels are acceptable from a medication error perspective. We have identified areas on the ferrule label and carton labeling that can be improved to increase prominence of important information. We provide recommendations in Section 3.1 for Slayback Pharma LLC to address our concerns.

3.1 RECOMMENDATIONS FOR SLAYBACK PHARMA LLC

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

A. Ferrule label

1. You did not submit a copy of the ferrule label with this submission. In your previous submission dated on April 4, 2019, you committed to include the cautionary statement "Dilute Before Using" to appear on the ferrule in addition to the cap overseal for future commercial batches of Bendamustine Hydrochloride Injection. We continue to recommend this to minimize the risk of a medication error where the drug is administered undiluted, because the 100 mg/4 mL presentation is a multi-dose vials and the cap overseal will be discarded during the pharmacy dispensing process. We also note that the inclusion of the cautionary statement, "Dilute Before Using" on the ferrule label is consistent with the reference listed drug, Belrapzo (bendamustine hydrochloride) Injection under NDA 205580.

B. Carton labeling

1.



2. The terminology within the Recommended Dosage statement, “Usual dosage” is inconsistent with the terminology in the Prescribing Information. To ensure consistency with the terminology in the Prescribing Information, we recommend revising the recommended dosage statement from, (b) (4) (b) (4) to read, “Recommended Dosage: See Prescribing Information.”
3. Revise the statement to proper nomenclature, “ (b) (4) (b) (4) to “Must dilute required dose in a (b) (4) mL infusion bag of 0.9% Sodium Chloride Injection, USP prior to administration.”

C. Container label

1. To ensure consistency with the terminology in the Prescribing Information and the carton labeling (see B.2), we recommend revising the recommended dosage statement from, “ (b) (4) (b) (4) ” to read, “Recommended Dosage: See Prescribing Information.”
2. Revise the statement to proper nomenclature, “... (b) (4) (b) (4) ” to “...immediately transfer to a (b) (4) mL infusion bag of 0.9% Sodium Chloride Injection, USP”.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bendamustine Hydrochloride Injection received on February 14, 2020 from Slayback Pharma LLC.

Table 2. Relevant Product Information for Bendamustine Hydrochloride, Belrapzo, Bendeka and Treanda				
Product Name	Bendamustine hydrochloride (NDA 212209)	Belrapzo (NDA 205580)	Bendeka (NDA 208194)	Treanda (NDA 022249)
Initial Approval Date	N/A	May 15, 2018	December 7, 2015	March 20, 2008
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	Intravenous infusion			
Dosage Form	Injection			Injection and For Injection
Strength	100 mg/4 mL (25 mg/mL) in a multiple dose vial	100 mg/4 mL (25 mg/mL) in a multiple-dose vial	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
Dose and Frequency	(b) (4)			
Preparation	Injection: <u>Dilute with (b) (4) mL infusion bag of</u> 0.9% Sodium Chloride Injection, USP. Resulting final concentration of bendamustine hydrochloride in the infusion bag should be within (b) (4) mg/mL (b) (4) mg/mL	Injection: <u>Dilute with 500 mL infusion bag of</u> 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 (b) (4) mg/mL-0.7 mg/mL	<u>Injection:</u> <u>Dilute with 50 mL infusion bag of</u> 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 hydrochloride in the infusion bag should be	Injection: <u>Dilute with 500 mL infusion bag of</u> 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP 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

			within ^{(b) (4)} mg/mL – 5.6 mg/mL	of only Sterile Water for Injection, USP <u>Dilute with</u> 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP
Storage	Store bendamustine HCl Injection in refrigerator, 2° to 8°C (36° to 46°F). Retain in original carton until time of use to protect from light.	Belrapzo 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. After first use, the multi-use vial should be stored in original carton at 2 °C to 8 °C, and then discarded after 28 days.	Store Bendeka in refrigerator, 2°-8°C (36° to 46°F). Retain in original package until time of use to protect from light.	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. 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.

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HINA S MEHTA
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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: April 24, 2019
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 212209
Product Name and Strength: Bendamustine Hydrochloride Injection, 100 mg/4 mL
Applicant/Sponsor Name: Slayback Pharma LLC
FDA Received Date: March 26, 2019, April 4, 2019 and April 10, 2019
OSE RCM #: 2018-1879-2
DMEPA Safety Evaluator: Nicole Garrison, PharmD, BCPS
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Division of Hematology Products (DHP) requested that we review the revised container labels for Bendamustine Hydrochloride (Appendix A) to determine if it is acceptable from a medication error perspective. The revision is in response to a recommendation that we made during a previous label and labeling review.^a We note that the Applicant has committed to include the cautionary statement, “Dilute Before Using” on the ferrule in addition to the cap overseal for the future commercial batches of Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL). We also note that the Applicant has removed the option of using the diluent, 2.5% Dextrose/0.45% Sodium Chloride Injection, USP from the Prescribing Information, container label and carton labeling in response to an inquiry from the Office of Pharmaceutical Quality (OPQ) regarding the in-use stability data for this diluent.

2 CONCLUSION

The revised container labels and carton labeling for Bendamustine Hydrochloride are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Garrison N. Label and Labeling Review for Bendamustine Hydrochloride (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 26. RCM No.: 2018-1879-1.

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NICOLE B GARRISON
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HINA S MEHTA
04/29/2019 07:49:12 AM

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

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

Memorandum

Date: April 11, 2019

To: Wanda Nguyen, Regulatory Project Manager
Division of Hematology Products (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, Team Leader, OPDP

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

NDA: 212209

In response to DHP's consult request dated September 20, 2018, OPDP has reviewed the proposed product labeling (PI) for the original NDA submission for BENDAMUSTINE HYDROCHLORIDE injection, for intravenous use.

PI: OPDP's comments on the proposed labeling are based on the draft PI emailed to OPDP on April 4, 2019. We have no comments on the draft PI at this time.

Thank you for your consult. If you have any questions, please contact Nisha Patel at (301) 796-3715 or nisha.patel@fda.hhs.gov.

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/s/

NISHA PATEL
04/11/2019 04:48:09 PM

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 26, 2019
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: NDA 212209
Product Name and Strength: Bendamustine Hydrochloride Injection, 100 mg/4 mL
Applicant/Sponsor Name: Slayback Pharma LLC
FDA Received Date: March 11, 2019
OSE RCM #: 2018-1879-1
DMEPA Safety Evaluator: Nicole Garrison, PharmD, BCPS
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Division of Hematology Products (DHP) requested that we review the revised container label 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 also note that the Applicant revised section 2.3 *Preparation for Intravenous Administration* and section 2.4 *Admixture Stability* of the Prescribing Information to identify the required storage conditions and hold time limitations for the drug following dilution with 2.5% Dextrose/0.45% Sodium Chloride Injection. Furthermore, Slayback Pharma LLC updated the Prescribing Information to be consistent with a recent update to the Prescribing Information of the reference listed drug, Belrapzo.

2 CONCLUSION

The revised Prescribing Information and carton labeling are acceptable from a medication error perspective. However, the revised container label does not contain the statement, "Dilute

^a Garrison N. Label and Labeling Review for Bendamustine Hydrochloride (NDA 212209). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 19. RCM No.:2018-1879.

Before Using” on the ferrule in addition to the cap overseal in accordance with United States Pharmacopeia (USP) General Chapter <7> Labeling standard.

3 RECOMMENDATIONS FOR SLAYBACK PHARMA LLC

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

A. Ferrule label

1. We recommend that you include the cautionary statement, “Dilute Before Using” on ferrule in addition to the cap overseal with your product to minimize the risk of a medication error where the drug is administered undiluted, because the 100 mg/4 mL presentation is a multi-dose vials and the cap overseal will be discarded during the pharmacy dispensing process. We also note that the inclusion the cautionary statement, “Dilute Before Using” on the ferrule label will be consistent with the reference listed drug Belrapzo (bendamustine Hydrochloride) Injection under NDA 205580.

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LABEL AND LABELING REVIEW
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)

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Date of This Review:	February 19, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 212209
Product Name and Strength:	Bendamustine Hydrochloride Injection, 100 mg/4 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Slayback Pharma LLC
FDA Received Date:	August 31, 2018 and October 17, 2018
OSE RCM #:	2018-1879
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

The Division of Hematology Products (DHP) requested that we review the proposed container label, carton labeling, and Prescribing Information for Bendamustine Injection (NDA 212209) for areas of vulnerability that may lead to medication errors. DHP requested this review as a part of their evaluation of the 505(b)(2) application for Bendamustine Injection.

1.1 REGULATORY HISTORY

Slayback Pharma LLC, submitted Bendamustine Hydrochloride (NDA 212209) on August 31, 2018, a 505(b)(2) application which relies upon the listed drug, Belrapzo (bendamustine Hydrochloride) Injection under NDA 205580. Belrapzo 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 Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C- N/A
ISMP Newsletters	D
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 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 that Bendamustine Hydrochloride Injection has the same active ingredient, strength (100 mg/4 mL), dosage form (injection), route of administration (intravenous), ^{(b) (4)} diluents, ^{(b) (4)} ^{(b) (4)} as the reference listed drug, Belrapzo. In addition, Bendamustine Hydrochloride Injection has the same storage requirements (store in the original carton until time of use) and is supplied in a multiple dose vial. We note there are several bendamustine hydrochloride products currently marketed (see Appendix A for product characteristics comparison of the

listed drug Bendeka (NDA 208194), Treanda (NDA 022249), and the proposed Bendamustine HCl product (NDA 212209)).

We searched ISMP to identify whether any additional medication errors occurred with Bendamustine Hydrochloride. Our search did not identify any relevant newsletter articles. DMEPA performed a risk assessment of the proposed PI to identify deficiencies that may lead to medication errors. The proposed PI, labels, 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. For the Division, we recommend using proper nomenclature for the diluents used in the heading in Table A. For the Applicant, we recommend bringing prominence to storage statement, defining the format for the expiration date, revising the nomenclature for the diluents used for preparation of the product, decreasing prominence of the Rx Only statement, and including product identifiers on the carton labeling.

4 CONCLUSION & RECOMMENDATIONS

We determined that the proposed PI, container labels and carton labeling is vulnerable to confusion that can lead to medication errors. We provide recommendations for the Division in Section 4.1 and for the Applicant in Section 4.2 to be implemented prior to approval of NDA 212209.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Highlights of Prescribing Information

a. Dosage Forms and Strengths

- i. To improve readability, revise the statement, (b) (4)
[REDACTED]
to “Injection: 100 mg/4 mL (25 mg/mL) of bendamustine hydrochloride in a multiple dose vial”

2. Full Prescribing Information

a. Section 2 *Dosage and Administration Section*

- i. Revise the title for Table A to “Volume (mL) of Bendamustine Hydrochloride Injection required for dilution into (b) (4) mL of 0.9% Sodium Chloride Injection or 2.5% Dextrose/0.45% Sodium Chloride Injection for a given dose (mg/m²) and Body Surface Area (m²).” We recommend this revision to use proper nomenclature for the diluents used to prepare solutions of Bendamustine Hydrochloride Injection.

b. Section 3 *Dosage Forms and Strengths*

- i. Revise the statement, “ (b) (4)
[REDACTED]
to “Bendamustine

Hydrochloride Injection: 100 mg/mL (25 mg/mL) as a colorless to yellow solution in a multiple-dose vial.”

c. Section 16.2 *How Supplied*

- i. Revise the statement, “... (b) (4) (b) (4) to “...multiple-dose vials containing 100 mg of bendamustine hydrochloride as a clear, colorless to yellow solution. (b) (4) .”

4.2 RECOMMENDATIONS FOR SLAYBACK PHARMA LLC

We recommend the following be implemented prior to approval of this NDA 212209:

A. General Comments (Container labels & Carton Labeling)

1. (b) (4) Provide adequate contrast between the strength statement, concentration and dilution information on the principal display panel to improve readability of this important information.
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 format for the expiration date is not defined. 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 hyphen or a space be used to separate the portions of the expiration date.

B. Container Labels

1. Revise the statement, (b) (4) (b) (4) .” To “...per Table A (see prescribing information) immediately transfer to a (b) (4) mL infusion bag of **0.9% Sodium Chloride Injection or 2.5% Dextrose/0.45% Sodium Chloride Injection.**” to be consistent with the Prescribing Information.
2. Revise the statement, “ (b) (4) (b) (4) to “**Must be diluted prior to administration (see**

prescribing information for instructions) to be consistent with the Prescribing Information.

3. Revise the statement, “ [REDACTED] (b) (4) [REDACTED] to “Must be diluted prior to administration (see Prescribing Information for instructions)”
4. 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 labels 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.^a

C. Ferrule label

1. You did not submit a copy of the ferrule label with the submission. If you intend to have a ferrule label we ask that you submit 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 the 100 mg/4 mL presentation is a multi-dose vials and the cap overseal will be discarded during the pharmacy dispensing process.

D. Carton Labeling

1. Decrease the prominence of the manufacturer name and logo as the information is more prominent than the required diluent statement above it. We recommend this to prominence to mitigate the risk of product preparation errors.
2. The Rx Only statement appears prominent than other important information on the principal display. Decrease the prominence by debolding the Rx Only statement.
3. Revise the statement, “ [REDACTED] (b) (4) [REDACTED] to “**Must dilute required dose in a [REDACTED] (b) (4) mL infusion bag of 0.9% Sodium Chloride Injection or 2.5% Dextrose/0.45% Sodium Chloride Injection prior to administration.**” to be consistent with the Prescribing Information.
4. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.¹ The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package

^a 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>.

and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

¹The draft guidance is available from: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bendamustine Hydrochloride received on August 31, 2018 from Slayback Pharma LLC.

Table 2. Relevant Product Information for Bendamustine Hydrochloride, Belrapzo, Bendeka and Treanda				
Product Name	Bendamustine hydrochloride (NDA 212209)	Belrapzo (NDA 205580)	Bendeka (NDA 208194)	Treanda (NDA 022249)
Initial Approval Date	N/A	May 15, 2018	December 7, 2015	March 20, 2008
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	Intravenous infusion			
Dosage Form	Injection			Injection and For Injection
Strength	100 mg/4 mL (25 mg/mL) in a multiple dose vial	100 mg/4 mL (25 mg/mL) in a multiple-dose vial	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

Dose and Frequency				
Preparation	Injection: <u>Dilute with (b) (4) mL infusion bag of</u> 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. Resulting final concentration of bendamustine hydrochloride in the infusion bag should be within (b) (4) mg/mL- (b) (4) mg/mL	Injection: <u>Dilute with 500 mL infusion bag of</u> 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 (b) (4) mg/mL-0.7 mg/mL	<u>Injection:</u> <u>Dilute with 50 mL infusion bag of</u> 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 hydrochloride in the infusion bag should be within (b) (4) mg/mL – 5.6 mg/mL	Injection: <u>Dilute with 500 mL infusion bag of</u> 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP 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 <u>Dilute with</u> 0.9% Sodium Chloride Injection, USP, or 2.5%

				Dextrose/0.45% Sodium Chloride Injection, USP
Storage	Store bendamustine HCl Injection in refrigerator, 2° to 8°C (36° to 46°F). Retain in original carton until time of use to protect from light.	Belrapzo 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. After first use, the multi-use vial should be stored in original carton at 2 °C to 8 °C, and then discarded after 28 days.	Store Bendeka in refrigerator, 2°-8°C (36° to 46°F). Retain in original package until time of use to protect from light.	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. 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 B. PREVIOUS DMEPA REVIEWS

On January 17, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, Bendamustine. Our search identified 11 previous reviews^{b,c,d,e,f,g,h,i,j,k,l}, and we confirmed that our previous recommendations were implemented.

^b Wright, K. Label, Labeling and Packaging Review for Treanda LQ (NDA 022249). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 JUN 27. RCM No.: 2013-694.

^c Wright, K. Label and Labeling Packaging Memorandum Review for Treanda (NDA 022249). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 JUL 02. RCM No.: 2013-694-1.

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

^e Rutledge, M. Label and Labeling Review for Bendeka (NDA 208194). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 SEP 16. RCM No.: 2015-353.

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

^g Garrison, N. Label and Labeling Review Memorandum for Bendamustine (NDA 205580). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAR 30. RCM No.: 2018-283-1.

^h Garrison, N. Label and Labeling Review Memorandum for Bendamustine (NDA 205580). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 19. RCM No.: 2018-1245.

ⁱ Garrison, N. Label and Labeling Review Memorandum for Bendamustine (NDA 205580). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUL 10. RCM No.: 2018-1245-1

^j Garrison, N. Label and Labeling Review for Bendamustine (NDA 211530). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 15. RCM No.: 2018-758.

^k Garrison, N. Label and Labeling Review Memorandum for Bendamustine (NDA 205580). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 10. RCM No.: 2018-1245-1.

^l Garrison, N. Label and Labeling Review Memorandum for Bendamustine (NDA 205580). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 DEC 14. RCM No.: 2018-1245-2.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On January 17, 2019, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care ISMP Medication Safety Alert Community/Ambulatory Care ISMP Medication Safety Alert Nurse Advise-ERR Long-Term Care Advise-ERR ISMP Canada Safety Bulletin Pennsylvania Patient Safety Advisory
Search Strategy and Terms	Match Exact Word or Phrase: Bendamustine

D.2 Results

The search retrieved no relevant articles associated with label and labeling for Bendamustine.

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,^m along with postmarket medication error data, we reviewed the following Bendamustine Hydrochloride labels and labeling submitted by Slayback Pharma LLC.

- Container label received on August 31, 2018
- Carton labeling received on August 31, 2018
- Prescribing Information (Image not shown) received on October 17, 2018

G.2 Label and Labeling Images

Container label



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

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Division of Hematology Products (DHP) Labeling Review

NDA Number	NDA 212209
Applicant	Slayback Pharma LLC
Non-Proprietary Name	Bendamustine Hydrochloride Injection
Receipt Date	08/31/18
PDUFA Goal Date	06/30/19
Review Classification	Standard
Type of Application	505(b)(2)
Dosing Regimen	(b) (4)
From	Virginia Kwitkowski, MS, ACNP-BC Associate Director for Labeling, DHP

Background of Application:

On 08/31/18, Slayback Pharma LLC submitted a New Drug Application pursuant to section 505(b)(2) of the Federal Food, Drug and Cosmetic Act for Bendamustine Hydrochloride Injection. The Listed Drug product referenced in this application is NDA 205580 (Belrapzo, Eagle Pharmaceuticals). Belrapzo was approved initially on 05/15/18 and the most recent labeling was approved on 08/31/18.

Documents Reviewed:

Submission 08/31/18

Module 1: Regional

- Forms (356h)
- Cover Letter
- Administrative Information (Patent and Exclusivity Information)
 - There is no unexpired exclusivity for the Listed Drug 205580 in the Orange Book Database; they plan to launch their product upon approval of this application.
 - Slayback submitted a Paragraph IV Certification stating that the patent numbers listed are invalid and/or unenforceable and/or will not be infringed by the manufacture, use

or sale of its Bendamustine Hydrochloride Injection, 100 mg/4 mL (25 mg/mL) for which this 505(b)(2) application is submitted.

- Pediatric Administrative Information: A Pediatric study waiver request was submitted to FDA on 11/03/17, and FDA replied that the application would not trigger PREA (b) (4)
(b) (4)
(b) (4) FDA also stated that an iPSP is not required for this application.
- Other Correspondence (Comparison of generic drug and reference listed drug)
- Request for Waiver of In Vivo Bioavailability Studies
- Labeling (Annotated Labeling, Draft Labeling, Listed Drug Labeling); also reviewed NDA 211530 (a bendamustine 505(b)(2) labeling more recently reviewed by FDA (received TA).

Review

During review of this labeling, I also referred to the most recently reviewed bendamustine labeling under NDA 211530.

In this review, I summarize the DHP labeling recommendations and edits in the Bendamustine Hydrochloride Injection labeling. These edits are made to ensure that the prescribing information is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of Bendamustine Hydrochloride Injection.

The following pages contain a summary of the labeling recommendations followed by the working version of the Bendamustine Hydrochloride Injection labeling with comments. At this time, the scientific review of the labeling is ongoing. The labeling recommendations in this review should be considered preliminary and may not represent DHP's final recommendations for the Bendamustine Hydrochloride Injection labeling.

Summary of Labeling Recommendations:

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

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