CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212209Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	212209
Applicant Name	Slayback Pharma, LLC
Drug Product Name	VIVIMUSTA (bendamustine hydrochloride injection)
Dosage Form.	Injection
Proposed Strength(s)	100 mg/ 4 mL (25 mg/mL)
Route of Administration	Intravenous
Maximum Daily Dose	(b) (4) mg/day
Rx/OTC Dispensed	Rx
Proposed Indication	Bendamustine is indicated for the treatment of Chronic Lymphocytic Leukemia (CLL) and Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen.
Drug Product Description	The drug product, Bendamustine HCl Injection,100 mg/4 mL (25 mg/mL) is supplied as a clear colorless to (b) (4) yellow, (b) (4) sterile solution in a multiple-dose vial. The drug product formulation is for the most part non-aqueous and contains no preservatives. The proposed product, like the listed drug, is designed to be diluted with 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. The final admix is stable for up to 24 hours when stored refrigerated or up to 3 hour when stored at room temperature (see USPI). **The current submission contains no new data but instead only includes a request for full approval.**
Co-packaged product information	N/A
Device information:	N/A

Storage Temperature/ Conditions	2°C to 8°C (36°F to 46°F). Retain in original carton until time of use to protect from light		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Paresma Patel	Paresma Patel
	Drug Product/ Labeling	Tefsit Bekele	Sherita McLamore
	Manufacturing	Djelila Mezzaache	Bogdan Kurtya
	Biopharmaceutics	N/A	N/A
	Microbiology	Bryan Riley	Bryan Riley
	Other (specify):	N/A	N/A
	RBPM	Dahlia Walters	
	ATL	Tefsit Bekele	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: 24 months when stored at 2-8 ℃

b. Additional Comments for Action: N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends APPROVAL of NDA 212209 for commercialization of Bendamustine Hydrochloride Injection, 100 mg/4 mL. Based on our evaluation of the available information, the applicant provided sufficient information to support an approval

recommendation from the product quality perspective. The applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**N/A**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: N/A

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U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM
NDA 212209
BENDAMUSTINE HYDROCHLORIDE INJECTION, 100 MG/ML
CMC REVIEW OF REVISED LABEL AND LABELING

VIVIMUSTA (bendamustine hydrochloride injection) was tentatively approved on July 2, 2020. The applicant, Slayback Pharma LLC submitted a class 2 resubmission for VIVIMUSTA on June 16, 2021 which included CMC changes such as reinstatement of the 2.5% dextrose/0.45% diluent, higher admixture concentrations and shorter infusion time. VIVIMUSTA was tentatively approved again on March 16, 2022. On June 27, 2022, the applicant submitted a Class I resubmission to provide CMC updates which included long-term drug product stability update and other minor CMC changes. The applicant requested for full approval however the product was only tentatively approved due to due to orphan exclusivity for Bendeka. A Class I resubmission was again submitted on October 7, 2022 to request a final approval. The submission doesn't contain any new data however CMC has recommendation for the prescribing information and carton labeling.

The container label and carton labeling submitted for this resubmission are shown below.

The following information request was sent to the applicant regarding the carton labeling on November 01, 2022.

Change " (b) (4) (b) (4) (b) (4) *" on the carton labeling to "Each mL contains 25 mg bendamustine hydrochloride equivalent to 22.7 mg bendamustine, 5 mg monothioglycerol, 39.45 mg dehydrated alcohol, and q.s. 1 mL polyethylene glycol 400. Sodium hydroxide is used to adjust pH of polyethylene glycol 400"*

The applicant agreed to make the changes via email on November 02, 2022, and also informed the agency that they have already manufactured (b) (4) drug product batches on commercial scale that are under the final stages of packaging. The applicant was preparing for commercial launch. They have requested Pre-Launch Activities Importation Requests (PLAIR) to import unapproved drug product. Considering the situation, they have requested that they market the drug product batches already manufactured without making the labeling changes upon approval. They are committed to implement the proposed change to the drug product carton labeling for the next production run. Since there are no safety issues related to labeling, CMC agreed to the applicant's plan to revise the labels for the next commercial batch.

Labeling negotiation for the prescribing information is ongoing. The container label and carton labeling are acceptable from the CMC perspective pending revision of what is noted above.

Container label for Vivimusta (Bendamustine hydrochloride injection), 100 mg/4 mL

(b) (4)

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Sherita McLamore

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NDA Executive Summary

1. Application/Product Information

NDA Number.	212209
Applicant Name	Slayback Pharma, LLC
Drug Product Name	Bendamustine HCl
Dosage Form.	Injection
Proposed Strength(s)	100 mg/ 4mL (25 mg/mL)
Route of Administration	Intravenous
Maximum Daily Dose	(b) (4) mg/day
Rx/OTC Dispensed	Rx
Proposed Indication	Bendamustine is indicated for the treatment of Chronic Lymphocytic Leukemia (CLL) and Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen.
Drug Product Description	The drug product, Bendamustine HCl Injection,100 mg/4 mL (25 mg/mL) is supplied as a clear colorless to (b) (4) yellow, (b) (4) sterile solution in a multiple-dose vial. The drug product formulation is for the most part non-aqueous and contains no preservatives. The proposed product, like the listed drug, is designed to be diluted with 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. The final admix is stable for up to 24 hours when stored refrigerated or up to 3 hour when stored at room temperature (see USPI). **The current submission contains no new data but instead only includes a request for full approval.**
Co-packaged product information	N/A
Device information:	N/A

Storage Temperature/ Conditions	(b) (4)		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Kabir Shahjahan	Haripada Sarker
	Drug Product/ Labeling	Tefsit Bekele	Sherita McLamore
	Manufacturing	Djelila Mezzaache	Bogdan Kurtya
	Biopharmaceutics	N/A	N/A
	Microbiology	Bryan Riley	Bryan Riley
	Other (specify):	N/A	N/A
	RBPM	Dahlia Walters	
	ATL	Sherita McLamore	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: 24 months when stored at 2-8°C

b. Additional Comments for Action: N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends APPROVAL of NDA 212209 for commercialization of Bendamustine Hydrochloride Injection, 100 mg/4 mL. Based on our evaluation of the available information, the applicant provided sufficient information to support an approval

recommendation from the product quality perspective. The applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**N/A**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: N/A

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM
NDA 212209
BENDAMUSTINE HYDROCHLORIDE INJECTION, 100 MG/ML
CMC REVIEW OF CLASS I RESUBMISSION

Bendamustine Hydrochloride Injection was tentatively approved on July 2, 2020. The applicant, Slayback Pharma LLC submitted a class 2 resubmission for Bendamustine Hydrochloride on June 16, 2021. CMC recommended approval of Bendamustine Hydrochloride Injection. FDA accepted the proposed expiration dating period of 24-months for the drug product when stored at 2–8 °C. The drug product was to be diluted to a final concentration of 0.1–1.36 mg/mL in 0.9% NaCl or 2.5% dextrose/0.45% sodium solutions before IV infusion administration. The admixtures are stable for 24 hours under refrigeration and 3 h at room temperature. Refer to the drug product review uploaded in Panorama on January 24, 2022 and CDTL review uploaded in DARRTS on 03/01/2022 for more details.

On June 27, 2022, the applicant submitted a Class I resubmission to provide CMC updates which included long-term drug product stability update. Stability update for Bendamustine Hydrochloride Injection (100 mg/mL), lot 9K06227V manufactured using a drug substance batch produced at (b) (4) (b) (4) (b) (4) was provided. The batch continued to meet the proposed specifications through 24 months when it is stored in both upright and inverted positions at 2–8 °C. There are no significant physical or chemical changes except the level of (b) (4) content (b) (4) from (b) (4)% to (b) (4)% after 24 months but it is well within the acceptance criterion of (b) (4) (b) (4)%. The applicant is not requesting to extend the previously agreed 24-month expiration dating period for the product. Minor specification updates to (b) (4) consistent to the corresponding USP monograph were also provided. CMC has no additional comments and still recommends approval.

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Sherita McLamore

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Dahlia A. Walters

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Recommendation: **APPROVAL**

NDA 212209
Review #4

Drug Name/Dosage Form	Bendamustine HCl Injection
Strength	100 mg/4 mL (25 mg/mL)
Route of Administration	IV
Rx/OTC Dispensed	R_x
Applicant	Slayback Pharma LLC
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Class 2 Resubmission	06/14/2021	All
Amendment 0033	09/07/2021	DP
Amendment 0035	11/17/2021	DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Paresma Patel	Paresma Patel
Drug Product	Tefsit Bekele	Sherita McLamore
Process	Steven Hertz	Yiwei Li
Microbiology	Erika Pfeiler	John Metcalfe
Facility	Steven Hertz	Yiwei Li
Regulatory Business Process Manager	Dahlia Waters	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	Tefsit Bekele	Sherita McLamore

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	n/a		Reviewed in conjunction with NDA
	Type III			n/a		Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type V			n/a	No Review	Adequate information provided in the NDA
	Type V			n/a	No Review	Adequate information provided in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	205580	Listed Drug

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 212209 Bendamustine HCl Injection, 100 mg/ 4mL (25 mg/mL). A 24-month drug product expiration period may be granted for the drug product when stored between 2–8 °C. There are no outstanding issues and no post-approval quality agreement to be conveyed to the applicant.

II. Summary of Quality Assessments

A. Product Overview

NDA 212209 was submitted for Bendamustine HCl Injection, 25 mg/mL in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act. Bendamustine acts as an alkylating agent causing intra-strand and inter-strand cross-links between DNA bases. The drug product, Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL) is indicated for the treatment of Chronic Lymphocytic Leukemia (CLL) and Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen. The Listed Drug (LD), Belrapzo (Bendamustine Hydrochloride) Injection 100 mg/4, was developed by Eagle Pharmaceutics. It was approved under NDA 205580 in May 2018. The proposed drug product is intended to have the same indication, dosage form, dose, route of administration and (b) (4) as the Listed Drug. The proposed product is comparable to the LD with the primary difference being the presence of dehydrated alcohol in place of propylene glycol.

Bendamustine is a small achiral molecule that is manufactured by (b) (4) (b) (4) (b) (4) The drug product, Bendamustine HCl Injection, 100 mg/4 mL is supplied as a clear, colorless to yellow colored, (b) (4) sterile solution. The drug product formulation is non-aqueous and includes the active, monothioglycerol, dehydrated alcohol, sodium hydroxide and polyethylene glycol.

The recommended dosing regimen for Bendamustine HCl Injection, 25 mg/mL for CLL is 100 mg/m^2 administered intravenously over (b) (4) minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles. The recommended dosing regimen for Bendamustine HCl Injection, 25 mg/mL for NHL is 120 mg/m^2 administered intravenously over (b) (4) minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles.

Based on the information provided in this application (original submission, responses to information requests and in the resubmission), OPQ considers all review issues adequately addressed and potential risks to patient safety and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 212209 and grants a 24-month drug product expiration period when stored at between 2–8 °C in the commercial packaging.

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of patients with 1. Chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established. 2. Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen
Duration of Treatment	6- 28 day cycles for CLL and 8- (b) (4) day cycles for NHL
Maximum Daily Dose	120 mg/m^2
Alternative Methods of Administration	n/a

B. Quality Assessment Overview

NDA 212209 was submitted in August of 2018 and was issued a Complete Response (CR) in June 2019 due to a withhold recommendation from the OPF. The withhold recommendation was issued as a result of outstanding risks associated with the drug substance manufacturing facility ((b) (4) based on the individual and composite evaluation of the facilities' inspectional history and compliance status. The applicant responded to the June 2019 CR in July of 2019; however, the status of (b) (4) remained unchanged from the 1st review cycle and NDA 212209 was issued a second CR on September 16, 2019. The applicant responded to the agency's September 2019 CR on February 14, 2020. At the time of review, all facilities associated with NDA 212209 were deemed acceptable to perform the responsibilities listed in the application and there were no other outstanding issues. Accordingly, NDA 212209 was recommended for approval from a product quality perspective with an assigned the expiration dating period of 24 months for the drug product when stored at stored between 2–8 °C and a 24h refrigerated/ 3h room temperature in-use period for the drug product when reconstituted with 0.9% NaCl. Of note, the original 2018 NDA submission included 2 diluents: 0.9% Sodium Chloride, USP and 2.5% Dextrose/0.45% Sodium Chloride, USP. After review, it was concluded that the in-use stability data for the drug product diluted with 2.5% dextrose/0.45% Sodium Chloride Injection USP did not support the proposed in-use period. Accordingly, the 2.5% dextrose/0.45% diluent was removed from the application and labeling and 0.9% NaCl was the only diluent recommended for approval with an infusion time and concentration range of (b) (4) minutes and (b) (4) mg/mL, respectively.

In the current submission, the Applicant reinstated the 2.5% dextrose/0.45% diluent along with 0.9% NaCl diluent and both at a higher concentration ((b) (4)–1.36 mg/mL) and consequently a shorter infusion time (20 min). A mass balance issue in the in-use stability data which persisted throughout this review cycle was ultimately resolved after multiple information requests and a clock extension (see drug product IQA for specific details). The drug product reviewer notes that the in use-stability data generated for three lots of the drug product diluted with 0.9% sodium chloride and with 2.5% dextrose/0.45% sodium chloride solutions at concentrations ranging from 0.4

mg/mL to 1.36 mg/mL supports the proposed in-use period (24 hours at 2–8 °C and 3 hours at room temperature). The reviewer notes that while there are no safety concerns related to the drug product and the admixtures there are outstanding issues associated with the analytical method that may need to be addressed in the future. The reviewer recommends that the applicant develop a uniform HPLC method for the assay and related substance and re-evaluate the in-use stability study using the new method (see Life Cycle Management Comment below).

> Life Cycle Management Considerations:
> *Mass balance discrepancies in the in-use stability data generated with drug product batches in 0.9% sodium chloride and 2.5% dextrose/0.45% sodium chloride solutions at* (b) (4) *mg/mL and 1.36 mg/mL concentrations were observed. The independent assay and related substance HPLC methods likely introduced some analytical errors. The applicant should develop one HPLC method to test assay and degradation products. This is a good starting point towards understanding the root cause for the mass balance problems in the in-use data and consequently minimize data reporting errors. Although the applicant is not required to do in-use stability study once the drug product is approved, they should re-evaluate the analytical methods for the product and re-do the in-use study to have a full insight and clearer picture of how the drug product performs when it is diluted with infusion diluents at the desired concentrations.*

There were no changes to the drug substance synthesis or drug product manufacturing process. The quality microbiology review noted that there were no changes to the previously assessed post-dilution holding times (3 hours RT/24 hours refrigerated).

NDA 212209 is recommended for approval from the microbiology, drug substance, drug product, and drug process perspectives with a recommended drug product expiry of **24-months**.

Facilities:
No changes are proposed to the manufacturing process or facilities. NDA 212209 included 2 sites and both sites were listed as ready for inspection:

(b) (4)

- **Corden pharma Latina S.p.A of Italy-** (b) (4) (b) (4) Packaging, (b) (4) Labeling, (b) (4)

Following completion of review of this application, it was determined that both sites remained acceptable to perform the responsibilities listed in the application.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment

n/a

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U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM
NDA 212209
BENDAMUSTINE HYDROCHLORIDE INJECTION, (b) (4) MG/ML
CMC REVIEW OF REVISED LABEL AND LABELING

Bendamustine Hydrochloride Injection was tentatively approved on July 2, 2020. The applicant, Slayback Pharma LLC submitted a class 2 resubmission for Bendamustine Hydrochloride on June 16, 2021. The original CMC labeling review for 100 mg/4 mL Bendamustine hydrochloride Injection was uploaded in panorama on May 10, 2019. CMC provided recommendation during the previous labeling reviews and the changes were accepted by the applicant. Since the last labeling review, the applicant made some changes which included the addition of a new diluent, 2.5% dextrose/0.45% sodium chloride and admixture concentration changes from (b) (4) mg/mL to (b) (4) –1.36 mg/mL. As a result, a revised container label, carton labeling, and prescribing information were submitted in the resubmission. CMC reviewed the changes as part of the evaluation of the 505(b)(2) NDA class 2-resubmission for Bendamustine Hydrochloride Injection.

Under section *2.3 Preparation and Administration* of the prescribing information an alternative diluent to 0.9% sodium chloride Injection, USP was added. The new diluent is 2.5% dextrose/0.45% sodium chloride injection, USP which is also a diluent used in the listed drug Belrapzo along with 0.9% sodium chloride. Moreover, due to updated admixture concentrations, the previous (b) (4) mL infusion bags containing the diluents changed to 250 mg infusion bags. In section *2.4 Admixture Stability*, the stability information for Bendamustine Hydrochloride Injection in 2.5%dextrose/0.45% sodium chloride diluent was also added which is identical to that of the admixture prepared in 0.9% NaCl.

The container label and carton labeling were updated to include the new diluent, 2.5% dextrose/0.45% sodium chloride injection as shown below. Currently, CMC has no additional recommendations.

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Sherita McLamore

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MEMORANDUM

DATE: 20 January 2022

TO: NDA 212209

FROM: Steven Hertz, P.E.

THROUGH: Yiwei Li, Ph.D.

SUBJECT: NDA 212209 Resubmission, 16 June 2021 (SDN 33)

This applicant received tentative approval for the product, Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL) on 02 July 2020. (Note that it was recommended for approval based on quality manufacturing in assessment 'N212209 Manufacturing R03.1 AQ', archived in Panorama.) After this tentative approval the applicant communicated with the Agency via a meeting request/package which received a written response dated 23 October 2020. The subject of this package was proposed labeling changes to end-user infusion volume, rate, and time.

The SDN 33 resubmission documentation contained a microbiological study to support the new proposed in-use parameters. These changes, as summarized by the applicant, are as follows:

	Existing Tentatively Approved NDA	Proposed Changes to Tentatively Approved NDA	Justification
Diluent	0.9% Sodium Chloride Injection USP	0.9% Sodium Chloride Injection USP and/or 2.5% Dextrose/0.45% Sodium Chloride Injection USP	To propose new diluent in line with the RLD (BELRAPZO™).
Recommended Diluent Volume (Infusion Bag Volume)	(b) (4) mL	250 mL	(b) (4)
Infusion Rate	**CLL:** (b) (4) Minutes **NHL:** (b) (4) Minutes	**CLL:** 20 Minutes **NHL:** 20 Minutes	
Final Diluted Drug Product Concentration	(b) (4) mg/mL to (b) (4) mg/mL	(b) (4) mg/mL to 1.36 mg/mL	

No changes are proposed to the manufacturing process or facilities. All facilities listed on the Form FDA 356h in SDN 33 were evaluated in either during the original application submission or in SDN 21, documented in 'N212209 Manufacturing R03.1 AQ', and are still in an acceptable compliance status.

Reviewer's Assessment - Adequate
The primary manufacturing reviewer deems the proposed commercial process and facilities as acceptable.

END

Steven Hertz

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Yiwei Li

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MEMORANDUM

DATE: 14 September 2021

TO: NDA 212209

FROM: Erika Pfeiler, Ph.D.

THROUGH: John Metcalfe, Ph.D.

SUBJECT: NDA 212209 Resubmission, 16 June 2021 (SDN 33)

This applicant received tentative approval for the product, Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL) on 02 July 2020. (Note that it was recommended for approval based on quality microbiology in assessment N212209MR01, archived in Panorama.) After this tentative approval the applicant communicated with the Agency via a meeting request/package which received a written response dated 23 October 2020. The subject of this package was proposed labeling changes to end-user infusion volume, rate, and time. (Note that the written responses requested that the applicant perform a 'microbial contamination study' to support the new proposed in-use period; however, no DMA assessor was assigned to this meeting package.)

The 16 June resubmission documentation contained a microbiological study to support the new proposed in-use parameters. These changes, as summarized by the applicant, are as follows:

	Existing Tentatively Approved NDA	Proposed Changes to Tentatively Approved NDA	Justification
Diluent	0.9% Sodium Chloride Injection USP	0.9% Sodium Chloride Injection USP and/or 2.5% Dextrose/0.45% Sodium Chloride Injection USP	To propose new diluent in line with the RLD (BELRAPZO™).
Recommended Diluent Volume (Infusion Bag Volume)	(b) (4) mL	250 mL	(b) (4)
Infusion Rate	**CLL:** (b) (4) Minutes **NHL:** (b) (4) Minutes	**CLL:** 20 Minutes **NHL:** 20 Minutes	
Final Diluted Drug Product Concentration	(b) (4) mg/mL to (b) (4) mg/mL	(b) (4) mg/mL to 1.36 mg/mL	

No changes to the previously assessed post-dilution holding times (3 hours RT/24 hours refrigerated.) Microbiological challenge studies were performed on the following dilutions:

Diluent	Drug concentration (mg/mL)	Storage condition RT = 15-30°C Refrigerated = 2-8°C	Sampling time points (hours)
0.9% Sodium Chloride	(b) (4)	RT	0, 3, 5, 6
0.9% Sodium Chloride		Refrigerated	0, 24
0.9% Sodium Chloride		RT	0, 3, 5, 6
0.9% Sodium Chloride		Refrigerated	0, 24
2.5% Dextrose/0.45%		RT	0, 3, 5, 6

M E M O R A N D U M

Sodium Chloride	(b) (4)		
2.5% Dextrose/0.45% Sodium Chloride		Refrigerated	0, 24
2.5% Dextrose/0.45% Sodium Chloride		RT	0, 3, 5, 6
2.5% Dextrose/0.45% Sodium Chloride		Refrigerated	0, 24

These admixtures were challenged with NMT (b) (4) CFU/mL of *Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, Candida albicans,* and *Aspergillus brasilensis*. Two batches of product (7G04376V, 9K06227V) were used in testing. Positive and negative controls were utilized. Following sampling, plating, and incubation, no log increases (in fact, several log decreases) were observed in the inoculated admixtures.

Reviewer's Assessment - Adequate
The applicant presented acceptable microbiological studies to support the proposed package insert information. The information was fully assessed; however, the proposed holding/infusion times did not exceed the limit for which no data is needed per DMA policy (4 hours at room temperature/24 hours refrigeration.) The applicant was advised to perform these unnecessary studies by a non-DMA assessor.

END

Erika Pfeiler

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John Metcalfe

Digitally signed by John Metcalfe
Date: 9/16/2021 02:10:30PM
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Comments: I concur.

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM
NDA 212209
BENDAMUSTINE HYDROCHLORIDE INJECTION, 100 MG/ML
CMC REVIEW OF REVISED LABEL AND LABELING

Bendamustine Hydrochloride Injection was tentatively approved on July 2, 2020. The applicant, Slayback Pharma LLC submitted a class 2 resubmission for Bendamustine Hydrochloride on June 16, 2021. The original CMC labeling review for 100 mg/4 mL Bendamustine hydrochloride Injection was uploaded in panorama on May 10, 2019. CMC provided recommendation during the previous labeling reviews and the changes were accepted by the applicant. Since the last labeling review, the applicant made some changes which included the addition of a new diluent, 2.5% dextrose/0.45% sodium chloride and admixture concentration changes from (b) (4) mg/mL to (b) (4)–1.36 mg/mL. As a result, a revised container label, carton labeling, and prescribing information were submitted in the resubmission. CMC reviewed the changes as part of the evaluation of the 505(b)(2) NDA class 2-resubmission for Bendamustine Hydrochloride Injection.

Under section *2.3 Preparation and Administration* of the prescribing information an alternative diluent to 0.9% sodium chloride Injection, USP was added. The new diluent is 2.5% dextrose/0.45% sodium chloride injection, USP which is also a diluent used in the listed drug Belrapzo along with 0.9% sodium chloride. Moreover, due to updated admixture concentrations, the previous (b) (4) mL infusion bags containing the diluents changed to 250 mg infusion bags. In section *2.4 Admixture Stability*, the stability information for Bendamustine Hydrochloride Injection in 2.5%dextrose/0.45% sodium chloride diluent was also added which is identical to that of the admixture prepared in 0.9% NaCl.

The container label and carton labeling were updated to include the new diluent, 2.5% dextrose/0.45% sodium chloride injection as shown below. Currently, CMC has no additional recommendations.

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

TEFSIT BEKELE

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Sherita McLamore

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Date: 2/23/2022 10:29:03AM
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MEMORANDUM

DATE: 20 January 2022

TO: NDA 212209

FROM: Steven Hertz, P.E.

THROUGH: Yiwei Li, Ph.D.

SUBJECT: NDA 212209 Resubmission, 16 June 2021 (SDN 33)

This applicant received tentative approval for the product, Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL) on 02 July 2020. (Note that it was recommended for approval based on quality manufacturing in assessment 'N212209 Manufacturing R03.1 AQ', archived in Panorama.) After this tentative approval the applicant communicated with the Agency via a meeting request/package which received a written response dated 23 October 2020. The subject of this package was proposed labeling changes to end-user infusion volume, rate, and time.

The SDN 33 resubmission documentation contained a microbiological study to support the new proposed in-use parameters. These changes, as summarized by the applicant, are as follows:

	Existing Tentatively Approved NDA	Proposed Changes to Tentatively Approved NDA	Justification
Diluent	0.9% Sodium Chloride Injection USP	0.9% Sodium Chloride Injection USP and/or 2.5% Dextrose/0.45% Sodium Chloride Injection USP	To propose new diluent in line with the RLD (BELRAPZO™).
Recommended Diluent Volume (Infusion Bag Volume)	(b) (4) mL	250 mL	(b) (4)
Infusion Rate	**CLL:** (b) (4) Minutes **NHL:** (b) (4) Minutes	**CLL:** 20 Minutes **NHL:** 20 Minutes	
Final Diluted Drug Product Concentration	(b) (4) mg/mL to (b) (4) mg/mL	(b) (4) mg/mL to 1.36 mg/mL	

No changes are proposed to the manufacturing process or facilities. All facilities listed on the Form FDA 356h in SDN 33 were evaluated in either during the original application submission or in SDN 21, documented in 'N212209 Manufacturing R03.1 AQ', and are still in an acceptable compliance status.

Reviewer's Assessment - Adequate
The primary manufacturing reviewer deems the proposed commercial process and facilities as acceptable.

END

Steven Hertz

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Yiwei Li

Digitally signed by Yiwei Li
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Recommendation: **APPROVAL**

NDA 212209
Review #3

Drug Name/Dosage Form	Bendamustine HCl Injection
Strength	100 mg/4 mL (25 mg/mL)
Route of Administration	IV
Rx/OTC Dispensed	R_x
Applicant	Slayback Pharma LLC
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission	14-Feb-20	All
Amendment 0023	20-Mar-20	Facilities
Amendment 0006	31-Mar-20	Drug Product and Facilities

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Kabir Shahjahan	Suong Tran
Drug Product	Tefsit Bekele	Anamitro Banerjee
Process	Djelila Mezaache	Bogdan Kurtyka
Microbiology	Christine Craig	Erika Pfeiler
Facility	Djelila Mezaache	Bogdan Kurtyka
Biopharmaceutics	Zhuojun Zhao	Banu Zolnik
Regulatory Business Process Manager	Rabiya Laiq	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	Tefsit Bekele	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	n/a		Reviewed in conjunction with NDA
	Type III			n/a		Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type V			n/a	No Review	Adequate information provided in the NDA
	Type V			n/a	No Review	Adequate information provided in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	205580	Listed Drug

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 212209 Bendamustine HCl Injection, 100 mg/ 4mL (25 mg/mL). A 24-month drug product expiration period may be granted when stored between 2–8 °C. There are no outstanding issues and no post-approval quality agreement to be conveyed to the applicant.

II. Summary of Quality Assessments

A. Product Overview

NDA 212209 was submitted for Bendamustine HCl Injection, 25 mg/mL in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act. Bendamustine acts as an alkylating agent causing intra-strand and inter-strand cross-links between DNA bases. The drug product, Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL) is indicated for the treatment of Chronic Lymphocytic Leukemia (CLL) and Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen. The Listed Drug (LD), Belrapzo (Bendamustine Hydrochloride) Injection 100 mg/4, was developed by Eagle Pharmaceutics. It was approved under NDA 205580 in May 2018. The proposed drug product is intended to have the same indication, dosage form, dose, route of administration and (b) (4) as the Listed Drug. The proposed product is comparable to the LD with the primary difference being the use of dehydrated alcohol in place of propylene glycol.

Bendamustine is a small achiral molecule that is manufactured by (b) (4) (b) (4) (b) (4) The drug product, Bendamustine HCl Injection, 100 mg/4 mL is supplied as a clear, colorless to yellow colored, (b) (4) sterile solution. The drug product formulation is non-aqueous and includes the active, monothioglycerol, dehydrated alcohol, sodium hydroxide and polyethylene glycol.

The recommended dosing regimen for Bendamustine HCl Injection, 25 mg/mL for CLL is 100 mg/m^2 administered intravenously over (b) (4) minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles. The recommended dosing regimen for Bendamustine HCl Injection, 25 mg/mL for NHL is 120 mg/m^2 administered intravenously over (b) (4) minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles.

Based on the information provided in this application (original submission, responses to information requests and in the resubmission), OPQ considers all review issues adequately addressed and potential risks to patient safety and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 212209 and grants a 24-month drug product expiration period when stored at between 2–8 °C in the commercial packaging.

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of patients with 1. Chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established. 2. Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen
Duration of Treatment	6- 28 day cycles for CLL and 8- (b) (4) day cycles for NHL
Maximum Daily Dose	120 mg/m^2
Alternative Methods of Administration	n/a

B. Quality Assessment Overview

NDA 212209 was submitted for Bendamustine HCl Injection, 25 mg/mL in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act in August of 2018 and was issued a Complete Response (CR) in June 2019 as a result of a withhold recommendation from OPF. The withhold recommendation was issued because there were outstanding risks associated with the drug substance manufacturing facility (b) (4)) based on the individual and composite evaluation of the listed facilities' inspectional history and compliance status. The applicant responded to the June 2019 Complete Response Letter (CRL) in July of 2019; however, the status of (b) (4) remained unchanged from the 1st review cycle. Accordingly, and the overall recommendation from facilities was **Withhold Approval** and NDA 212209 was issued a second CR.

The following comment was conveyed to the applicant in the agency's September 16, 2019 Complete Response Letter.

> *During a recent inspection of (b) (4) drug substance manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved. Please list communications submitted to, or held with, the Agency to facilitate resolution of the observed objectionable conditions, or deficiencies, noted at the facility.*

The applicant provided a response to the agency's September 16, 2019 CRL on February 14, 2020. At the time of review, all facilities associated with the NDA 212209 are approvable and were deemed acceptable to perform the responsibilities listed in the application.

In addition to the response to the CMC deficiency noted in the September 16, 2019 CRL, the applicant provided updated stability data for the finished product in support of the proposed 24-month expiry. Based on the information provided, Slayback Pharma LLC. proposed and the FDA accepts the expiration dating period of **24 months** for the drug product when stored at stored between 2–8 °C.

Additionally, the multi-puncture studies justifies the proposed 28 days shelf life for the multi-dose product after the first puncture when it is stored in the original carton at 2–8 °C and the in use study supports a 24 hour in use period for the drug product when reconstituted with 0.9% sodium chloride and stored at 2–8 °C and a 3 in use period when stored at room temperature.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment

n/a

Attachment 1

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/s/

SHERITA D MCLAMORE
06/29/2020 11:35:49 AM

Recommendation: COMPLETE RESPONSE

NDA 212209
Review #2

Drug Name/Dosage Form	Bendamustine HCl Injection
Strength	100 mg/4 mL (25 mg/mL)
Route of Administration	IV
Rx/OTC Dispensed	R_x
Applicant	Slayback Pharma LLC
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission	1-Jul-19	Facilities
Amendment 00019	5-Jun-19	DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Kabir Shahjahan	Suong Tran
Drug Product	Tefsit Bekele	Anamitro Banerjee
Process	Djelila Mezaache	Bogdan Kurtyka
Microbiology	Christine Craig	Erika Pfeiler
Facility	Djelila Mezaache	Bogdan Kurtyka
Biopharmaceutics	Zhuojun Zhao	Banu Zolnik
Regulatory Business Process Manager	Rabiya Laiq	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	Tefsit Bekele	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	n/a		Reviewed in conjunction with NDA
	Type III			n/a		Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type V			n/a	No Review	Adequate information provided in the NDA
	Type V			n/a	No Review	Adequate information provided in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	205580	Listed Drug

2. CONSULTS

N/A

Executive Summary

1. Recommendations and Conclusion on Approvability

OPQ recommends **COMPETE RESPONSE** for the resubmission of NDA 212209 Bendamustine HCl Injection, 100 mg/ 4mL (25 mg/mL) as a result of a WITHOLD recommendation from OPF. The following deficiency will be included in the Agency's Compete Response (CR) letter:

> *During a recent inspection of* (b) (4) *drug substance manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved.*

2. Summary of Quality Assessments

1. Product Overview

NDA 212209 was submitted for Bendamustine HCl Injection, 25 mg/mL in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act. Bendamustine acts as an alkylating agent causing intra-strand and inter-strand cross-links between DNA bases. The drug product, Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL) is indicated for the treatment of Chronic Lymphocytic Leukemia (CLL) and Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen. The Listed Drug (LD), Belrapzo (Bendamustine Hydrochloride) Injection 100 mg/4, was developed by Eagle Pharmaceutics. It was approved under NDA 205580 in May 2018. The proposed drug product is intended to have the same indication, dosage form, dose, route of administration and (b) (4) as the Listed Drug. The proposed product is comparable to the LD with the primary difference being the use of dehydrated alcohol in place of propylene glycol.

Bendamustine is a small achiral molecule that is manufactured by (b) (4) (b) (4) (b) (4) The drug product, Bendamustine HCl Injection, 100 mg/4 mL is supplied as a clear, colorless to yellow colored, (b) (4) sterile solution. The drug product formulation is non-aqueous and includes the active, monothioglycerol, dehydrated alcohol, sodium hydroxide and polyethylene glycol.

The recommended dosing regimen for Bendamustine HCl Injection, 25 mg/mL for CLL is 100 mg/m^2 administered intravenously over (b) (4) minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles. The recommended dosing regimen for Bendamustine HCl Injection, 25 mg/mL for NHL is 120 mg/m^2 administered intravenously over (b) (4) minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles.

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of patients with 1. Chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established **2.** Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.
Duration of Treatment	6- 28 day cycles for CLL and 8- (b) (4) day cycles for NHL
Maximum Daily Dose	120 mg/m^2
Alternative Methods of Administration	None

3. Quality Assessment Overview

NDA 212209 was submitted for Bendamustine HCl Injection, 25 mg/mL in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act in August of 2018 and was issued a Complete Response (CR) in June 2019 as a result of a withhold recommendation from OPF. The withhold recommendation was issued because there were outstanding risks associated with the drug substance manufacturing facility ((b) (4) based on the individual and composite evaluation of the listed facilities' inspectional history and compliance status. (b) (4) was one of two facilities included in the original submission and was responsible for receipt of materials, production, packaging, labelling, quality control, release, stability testing, storage and distribution of the API.

The applicant responded to the June 2019 Complete Response Letter in July of 2019; however, the status of (b) (4) remained unchanged from the 1st review cycle with an OAI compliance status. Accordingly, this facility is not acceptable support the approval of NDA 212209 and the overall recommendation from facilities is **Withhold Approval.** A satisfactory resolution of all deficiencies is required before this NDA may be recommended for approval.

The following deficiency will be included in the Agency's CR letter:

> *During a recent inspection of* (b) (4) *drug substance manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved.*

There were no other changes noted in the July 2019 resubmission; however, during the previous review cycle the Applicant submitted an amendment (SD 19) that was not

reviewed due to the timing of the submission (June 5, 2019). This amendment included the finalized investigational report. The finalized investigational report included simulated in-use stability study report, OOS investigation for simulating in-use stability study report and dilution compatibility study report. The drug product reviewer determined that the new data submitted were adequate.

4. Special Product Quality Labeling Recommendations (NDA only)

n/a

5. **Final Risk Assessment (see Attachment)**

No changes

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/s/

SHERITA D MCLAMORE
09/09/2019 04:59:01 PM

Recommendation: COMPLETE RESPONSE

NDA 212209
Review #1

Drug Name/Dosage Form	Bendamustine HCl Injection
Strength	100 mg/4 mL (25 mg/mL)
Route of Administration	IV
Rx/OTC Dispensed	R_x
Applicant	Slayback Pharma LLC
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	31-Aug-18	All
Amendment 0001	19-Sept-18	Facilities
Amendment 0006	14-Feb-19	Facilities
Amendment 0007	25-Jan-19	Facilities
Amendment 0009	1-Mar-19	DP
Amendment 00011	26-Mar-19	DP
Amendment 0014	10-Apr-19	DP
Amendment 00015	24-Apr-19	DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Kabir Shahjahan	Suong Tran
Drug Product	Tefsit Bekele	Anamitro Banerjee
Process	Djelila Mezaache	Bogdan Kurtyka
Microbiology	Christine Craig	Erika Pfeiler
Facility	Djelila Mezaache	Bogdan Kurtyka
Biopharmaceutics	Zhuojun Zhao	Banu Zolnik
Regulatory Business Process Manager	Rabiya Laiq	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	Tefsit Bekele	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	n/a		Reviewed in conjunction with NDA
	Type III			n/a		Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type V			n/a	No Review	Adequate information provided in the NDA
	Type V			n/a	No Review	Adequate information provided in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	205580	Listed Drug

2. CONSULTS

N/A

Executive Summary

1. Recommendations and Conclusion on Approvability

OPQ recommends **COMPETE RESPONSE** for NDA 212209 Bendamustine HCl Injection, 100 mg/ 4mL (25 mg/mL) as a result of a WITHOLD from the Office of Compliance.

2. Summary of Quality Assessments

1. Product Overview

NDA 212209 was submitted for Bendamustine HCl Injection, 25 mg/mL in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act. Bendamustine acts as an alkylating agent causing intra-strand and inter-strand cross-links between DNA bases. The drug product, Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL) is indicated for the treatment of Chronic Lymphocytic Leukemia (CLL) and Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen. The Listed Drug (LD), Belrapzo (Bendamustine Hydrochloride) Injection 100 mg/4, was developed by Eagle Pharmaceutics. It was approved under NDA 205580 in May 2018. The proposed drug product is intended to have the same indication, dosage form, dose, route of administration and (b) (4) as the Listed Drug. The proposed product is comparable to the LD with the primary difference being the use of dehydrated alcohol in place of propylene glycol.

Bendamustine is a small achiral molecule that is manufactured by (b) (4) (b) (4) (b) (4) The drug product, Bendamustine HCl Injection, 100 mg/4 mL is supplied as a clear, colorless to yellow colored, (b) (4) sterile solution. The drug product formulation is non-aqueous and includes the active, monothioglycerol, dehydrated alcohol, sodium hydroxide and polyethylene glycol.

The recommended dosing regimen for Bendamustine HCl Injection, 25 mg/mL for CLL is 100 mg/m^2 administered intravenously over (b) (4) minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles. The recommended dosing regimen for Bendamustine HCl Injection, 25 mg/mL for NHL is 120 mg/m^2 administered intravenously over (b) (4) minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles.

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of patients with 1. Chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established 2. Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months

	of treatment with rituximab or a rituximab-containing regimen.
Duration of Treatment	6- 28 day cycles for CLL and 8- (b) (4) day cycles for NHL
Maximum Daily Dose	120 mg/m^2
Alternative Methods of Administration	None

3. Quality Assessment Overview

Drug Substance

Bendamustine is a small achiral molecule that is manufactured and release tested by (b) (4) (b) (4) (b) (4) (b) (4).). It is a white to off-white, non-hygroscopic powder that is slightly soluble in water and methanol and soluble in DMF and DMSO. Bendamustine Hydrochloride Monohydrate exhibits polymorphic behaviour and has a melting range of 151-154°C. It is manufactured (b) (4) (b) (4) (b) (4) Complete chemistry manufacturing and control information for the bendamustine drug substance is cross referenced in DMF (b) (4) DMF (b) (4) was reviewed in conjunction with this application and was deemed adequate to support the approval of the NDA. Based on the information in the referenced DMF, a (b) (4) month retest period has been established for the drug substance. NDA 212209 is recommended for approval from a drug substance perspective.

Drug Product and Drug Process

The drug product, Bendamustine HCl Injection,100 mg/4 mL (25 mg/mL) is supplied as a clear colorless to (b) (4) yellow, (b) (4) sterile solution in a multiple-dose vial. The drug product formulation is for the most part non-aqueous. The formulation includes the active, monothioglycerol, dehydrated alcohol, sodium hydroxide and polyethylene glycol 400. All excipients are compendial grades and there are no novel excipients or overages in the formulation. The drug product contains no antimicrobial preservatives. (b) (4) The selection of excipients was based on the excipients listed in PI of the LD with the exception of dehydrated alcohol which replaced propylene glycol.

The recommended dosing regimen for Bendamustine HCl Injection, 100 mg/4 mL for CLL is 100 mg/m^2 infused intravenously over (b) (4) minutes on Days 1 and 2 of a 28-day cycle for up to 6 cycles. The recommended dose for NHL is 120 mg/m^2 infused intravenously over (b) (4) minutes on Days 1 and 2 of a 21-day cycle for up to 8 cycles.

The product is designed to be diluted with 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. The applicant stated that the final admix is stable for up to 24 hours when stored refrigerated or up to 3 hours when stored at room temperature. The applicant also notes that partially used vials are stable

for up to 28 days when stored in the original container closure system under refrigeration (2° to 8°C or 36° to 46°F) but notes that each vial is recommended for no more than six (6) dose withdrawals.

The drug product is manufactured at the Corden pharma Latina S.p.A of Italy at a commercial batch size of (b) (4) The drug product manufacturing process (b) (4) (b) (4) The manufacturing process includes clearly defined IPCs, CPPs and CQAs. All were described in sufficient detail and adequately justified. The applicant demonstrated the suitability of the manufacturing process for the drug product at commercial scale. The description of the manufacturing process includes appropriate in-process controls and operating parameters.

The container closure system for the drug product consists of (b) (4) a glass vial, an elastomeric closure and an aluminum seal. The glass vials are comprised of (b) (4) clear glass ((b) (4)). The elastomeric closure is described as 20 mm (b) (4) (b) (4) rubber and the aluminum seal is a 20 mm aluminum seal with a (b) (4) (b) (4) The aluminum seal does not have direct contact with the solution and is therefore not considered a primary packaging component. The primary container closure system was deemed suitable for the intended use and the rubber closure was demonstrated to be compatible with the drug product based on stability and leachable and extractable studies.

The drug product specifications included description, identification, pH, color of solution, assay, related substances, (b) (4) container content, viscosity, (b) (4) extractable volume, particulate matter, sterility, and bacterial endotoxins. The applicant included a risk assessment for elemental impurities as per ICH Q3D/USP <232>. The data demonstrated that the Class I, II and III elements were below the (b) (4)% PDE limits for individual elements for a parenteral drug product. Accordingly, the risk assessment is acceptable and a test for elemental impurities was not proposed and is not required in the drug product release specifications. The proposed drug product specification is consistent with ICH Q6A and are based on batch analyses and stability data. The drug product specification is adequate to establish the drug product identity, potency and purity and provide adequate controls to ensure the quality of the drug product through the product expiry. The proposed specification and acceptance criteria for the drug product, together with controls for impurities in the drug substance are adequate to ensure that the critical quality attributes of this product are well controlled.

In support of the proposed 24-month expiry, 12 months of primary stability data were provided for three registration batches (batches 7G04376V, 7G04377V and

7G04378V) of the drug product packaged in aforementioned container closure system. The drug product was stored inverted and upright under long term (5°C) and accelerated conditions (25ºC/60%RH). In addition to the primary stability data, the applicant provided results from a multi-puncture study, a photo stability a thermal cycling studies and in-use stability data to demonstrate compatibility of drug product when co-mixed with the following infusion solutions:

1. 0.9% Sodium Chloride Injection USP;
2. 2.5% Dextrose/0.45% Sodium Chloride Injection USP and

The applicant requested a 24-month expiry for the drug product when stored under controlled refrigerated conditions (2-8ºC) and a 24h refrigerated/ 3h room temperature in-use period for the 0.9% NaCl admixture and the 2.5% dextrose/0.45% Sodium Chloride Injection USP admixture. The available long term stability data demonstrates consistency; however, under accelerated storage conditions changes in assay and impurities are reported. The in-use stability data provided for the 2.5% dextrose/0.45% Sodium Chloride Injection USP infusion solution does not support the proposed in-use period. Accordingly, the 2.5% dextrose/0.45% infusion solution was removed from the labeling. All other label claims are adequately supported (see appended drug product IQA for details).

Based on the stability submitted, the ***FDA rejects the proposed 24 month expiry and based on ICH Q1E and Q1A (R2) recommends a 15 month expiry*** for the drug product when stored at stored under refrigerated conditions in the original carton. The agency accepts the proposed in-use time (i.e. 24 h under refrigeration and 3 h at room temperature) for the 0.9% NaCl admixture and the 28-day shelf life for the multi-dose drug product after the first puncture when it is stored in its original carton at 2–8 °C. The 2.5% dextrose/0.45% Sodium Chloride Injection USP infusion solution was not adequately supported and was removed from the PI.

NDA 212209 is recommended for approval from a drug product and drug process perspective with a recommended drug product expiry of **15-months**.

Biopharmaceutics

The proposed Bendamustine HCl for injection, 100 mg/4 mL (25 mg/mL) formulation has the same indications, active ingredient, dosage form, dose, (b) (4) and route of administration as the LD but contains different excipients. The applicant requested a waiver of *in vivo* bioequivalence of the drug product; however, the biopharm reviewer concluded that a waiver of the requirement to conduct *in vivo* bioequivalence studies is not feasible as the proposed drug product contains excipients that are not present in the LD (i.e. proposed product includes presence of dehydrated alcohol and the absence of propylene glycol). It was concluded that a bridge between the proposed Bendamustine HCl Injection and the LD could be established for the following reasons:

1. the proposed Bendamustine HCl Injection has the same active ingredient, same bendamustine concentration, same (b) (4) and is intended for

administration by intravenous infusion with the (b) (4) as the approved LD product;
2. the different excipients in the proposed drug product is not expected to alter the disposition kinetics of bendamustine in humans
3. physicochemical properties (pH, density, gravity, viscosity, and osmolality) of the proposed drug product and the LD are similar

Based on the information provided by the applicant in response to this IR, bridging between the proposed drug product and the LD is established and this application is recommended for approval from a biopharmaceutics perspective.

Quality Microbiology

The drug product is a sterile solution that is (b) (4) (b) (4) (b) (4) The primary container closure system was deemed acceptable to maintain product sterility and it was concluded that the applicant provided adequate microbiology data pertaining to the product sterility and endotoxin levels. The drug product is non-aqueous and therefore does not require AET

This application is recommended for approval from a quality microbiology perspective.

Facilities:

NDA 212209 included 2 sites and both sites were listed as ready for inspection: (b) (4)

- **Corden pharma Latina S.p.A of Italy-** (b) (4) (b) (4) Packaging, (b) (4) Labeling, (b) (4)

Following completion of review of this application, it was determined that the drug substance site has an unacceptable compliance history. During a recent inspection of the site, the field investigator observed objectionable conditions at the facility. Accordingly, this application is deemed inadequate from a compliance perspective and is recommended for **WITHHOLD.** A satisfactory resolution of all deficiencies is required before this NDA may be recommended for approval.

Environmental Assessment

The applicant provided a claim for categorical exclusion and a statement of no extraordinary circumstances under 21 Code of Federal Regulations (CFR) Sections 25.31(b). The categorical exclusion cited is appropriate based on the estimated amount of drug to be produced for direct use. The claim of categorical exclusion is therefore acceptable and granted.

4. Special Product Quality Labeling Recommendations (NDA only)

n/a

5. **Final Risk Assessment (see Attachment)**

Attached.

LABELING

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Established Name: Bendamustine Hydrochloride Injection
Dosage form, route of administration	Injection, for intravenous use
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Injection: 100 mg/4 mL (25 mg/mL) in a multiple-dose vial

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	When refrigerated, the contents may partially freeze. Allow the vial to reach room temperature (15-30 °C or 59-86 °F) prior to use. Do not use the product if solid or particulate matter is observed after reaching room temperature. Aseptically withdraw the volume needed for the required dose (based on 25 mg/mL concentration) and immediately transfer to a (b) (4) **mL infusion bag** of 0.9% Sodium Chloride Injection.

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Injection: 100 mg/4 mL (25 mg/mL)
Strengths: in metric system	25 mg/mL
Active moiety expression of strength with equivalence statement (if applicable)	Not required in section 3
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	A (b) (4) clear and colorless to yellow solution in a multiple-dose vial.

4. *Section 11 Description*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Bendamustine Hydrochloride injection
Dosage form and route of administration	Injection
Active moiety expression of strength with equivalence statement (if applicable)	Included
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Each milliliter of injection contains 25 mg of bendamustine hydrochloride equivalent to 22.7 mg of bendamustine, 5 mg of monothioglycerol, NF, 39.45 mg dehydrated alcohol, USP and q.s. to 1mL polyethylene glycol 400, NF.
Statement of being sterile (if applicable)	It is supplied as a sterile multiple-dose, clear, and colorless to yellow (b) (4) (b) (4) solution in a multiple-dose clear glass vial.
Pharmacological/ therapeutic class	Bendamustine hydrochloride injection is an alkylating agent.
Chemical name, structural formula, molecular weight	The chemical name of bendamustine hydrochloride is 5-[Bis(2-chloroethyl)-amino]-1-methyl-1H-benzimidazole-2-butanoic acid hydrochloride Monohydrate. Its empirical molecular formula is $C_{16}H_{21}Cl_2N_3O_2 \cdot HCl.H_2O$ The molecular weight is 412.74.
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	N/A

5. ***Section 16 How Supplied/Storage and Handling***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	100 mg/4 mL
Available units (e.g., bottles of 100 tablets)	Bendamustine Hydrochloride injection is supplied in individual cartons of 5 mL clear multiple-dose vials containing 100 mg of bendamustine hydrochloride as a clear, colorless to yellow (b) (4) (b) (4) solution.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC 71225-120-01, 100 mg/4 mL (25 mg/mL) Bendamustine Hydrochloride Injection is supplied in individual cartons of 5 mL clear multiple-dose vials containing 100 mg of bendamustine hydrochloride as a clear, colorless to yellow (b) (4) (b) (4) solution.
Special handling (e.g., protect from light)	Bendamustine Hydrochloride injection is a (b) (4) drug. Follow applicable special handling and disposal procedures[1]. Care should be exercised in the handling and preparation of solutions prepared from Bendamustine Hydrochloride injection. The use of gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage
Storage conditions	In refrigerator, 2°-8 °C (36°-46 °F). Retain in original carton until time of use to protect from light.

Manufacturer/distributor name (21 CFR 201.1(h)(5))	Slayback Pharma LLC, 301 Carnegie Center, Suite 303 Princeton, New Jersey 08540 Manufactured at: Corden Pharma Latina S.p.A. 04013 Sermoneta (LT), Italy. Under section 17.

II. Labels:

Container and Carton Labels

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Bendamustine Hydrochloride Injection	Bendamustine Hydrochloride Injection
Dosage strength	100 mg/4 mL (25 mg/mL)	100 mg/4 mL (25 mg/mL)
Net contents	100 mg/4 mL	100 mg/4 mL
"Rx only" displayed prominently on the main panel	Provided	Provided
NDC number (21 CFR 207.35(b)(3)(i))	NDC 71225-**120**-01	NDC-71225-**120**-01
Lot number and expiration date (21 CFR 201.17)	Space provided, adequate	Space provided, adequate
Storage conditions	2 to 8 °C (36 to 46 °F)	2 to 8 °C (36 to 46 °F)
Bar code (21CFR 201.25)	Provided	Provided
Name of manufacturer/distributor	Manufactured for Slayback Pharma LLC Princeton, NJ 08540 Manufactured by Corden Pharma Latina S.p.A 04013 Sermoneta (LT) Italy	Manufactured for Slayback Pharma LLC Princeton, NJ 08540 Manufactured by Corden Pharma Latina S.p.A 04013 Sermoneta (LT) Italy
Must be diluted prior to administration	Must dilute required dose in (b) (4) mL admixture prior to administration. Also, Aseptically withdraw…. Immediately transfer to a (b) (4) mL infusion bag of 0.9% sodium chloride injection prior to administration...	Must dilute required dose in (b) (4) mL infusion bag of 0.9% sodium chloride injection or 2.5% dextrose/0.45% sodium chloride injection prior to administration
Route of administration	For intravenous infusion only	For intravenous infusion only

Multi-dose/single dose labeling	(b) (4) vial	(b) (4) vial

Reviewer's Assessment: Adequate with comments

The labeled name "Bendamustine Hydrochloride" doesn't comply with the USP policy entitled, *Monograph Naming Policy for Salt Drug substance in Drug Products and compounded Preparations*. However, the name of the salt can be retained to be consistent with the listed drug whose drug product strength is based on the salt form as it is the case with the proposed drug product. But the carton label should have an equivalency statement information indicating the strength in terms of the active moiety.

On the container and carton label, the applicant refers to the "prescribing information" (b) (4)

The following IRs were sent to the applicant on April 04, 2019:

1. Update the carton label to incorporate an equivalency statement indicating the amount of active moiety related to the amount of the active ingredient (salt) per USP salt policy.
2. Replace the phrase (b) (4)" with "prescribing information" on the container and carton labels.

The applicant responded to the IRs above on April 10, 2019

The sponsor replaced (b) (4)" with "prescribing information" on the container and carton labels. They have also updated the carton label to add equivalency statement.

Overall Assessment and Recommendation:

The labels comply with all regulatory requirements and it is recommended for approval from a CMC perspective.

Primary Labeling Reviewer Name and Date: Tefsit Bekele May 03, 2019

Secondary Reviewer Name and Date: Anamitro Banerjee

TEFSIT BEKELE

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Date: 5/07/2019 09:57:46AM
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Anamitro Banerjee

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Date: 5/10/2019 02:30:18PM
GUID: 5075764700003844b7bc89632228509f

MICROBIOLOGY

Product Background:

ANDA: 212209

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

Route of Administration: Intravenous Injection

Applicant Name: Slayback Pharma LLC

Manufacturing Site: Corden pharma Latina S.p.A, Via del Murillo km. 2.800, Sermoneta, (LT) 04013, Italy (ITA)

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

Review Summary:

List Submissions Being Reviewed: 8/31/2018 and 2/27/19

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: This drug product is proposed for the treatment of patients with Chronic lymphocytic leukemia (CLL).

Concise Description Outstanding Issues Remaining: Additional information is requested for the container closure integrity validation studies.

Supporting Documents:

The Type V DMF (b) (4) is referenced for the (b) (4) (b) (4). The referenced information ((b) (4) (b) (4)) was reviewed and deemed adequate from the perspective of product quality microbiology on 4/9/2018 ((b) (4) doc).

The Type V DMF (b) (4) is referenced for the (b) (4) (b) (4)

original DMF (b) (4) submission and subsequent annual reports have been repeatedly reviewed for sterility assurance and deemed adequate from the perspective of product

quality microbiology. The following supporting documents pertaining to DMF (b) (4) are referenced in this review: (b) (4) (4/23/2013), (b) (4) (12/17/15), (b) (4) doc (1/12/2015), (b) (4) (11/20/2017), and (b) (4) (2/19/19). In addition, (b) (4) (6/25/2018) is referenced as it contains a review of DMF (b) (4) environmental monitoring data provided in response to an information request within the ANDA submission.

S Drug Substance

The drug substance is not provided sterile. Therefore, a product quality microbiology review of the drug substance was not performed.

P.1 Description of the Composition of the Drug Product

(3.2.P.1, Description and Composition of the Drug Product)

- **Description of drug product –** Bendamustine Hydrochloride Injection 100 mg/4mL (25mg/mL), is a sterile, clear, colorless to (b) (4) yellow solution (pg. 1).
- **Drug product composition** (pg. 1)

Ingredients	Reference to Quality Standards	Pharmaceutical Function	100mg/4mL (25mg/mL)	
			Quantity per mL	Quantity per Vial
Bendamustine Hydrochloride#	In-house	Active pharmaceutical ingredient	25 mg	100 mg
Monothioglycerol	USP-NF	(b) (4)	5 mg	20 mg
Dehydrated Alcohol@@	USP		39.45 mg @	157.8 mg@
Sodium Hydroxide*	USP-NF	(b) (4)	q.s	q.s
Polyethylene glycol 400	USP-NF	(b) (4)	q.s to 1.0 mL	q.s to 4.0 mL
(b) (4)				

q.s - quantity sufficient

(b) (4)

(b) (4)

(b) (4)

- **Description of container closure system** (3.2.P.7, Container Closure System, pg. 1)

Component	Description	Manufacturer
Vial	(b) (4)	
Stopper		
Seal		

Adequate

Reviewer's Assessment: The applicant provided an adequate description of the drug product, its composition, and the primary container closure system designed to maintain product sterility.

ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – **NDA 212209 (Bendamustine HCl Injection, 25 mg/mL)**

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach** (b) (4)	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipments • Site	H		Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M		Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place, continue stability monitoring post approval
Uniformity of Dose (Fill Volume/deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place, continue stability monitoring post approval
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipments	L		Acceptable	Similar to the reference drug.

	• Site		(b) (4)		
pH- (Low)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place during stability testing. Continue stability monitoring post approval
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M		Acceptable	Controls are in place. Continue stability monitoring post approval
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place

APPEARS THIS WAY ON ORIGINAL

Sherita McLamore

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BIOPHARMACEUTICS

Application No: NDA 212209

Drug Product Name / Strength: Bendamustine HCl for injection, 100 mg/4 mL (25 mg/mL)

Route of Administration: Intravenous

Applicant Name: Slayback Pharma LLC

List Submissions being reviewed: Original dated August 31, 2018

Primary Reviewer: Zhuojun Zhao, Ph.D.

Secondary Reviewer: Banu S. Zolnik, Ph.D.

Background:

Slayback Pharma LLC 's proposed Bendamustine HCl for injection, 100 mg/4 mL (25 mg/mL) is a (b) (4) concentrate with the same strengths and dosage form as the listed drug (LD) product, BELRAPZO™ (Eagle Pharmaceuticals Inc.'s NDA 205580, approved in May 2018).

Review Summary:

This Biopharmaceutics Review evaluated the overall data supporting the bridge between the proposed drug product and the LD.

The Slayback's proposed Bendamustine HCl is intended for the same indications and has the same active ingredient, dosage form, dose, (b) (4) and route of administration as the LD, but contains different excipients. Due to the difference in the excipients, a biowaiver under 21 CFR 320.22 is not feasible. However, a bridge between the proposed drug product and the listed drug product can be established based on 21 CFR 320.24 (b)(6), justifying the reliance of the proposed drug product on the listed drug product.

The proposed drug product contains dehydrated alcohol, which are not present in the listed drug, BELRAPZO™ for injection. The dehydrated alcohol level in Slayback's Bendamustine HCl for injection is found acceptable based on the previously approved amount for i.v. injection products. The presence of dehydrated alcohol as well as the absence of propylene glycol in the proposed drug product is not expected to impact the disposition kinetics of Bendamustine HCl in humans; therefore, similar Bendamustine plasma concentrations are expected after administration of the proposed drug product or the LD.

To support the bridge, the Applicant has provided comparative physicochemical data, which showed similar pH data between the proposed and the LD products.

Recommendation:

The Applicant has provided sufficient information to support the bridge between the proposed drug product and the listed drug, BELRAPZO™ for injection under *21CFR 320.24 (b) (6)*. From the Biopharmaceutics perspective, NDA 212209 for Bendamustine HCl for injection, 100 mg/4 mL (25 mg/mL) is recommended for **APPROVAL**

BIOPHARMACEUTICS ASSESSMENT

➢ DRUG SUBSTANCE

The drug substance is Bendamustine HCl, same as the API in the listed drug BELRAPZO™ for injection (concentrate).

The Applicant provided the solubility of the API in buffers and solvents at 26 C and 37°C in Table 1:

Table 1 Solubility of Bendamustine HCl

S. No	Buffer solution	Solvent Media	Solubility Specification as per USP	Descriptive term
1.	Water	---	0.1 g of substance is soluble in 100 ml of solvent	Slightly soluble
2.	1.2 Buffer	3.73 g of KCl are dissolved in a mixture of 425 ml of 0.2M HCl and 575 ml of H_2O.	0.1 g of substance is soluble in 100 ml of solvent	Slightly soluble
3.	4.5 Buffer	2.99 g of sodium acetate trihydrate are dissolved in a mixture of 14 ml of 2N acetic acid and 986 ml of H_2O.	0.1 g of substance is soluble in 100 ml of solvent	Slightly soluble
4.	6.8 Buffer	6.81 g of KH_2PO4 are dissolved in a mixture of 112 ml of 0.2M NaOH and 888 ml of H_2O.	0.01 g of substance is soluble in 100 ml of solvent	Very Slightly soluble

S. No	Name of the solvent	Solubility specifications as per USP	Descriptive term
1.	Methanol	0.1g of substance is soluble in 100 ml of solvent	Slightly soluble
2.	Acetonitrile	0.01 g of substance is soluble in 100 ml of solvent	Very Slightly soluble
3.	N,N-Dimethylformamide	3.33g of substance is soluble in 100 ml of solvent	soluble
4	N,N-Dimethylsulfoxide	3.33g of substance is soluble in 100 ml of solvent	soluble

➢ DRUG PRODUCT

The composition of the proposed Bendamustine HCl injection is shown in Table 2:

Table 2 Amount of active and inactive ingredients in the proposed Bendamustine HCl Injection

Ingredients	Reference to Quality Standards	Pharmaceutical Function	100mg/4mL (25mg/mL)	
			Quantity per mL	Quantity per Vial
Bendamustine Hydrochloride#	In-house	Active pharmaceutical ingredient	25 mg	100 mg
Monothioglycerol	USP-NF	(b) (4)	5 mg	20 mg
Dehydrated Alcohol@@	USP		39.45 mg @	157.8 mg@
Sodium Hydroxide*	USP-NF	(b) (4)	q.s	q.s
Polyethylene glycol 400	USP-NF	(b) (4)	q.s to 1.0 mL	q.s to 4.0 mL
				(b) (4)

q.s quality sufficient

(b) (4)

(b) (4)

(b) (4)

- **BRIDGE BETWEEN THE PROPOSED DRUG PRODUCT AND THE LISTED DRUG PRODUCT.**

The following information is evaluated in support of the bridging between the proposed drug product and the listed drug product:

1) Formulation before and after dilution, dosage form administered volume
2) Comparative physicochemical data

1) <u>Formulation before and after reconstitution and dilution, dosage form administered volume</u>

The proposed Bendamustine Hydrochloride injection is presented as a 100 mg/4mL (25 mg/mL) multidose vial. The quantitative composition before dilution between the proposed Bendamustine HCl injection and the LD products (NDA 205580) are shown in Table 3.

Table 3. Qualitative and Quantitative Composition Before Dilution

Ingredients	Function	Qualitative and Quantitative Composition	
		Slayback's drug product (Quantity/vial)	Bendamustine Hydrochloride Injection NDA NoN205580 (Quantity/vial)
Bendamustine Hydrochloride	Active pharmaceutical ingredient	100 mg#	100 mg
Monothioglycerol	(b) (4)	20 mg	20 mg
Propylene Glycol		---	0.4 mL
Dehydrated Alcohol@@		157.8 mg@	---
Sodium Hydroxide	(b) (4)	q. s*	q. s
Polyethylene glycol 400	(b) (4)	q.s to 4.0 mL	q.s to 4.0 mL
			(b) (4)

q.s quality sufficient

(b) (4)

(b) (4)

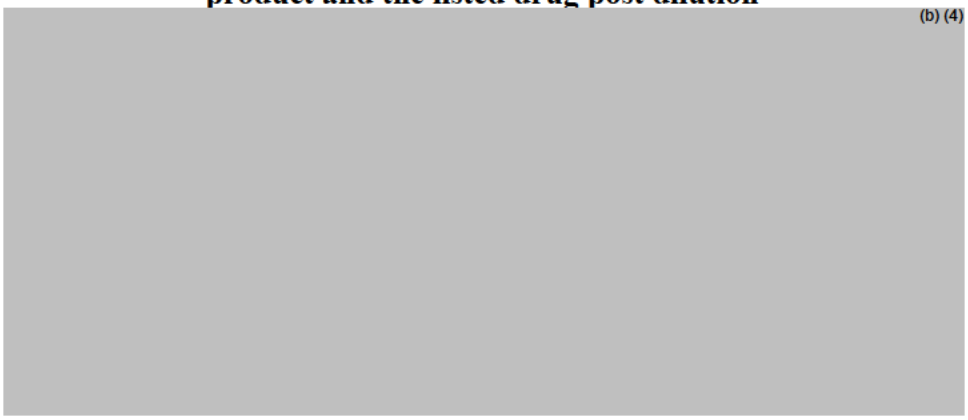
(b) (4)

Per BELRAPZOL™ Label, the drug product is for intravenous infusion only[1]. The required volume needs to be withdrawn from the vial and immediately transferred to a (b) (4) mL infusion bag of containing one of the following diluents: 0.9% Sodium Chloride Injection, USP, 2.5% Dextrose/0.45% Sodium Chloride Injection USP. The resulting final concentration of Bendamustine hydrochloride in the infusion bag should be within (b) (4) mg/mL- (b) (4) mg/mL. The Applicant provided the qualitative and quantitative composition of Slayback's proposed Bendamustine HCl for injection and LD product post dilution in Table 4.

[1] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9759a4ae-82ca-40cf-9c02-e1cadb21cbdc

Table 4. Comparative Table of active and inactive ingredients in the proposed drug product and the listed drug post dilution

(b) (4)



Reviewer's Assessment:

As shown in Table 3 and Table 4, the qualitative and quantitative composition of Slayback's Bendamustine HCl for injection and LD product (b) (4) (b) (4) with the exception of the use of Dehydrated Alcohol in Slayback's product in place of Propylene Glycol.

a) **The Impact Absence of Propylene Glycol**

Based on the LD product label[1], the maximum dose of propylene glycol form LD product is 8.64 mL (Table 5).

Table 5. Comparison of Primary Solvents

Attribute	Listed Drug	Slayback proposed formulation
Excipient	Propylene glycol	Dehydrated alcohol
Maximum daily dose of Bendamustine Hydrochloride Injection	216 mg (120 mg/m^2)	216 mg (120 mg/m^2)
Maximum amount of drug product to be infused per day to deliver 216mg of Bendamustine	8.64 mL	8.64 mL
Amount of excipient in the formulation	0.10 mL/mL	0.05 mL/mL
Amount of excipient per maximum dose to be infused for an adult patient of 1.8m^2	0.864 mL*	0.432 mL**

(b) (4)

Reviewer's Assessment:

The absence of propylene glycol in the proposed product is not likely to affect the in vivo disposition of Bendamustine HCl[2].

b) **The Impact Presence of Alcohol**

Dehydrate Alcohol is present in Slayback's proposed Bendamustine HCl for injection, which is not included in the LD (shown in Table 3).

The Applicant provided maximum dose of dehydrated alcohol from Slayback's Bendamustine HCl for injection for the highest proposed dose (120 mg/m^2) as 0.432 mL (i.e. 340.8 mg) Dehydrate Alcohol (Table 5**Error! Reference source not found.**).

[2] Biopharmaceutics Review on NDA 205580 By Dr. Elsbeth Chikhale.

(b) (4)

[redacted]

Reviewer's Assessment:
The pharmacokinetic parameters of Bendamustine in humans with Slayback's formulation which contained (b) (4) as an excipient is not expected to be different from that from that of the Listed drug.

Although the level of (b) (4) included in the proposed formulation of Bendamustine HCl injection was found acceptable, the clinical and nonclinical reviewers would decide if safety information related to (b) (4) content should be included in Warnings and Precaution.

2) **Comparative Physicochemical Data**
The Applicant provided chemical characterization data of the proposed Bendamustine HCl and LD product (Table 7).

(b) (4)

[redacted]

APPEARS THIS WAY ON ORIGINAL

Table 7. Comparison of Chemical Characterization Data[5]

Product details		Submission batches of Slayback proposed Bendamustine Hydrochloride Injection 100mg/4mL (25mg/mL)									BENDEKA batches					
Batch number		7G04376V			7G0437V			7G04378V			APB060			F118C023		
Batch manufacturing date		08/2017			08/2017			08/2017			NA			NA		
Expiry date		NA			NA			NA			30 SEP 2019			28 FEB 2020		
											Date of analysis: August 2018					
Test parameter	Acceptance criteria	T-1	T-2	T-3	T-1	T-2	T-3	T-1	T-2	T-3	T-1	T-2	T-3	T-1	T-2	T-3
Description	(b) (4)	Clear colourless solution			Clear colourless solution			Clear colourless solution			Clear colourless solution			Clear colourless solution		
pH (10% v/v in purified water) (USP <791>)																(b) (4)
Assay of Bendamustine (By HPLC)																
Related substances (by HPLC)																(b) (4)

Reviewer's Assessment:

Slayback's proposed drug product Bendamustine Hydrochloride Injection 100 mg/4mL (25 mg/mL) and Listed Drug product are to be infused only after dilution with isosmotic diluents (0.9% Sodium chloride USP Injection or 0.45% Sodium chloride and 2.5% Dextrose Injection USP) and not for direct injection[1]. As the concentration of the Bendamustine after dilution with above mentioned diluents ((b) (4) mg/mL to (b) (4) mg/mL) is very low, the osmolality of the diluents would not be altered. Hence, it is acceptable that the Applicant did not test osmolality.

The physicochemical property of the proposed drug product and the LD are similar based on pH data in Table 7.

[5] It is noted that the Applicant marked the sample as BENDEKA (Eagle's NDA 208194), which has the same composition as BELRAPZO™ (Eagle's NDA 205580), per Memorandum Review of revised label and labeling NDA 205580.

Zhuojun Zhao

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NDA 212209 Bendamustine HCl Injection, 100 mg/4mL Risk Assessment

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN
Sterility	• Formulation • Container closure • Process parameters • Scale/equipments • Site	• Non-sterile unit(s)	4	5	5	100
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	• Excessive Endotoxin Levels	2	4	4	32
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	• Impurity formation due to excipient reactions or unspecified reactions (b) (4)	4	2	1	8
Uniformity of Dose (Fill Volume/deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipments • Site	• Insufficient dose	2	2	2	8
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	• Irritation • Edema	2	5	2	20

NDA 212209 Bendamustine HCl Injection, 100 mg/4mL Risk Assessment

PRODUCT PROPERTY/IMPACT OF CHANGE/CQAS	CHANGES & VARIATIONS	FAILURE MODE	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN
pH- (b) (4)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	• Irritation	2	2	1	4
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	• Irritation • Embolism	3	5	3	45
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	• Generation of impurities	2	4	3	24

Sherita McLamore

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