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APPLICATION NUMBER:

212209Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 01, 2022
From	Tefsit Bekele, Ph.D.
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA	212209
Type of Application	505(b)(2)
Applicant	Slayback Pharma, LLC
Date of Receipt	October 07, 2022
PDUFA Goal Date	December 07, 2023
Proposed Proprietary/Established Names	VIVIMUSTA (bendamustine hydrochloride injection)
Dosage forms / Strength	Injection/ 100 mg/4 mL
Route of Administration	Intravenous
Proposed Indication(s)	•Indicated for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established. •Indicated for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.
Recommended:	**APPROVAL**

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Clinical (Candis Morrison, M.D.)
- Pharmacology/Toxicology (Michael Manning, Ph.D.)
- Drug Product (Tefsit Bekele, Ph.D.)
- Drug Substance (Paresma Patel, Ph.D.)
- Microbiology (Bryan Riley, Ph.D.)
- Manufacturing Process and Facilities (Djelila Mezaache, Ph.D.)
- Associate Director for Labeling (Elizabeth Everhart, MSN, RN, ACNP)

1. Introduction

NDA 212209 was submitted for VIVIMUSTA (bendamustine hydrochloride injection), 100 mg/4 mL (25 mg/mL) in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act by Slayback Pharma LLC. This application presents a new formulation of bendamustine hydrochloride. Bendamustine hydrochloride is a small molecule, antitumor, alkylating agent that exhibits unique activity. Bendamustine was originally approved under the brand name Treanda (discontinued in 2016) for the treatment of 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. Most recently, Belrapzo (bendamustine

hydrochloride) Injection 100 mg/4 mL, manufactured by Eagle Pharmaceuticals was approved under NDA 205580 (May 2018). Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL is the listed drug (LD) for this application.

Belrapzo (bendamustine hydrochloride injection) 100 mg/4 mL, is presented as a multiple-dose, ready-to-dilute, non-aqueous solution containing the active (bendamustine hydrochloride), monothioglycerol and propylene glycol in polyethylene glycol 400. The proposed drug product, bendamustine hydrochloride injection,100 mg/4 mL (25 mg/mL) is supplied as a clear colorless to (b) (4) yellow, sterile solution in a multiple-dose vial. The non-aqueous formulation includes the active, monothioglycerol, dehydrated alcohol and sodium hydroxide in polyethylene glycol 400. The selection of excipients was based on the excipients listed in PI of the LD with the exception of the presence of dehydrated alcohol which replaced propylene glycol.

The proposed drug product and the LD are both (b) (4) and sterile. Like the listed drug, the proposed drug product must be diluted prior to use. Dilution was designed to be accomplished with either 0.9% Sodium Chloride Injection USP or with a 2.5% Dextrose/0.45% Sodium Chloride Injection admixture prior to intravenous administration. The recommended dosing regimen for the LD is 100 mg/m^2 infused intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle for up to 6 cycles for CLL and 120 mg/m^2 infused intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle for up to 8 cycles for NHL. The recommended dosing regimen for Slayback formulation is the same except the infusion takes place over 20 minutes for both CLL and NHL indication.

The proposed drug product has the same indications, dosage form, route of administration, and (b) (4) as Eagle's formulation but differs in infusion time and in the excipient profile (i.e. dehydrated alcohol used in the Slayback formulation replaced propylene glycol in the LD). For that reason, NDA 212209 contained no clinical data, but instead relied upon information in the public domain, and on the Agency's determination of safety and efficacy for the listed drug, Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, which was previously approved for marketing under NDA 205580.

2. Background

NDA 212209 has been issued two Complete Responses as a result of issues related to product quality and three Tentative Approvals since it was originally submitted in 2018.

1st Review Cycle: August 31, 2018

Original submission (PDUFA Date: June 30, 2019): The application was issued a Complete Response (CR) on June 17, 2019 for matters related to product quality. Specifically, the drug substance manufacturing site ((b) (4) had an unacceptable compliance history and the field investigator observed objectionable conditions at the facility. As a result, the OPF recommended WITHHOLD and the application was issued a Complete Response (CR).

2nd Review Cycle: July 1, 2019

This submission represented the Applicant's response to the Agency's June 17, 2019 Complete Response (PDUFA Date: 1-Jan-20). In this submission, the Applicant responded to the facility issue; however, the status of (b) (4) remained unchanged from the 1st review cycle and this submission was issued a CR in July of 2019 as a result of a WITHHOLD recommendation from OPF.

3rd Review Cycle: February 14, 2020

This submission represented the Applicant's response to the Agency's July 1, 2019 Complete Response Letter (PDUFA Date: August 14, 2020). In this submission, the Applicant addressed the outstanding facility issue and received a Tentative Approval (TA) as NDA 212209 was not eligible for full approval due to the orphan exclusivity granted to Eagle Pharmaceuticals Incorporation's product, Bendeka and may be granted full approval once the exclusivity period has expired.

4th Review Cycle: June 16, 2021

This submission provided for the reinstatement of the 2.5% dextrose/0.45% diluent at a higher concentration ((b) (4)–1.36 mg/mL as opposed to (b) (4) mg/mL) and a shorter infusion time (see table below). NDA 212209 was tentatively approved on March 16, 2022. At the conclusion of the first review cycle, the agency accepted the proposed in-use time (i.e. 24 h under refrigeration and 3 h at room temperature) for dilution with 0.9% NaCl 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. At that time, dilution with 2.5% dextrose/0.45% Sodium Chloride Injection, USP infusion solution was not adequately supported, and the 2.5% dextrose/0.45% Sodium Chloride admixture was removed from all labeling.

5th Review Cycle: June 27, 2022

This submission contained no new data but included a request for final approval minor changes to reflect updates to the USP general chapters and/or monographs, updated drug product stability and other non-substantive changes. There are no other changes proposed as a part of this resubmission. The request for final approval was premature as the exclusivity period remained in effect until December 7, 2022. This submission was tentatively approved on August 26, 2022.

6th Review Cycle: October 07, 2022

This resubmission contains no new data but instead only includes a request for full approval.

3. Product Quality

This resubmission contains no CMC information but instead only includes a request for full approval. All facilities associated with this application remain adequate and are acceptable to support approval of this NDA. The previously accepted expiration dating period of **24-months** for the drug product when stored at stored between 2–8 °C remains unchanged.

Overall Product Quality Recommendation: The Office of Pharmaceutical Quality (drug substance, drug product, drug process, microbiology, biopharmaceutics, and facilities) recommends **APPROVAL** of NDA 212209.

6. Clinical Pharmacology

N/A

7. Non-Clinical Pharmacology/Toxicology

The non-clinical pharmacology/toxicology team confirmed that no new data was included in this submission. Accordingly, NDA 212209 remains approvable from a pharmacology/toxicology perspective.

8. Clinical/Statistical-Efficacy

The clinical team confirmed that no new data was included in this submission. Accordingly, NDA 212209 remains approvable from a clinical perspective.

9. Safety

N/A

10. Advisory Committee Meeting **N/A**

11. Pediatrics N/A

12. Other Relevant Regulatory Issues N/A

13. Labeling

Labeling negotiations were completed during the previous review cycle. A joint ADL and clinical memo described additional minor recommendations on the content and format of the United States Prescribing Information (USPI) and acknowledged the addition of the proprietary name, Vivimusta.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product relies on the safety and efficacy of the Listed Drug, Belrapzo. The Slayback product is nearly identical to the LD, as the active product has the same active ingredient, is the same dosage form and has the same routes of administration and concentration of bendamustine prior to (b) (4) dilution as the Listed Drug. There were no new clinical or nonclinical studies conducted for this 505(b)(2) application.

NDA 212209 is eligible for full approval once orphan exclusivity granted to Eagle Pharmaceuticals Incorporation's product, Belrapzo expires on December 07, 2022. Accordingly, the CDTL recommends full **APPROVAL** of NDA 212209 for VIVIMUSTA (bendamustine hydrochloride injection), 100 mg/4 mL (25 mg/mL) for the treatment of patients with chronic lymphocytic leukemia (efficacy relative to first line therapies other than chlorambucil has not been established) and for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

- **Risk Benefit Assessment**

Please refer to NDA 205580.

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/s/

TEFSIT BEKELE
12/05/2022 08:56:19 AM

Cross-Discipline Team Leader Review

Date	17-Aug-2022
From	Sherita D. McLamore, Ph.D.
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA	212209
Type of Application	505(b)(2)
Applicant	Slayback Pharma, LLC
Date of Receipt	14-Feb-2020
PDUFA Goal Date	14-aUG-2020
Proposed Proprietary/Established Names	Bendamustine HCl
Dosage forms / Strength	Injection/ 100 mg/4 mL
Route of Administration	Intravenous
Proposed Indication(s)	•Indicated for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established. •Indicated for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.
Recommended:	**TENATIVE APPROVAL**

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Clinical (Candis Morrison, M.D.)
- Pharmacology/Toxicology (Michael Manning, Ph.D.)
- Drug Product (Tefsit Bekele, Ph.D.)
- Drug Substance (Kabir Shahjahan, Ph.D.)
- Microbiology (Bryan Riley, Ph.D.)
- Manufacturing Process and Facilities (Djelila Mezaache, Ph.D.)
- Associate Director for Labeling (Elizabeth Everhart, MSN, RN, ACNP)

1. Introduction

NDA 212209 was submitted for Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL) in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act by Slayback Pharma LLC. This application presents a new formulation of bendamustine hydrochloride. Bendamustine hydrochloride is a small molecule, antitumor, alkylating agent that exhibits unique activity. Bendamustine was originally approved under the brand name Treanda (discontinued in 2016) for the treatment of 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. Most recently, Belrapzo (bendamustine hydrochloride) Injection 100

mg/4 mL, manufactured by Eagle Pharmaceuticals was approved under NDA 205580 (May 2018). Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL is the listed drug (LD) for this application.

Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, is presented as a multiple-dose, ready-to-dilute, non-aqueous solution containing the active (bendamustine hydrochloride), monothioglycerol and propylene glycol in polyethylene glycol 400. The proposed 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 non-aqueous formulation includes the active, monothioglycerol, dehydrated alcohol and sodium hydroxide in polyethylene glycol 400. The selection of excipients was based on the excipients listed in PI of the LD with the exception of the presence of dehydrated alcohol which replaced propylene glycol.

The proposed drug product and the LD are both (b) (4) and sterile. Like the listed drug, the proposed drug product must be diluted prior to use. Dilution was designed to be accomplished with either 0.9% Sodium Chloride Injection USP or with a 2.5% Dextrose/0.45% Sodium Chloride Injection admixture prior to intravenous administration. The recommended dosing regimen for the (b) (4) Slayback formulation 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 for CLL and 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 for NHL.

The proposed drug product has the same indications, dosage form, route of administration, and (b) (4) as Eagle's formulation but differs in the excipient profile (i.e. dehydrated alcohol used in the Slayback formulation replaced propylene glycol in the LD). For that reason, NDA 212209 contained no clinical data, but instead relied upon information in the public domain, and on the Agency's determination of safety and efficacy for the listed drug, Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, which was previously approved for marketing under NDA 205580.

2. Background

Since NDA 212209 was originally submitted in 2018 it has been issued two Complete Responses as a result of issues related to product quality and two Tentative Approvals.

1st Review Cycle: August 31, 2018

NDA 212209 was originally submitted to the Agency in August 2018 (PDUFA Date: 30-Jun-19). This submission was issued a Complete Response on June 17, 2019 for matters related to product quality. Specifically, the drug substance manufacturing site ((b) (4) had an unacceptable compliance history and the field investigator observed objectionable conditions at the facility. As a result the OPF recommended WITHHOLD and the application was issued a Complete Response (CR).

2nd Review Cycle: July 1, 2019

This submission represents the Applicant's response to the Agency's June 16, 2019 Complete Response (PDUFA Date: 1-Jan-20). In this submission, the Applicant responded to the facility issue; however, the status of (b) (4) remained unchanged from the 1st review cycle and this submission was issued a Complete Response in July of 2019 as a result of a WITHHOLD recommendation from OPF.

3rd Review Cycle: February 14, 2020

This submission represents the Applicant's response to the Agency's July 1, 2019 Complete Response Letter (PDUFA Date: August 14, 2020). In this submission, the Applicant addressed the outstanding facility issue and received a Tentative Approval (TA) as NDA 212209 was not eligible for full approval due to the orphan exclusivity granted to Eagle Pharmaceuticals Incorporation's product, Bendeka and may be granted full approval once the exclusivity period has expired.

4th Review Cycle: June 16, 2021

The current submission provides for the reinstatement of the 2.5% dextrose/0.45% diluent at a higher concentration ((b) (4)–1.36 mg/mL as opposed to (b) (4) mg/mL) and a shorter infusion time (see table below). Of note in the first review cycle the agency accepted the proposed in-use time (i.e. 24 h under refrigeration and 3 h at room temperature) for dilution with 0.9% NaCl 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. At that time, dilution with 2.5% dextrose/0.45% Sodium Chloride Injection USP infusion solution was not adequately supported, and the 2.5% dextrose/0.45% Sodium Chloride admixture was removed from all labeling.

This current amendment contains no new data but includes a request for final approval. Other changes to the NDA include minor changes to reflect changes in updates of USP General Chapters and/or Monographs, updated drug product stability data and other non-substantive changes. **There are no other changes proposed as a part of this amendment**. The request for final approval is premature as the exclusivity period remains in effect until December 7, 2022.

3. Product Quality

There was nominal new CMC information included in this submission. All facilities associated with the application remain adequate and are acceptable to support approval of this NDA. The previously accepted expiration dating period of **24-months** for the drug product when stored at stored between 2–8 °C remains unchanged.

Overall Product Quality Recommendation: The Office of Pharmaceutical Quality (drug substance, drug product, drug process, microbiology, biopharmaceutics and facilities) recommends **APPROVAL** of NDA 212209.

6. Clinical Pharmacology

N/A

7. Non-Clinical Pharmacology/Toxicology

The non-clinical pharmacology/toxicology team confirmed that no new data was included in this submission. Accordingly, NDA 212209 remains approvable from a pharmacology/toxicology perspective.

8. Clinical/Statistical-Efficacy

The clinical team confirmed that no new data was included in this submission. Accordingly, NDA 212209 remains approvable from a clinical perspective.

9. Safety

N/A

10. Advisory Committee Meeting **N/A**

11. Pediatrics N/A

12. Other Relevant Regulatory Issues N/A

13. Labeling

Labeling negotiations were completed during the previous review cycle. ADL included a memo regarding the revision date.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product relies on the safety and efficacy of the Listed Drug, the Slayback product is nearly identical to the LD, as the active product has the same active ingredient, is the same dosage form and has the same routes of administration and concentration of bendamustine prior to (b) (4) dilution as the Listed Drug. There were no new clinical or nonclinical studies conducted for this 505(b)(2) application.

The CDTL recommends **TENATIVE APPROVAL** of NDA 212209 Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL) for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established and for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. NDA 212209 is not eligible for full approval due to the orphan exclusivity granted to Eagle Pharmaceuticals Incorporation's product, Bendeka and may be granted full approval once the exclusivity period has expired.

- **Risk Benefit Assessment**

Please refer to NDA 205580.

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/s/

SHERITA D MCLAMORE
10/18/2022 12:24:21 PM

Cross-Discipline Team Leader Review

Date	1-March-2022
From	Sherita D. McLamore, Ph.D.
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA	212209
Type of Application	505(b)(2)
Applicant	Slayback Pharma, LLC
Date of Receipt	06/16/2021
PDUFA Goal Date	03/16/2022
Proposed Proprietary/Established Names	Bendamustine HCl
Dosage forms / Strength	Injection/ 100 mg/4 mL
Route of Administration	Intravenous
Proposed Indication(s)	•Indicated for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established. •Indicated for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.
Recommended:	**TENATIVE APPROVAL**

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Clinical (Candis Morrison, M.D.)
- Pharmacology/Toxicology (Michael Manning, Ph.D.)
- Drug Product (Tefsit Bekele, Ph.D.)
- Microbiology (Erika Pfeiler, Ph.D.)
- Manufacturing Process and Facilities (Steven Hertz, Ph.D.)
- Associate Director for Labeling (Elizabeth Everhart, MSN, RN, ACNP))

1. Introduction

NDA 212209 was submitted for Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL) in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act by Slayback Pharma LLC. This application presents a new formulation of bendamustine hydrochloride. Bendamustine hydrochloride is a small molecule, antitumor, alkylating agent that exhibits unique activity. Bendamustine was originally approved under the brand name Treanda (discontinued in 2016) for the treatment of 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. Most recently, Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, manufactured by Eagle Pharmaceuticals was approved under NDA 205580 (May 2018).

Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL is the listed drug (LD) for this application.

Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, is presented as a multiple-dose, ready-to-dilute, non-aqueous solution containing the active (bendamustine hydrochloride), monothioglycerol and propylene glycol in polyethylene glycol 400. The proposed 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 non-aqueous formulation includes the active, monothioglycerol, dehydrated alcohol and sodium hydroxide in polyethylene glycol 400. The selection of excipients was based on the excipients listed in PI of the LD with the exception of the presence of dehydrated alcohol which replaced propylene glycol.

The proposed drug product and the LD are both (b) (4) and sterile. Like the listed drug, the proposed drug product must be diluted prior to use. Dilution was designed to be accomplished with either 0.9% Sodium Chloride Injection USP or with a 2.5% Dextrose/0.45% Sodium Chloride Injection admixture prior to intravenous administration. The recommended dosing regimen for the (b) (4) the Slayback formulation 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 for CLL and 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 for NHL.

The proposed drug product has the same indications, dosage form, route of administration, and (b) (4) as Eagle's formulation but differs in the excipient profile (i.e. dehydrated alcohol used in the Slayback formulation replaced propylene glycol in the LD). For that reason, NDA 212209 contained no clinical data, but instead relied upon information in the public domain, and on the Agency's determination of safety and efficacy for the listed drug, Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, which was previously approved for marketing under NDA 205580.

2. Background

Since NDA 212209 was submitted in 2018 it has been issued two Complete Responses (06/17/2019 and 9/16/2020) due to issues related to product quality and one tentative approval (07/02/2020).

1st Review Cycle: August 31, 2018

NDA 212209 was originally submitted to the Agency in August 2018 (PDUFA Date: 30-Jun-19). This submission was issued a Complete Response on June 17, 2019 for matters related to product quality. Specifically, the drug substance manufacturing site ((b) (4) had an unacceptable compliance history and the field investigator observed objectionable conditions at the facility. Consequently, OPF recommended WITHHOLD and the application was issued a Complete Response (CR).

2nd Review Cycle: July 1, 2019

This submission represents the Applicant's response to the Agency's June 16, 2019 Complete Response (PDUFA Date: January 1, 2020). In this submission, the Applicant responded to the facility issue; however, the status of (b) (4) remained unchanged from the 1st review cycle and this submission was issued a Complete Response in July of 2019 as a result of a WITHHOLD recommendation from OPF.

3rd Review Cycle: February 14, 2020

This submission represents the Applicant's response to the Agency's July 1, 2019 Complete Response (PDUFA Date: August 14, 2020). In this submission, the Applicant addressed the outstanding facility issue.

4th Review Cycle: June 16, 2021

The current submission provides for the reinstatement of the 2.5% dextrose/0.45% diluent at a higher concentration ((b) (4)–1.36 mg/mL as opposed to (b) (4) mg/mL) and a shorter infusion time (see table below). Of note in the first review cycle the agency accepted the proposed in-use time (i.e. 24 h under refrigeration and 3 h at room temperature) for dilution with 0.9% NaCl 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. At that time, dilution with 2.5% dextrose/0.45% Sodium Chloride Injection USP infusion solution was not adequately supported, and the 2.5% dextrose/0.45% Sodium Chloride admixture was removed from all labeling.

	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	

3. Product Quality

The proposed changes in this 4th review cycle are included the reinstatement of the 2.5% dextrose/ 0.45% diluent and a revised concentration range of the final diluted drug product. The final diluted drug product concentration was tentatively approved from (b) (4) mg/mL. The current submission provides for a change in the final diluted drug product from **0.1**–1.36 mg/mL. Of note, the 2021 original resubmission included final diluted drug product concentrations that ranged from (b) (4) to 1.36 mg/mL. During the labeling review, the following comment was communicated to the Applicant:

> "The concentration range of (b) (4) mg/mL to 1.36 mg/mL is not consistent with the expected range as outlined in Table 1. For example, the final concentration for an individual with a BSA of 1 m^2 being administered a 25 mg/m^2 dose due to dose reductions would be 0.1 mg/mL in a 250 mL infusion bag. Revise Table 1 to be consistent with the concentration range of (b) (4) mg/mL to 1.36 mg/mL or provide data supporting the concentration range as proposed in Table 1, with a lower range of 0.1 mg/mL"

Realizing the limitations associated with the product as developed and in response to the agency's labeling comments, the Applicant expressed the following:

> "…We believe that adding the statement recommended in the Labelling comments dated February 18, 2022 puts Slayback's product at a disadvantage compared to the listed product w.r.t the flexibility of catering to patients having a lower body surface area and thus a reduced dose. Thus, Slayback would like to provide the diluent compatibility data to support

> the lower concentration of Bendamustine hydrochloride after dilution i.e., 0.1 mg/mL. The dilution admixture compatibility for the proposed drug product and the RLD were studied at 0.05 mg/mL concentration since this concentration is the lowest possible concentration for RLD Belarapzo™..."

The applicant provided new data at 0.05 mg/mL to support the compatibility of the 0.1 mg/mL as the 0.1 mg/mL is bracketed by the 0.05 mg/mL and the previously submitted (b) (4) mg/mL data. All data was evaluated and deemed acceptable to support the proposed label claims.

At the time of review, all facilities associated with the application are adequate and are acceptable to support approval of this NDA.

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 agency accepts the proposed in-use time (i.e. 24h under refrigeration and 3h at room temperature) for the 0.9% Sodium Chloride infusate and for the 2.5% dextrose/0.45% Sodium Chloride infusate as well as 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.

Overall Product Quality Recommendation: The Office of Pharmaceutical Quality (drug substance, drug product, drug process, microbiology, biopharmaceutics and facilities) recommends **APPROVAL** of NDA 212209.

6. Clinical Pharmacology

There was no clinical pharmacology information included in this resubmission.

7. Non-Clinical Pharmacology/Toxicology

The non-clinical pharmacology/toxicology team confirms that there was no new clinical pharmacology information included in this resubmission and recommends granting approval of NDA 212209.

8. Clinical/Statistical-Efficacy

There was no clinical data include in this resubmission and efficacy was based on the Prescribing Information for Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, the relied-upon listed drug. The clinical team recommends granting tentative approval of NDA 212209.

9. Safety

There was no new safety information included in this resubmission. Safety was based on the Prescribing Information for the Listed Drug, Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL.

10. Advisory Committee Meeting **N/A**

11. Pediatrics N/A

12. Other Relevant Regulatory Issues N/A

13. Labeling

Labeling negotiations are ongoing at the time of this review

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product relies on the safety and efficacy of the Listed Drug, the Slayback product is nearly identical to the LD, as the active product has the same active ingredient, is the same dosage form and has the same routes of administration and concentration of bendamustine prior to (b) (4) dilution as the Listed Drug. There were no new clinical or nonclinical studies conducted for this 505(b)(2) application.

The CDTL recommends **TENATIVE APPROVAL** of NDA 212209 Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL) for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established and for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. NDA 212209 is not eligible for full approval due to the orphan exclusivity granted to Eagle Pharmaceuticals Incorporation's product, Belrapzo and may be granted full approval once the exclusivity period has expired.

- **Risk Benefit Assessment**

Please refer to NDA 205580.

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/s/

SHERITA D MCLAMORE
03/01/2022 12:11:47 PM

Cross-Discipline Team Leader Review

Date	2-Jul-2020
From	Sherita D. McLamore, Ph.D.
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA	212209
Type of Application	505(b)(2)
Applicant	Slayback Pharma, LLC
Date of Receipt	14-Feb-2020
PDUFA Goal Date	14-aUG-2020
Proposed Proprietary/Established Names	Bendamustine HCl
Dosage forms / Strength	Injection/ 100 mg/4 mL
Route of Administration	Intravenous
Proposed Indication(s)	•Indicated for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established. •Indicated for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.
Recommended:	**TENATIVE APPROVAL**

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Clinical (Candis Morrison, M.D.)
- Pharmacology/Toxicology (Michael Manning, Ph.D.)
- DEMPA (Nicole Garrison, Pharm. D.)
- Drug Product (Tefsit Bekele, Ph.D.)
- Drug Substance (Mohd Kabir, Ph.D.)
- Microbiology (Christine Craig, Ph.D.)
- Manufacturing Process and Facilities (Djelila Mezaache, Ph.D.)
- Biopharmaceutics (Joan Zhao, Ph.D.)
- OPDP Consult (Trung-Hieu Tran)

1. Introduction

NDA 212209 was submitted for Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL) in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act by Slayback Pharma LLC. This application presents a new formulation of bendamustine hydrochloride. Bendamustine hydrochloride is a small molecule, antitumor, alkylating agent that exhibits unique activity. Bendamustine was originally approved under the brand name Treanda (discontinued in 2016) for the treatment of 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. Most recently, Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, manufactured by Eagle Pharmaceuticals was approved under NDA 205580 (May 2018). Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL is the listed drug (LD) for this application.

Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, is presented as a multiple-dose, ready-to-dilute, non-aqueous solution containing the active (bendamustine hydrochloride), monothioglycerol and propylene glycol in polyethylene glycol 400. The proposed 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 non-aqueous formulation includes the active, monothioglycerol, dehydrated alcohol and sodium hydroxide in polyethylene glycol 400. The selection of excipients was based on the excipients listed in PI of the LD with the exception of the presence of dehydrated alcohol which replaced propylene glycol.

The proposed drug product and the LD are both (b) (4) and sterile. Like the listed drug, the proposed drug product must be diluted prior to use. Dilution was designed to be accomplished with either 0.9% Sodium Chloride Injection USP or with a 2.5% Dextrose/0.45% Sodium Chloride Injection admixture prior to intravenous administration. The recommended dosing regimen for the (b) (4) the Slayback formulation 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 for CLL and 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 for NHL.

The proposed drug product has the same indications, dosage form, route of administration, and (b) (4) as Eagle's formulation but differs in the excipient profile (i.e. dehydrated alcohol used in the Slayback formulation replaced propylene glycol in the LD). For that reason, NDA 212209 contained no clinical data, but instead relied upon information in the public domain, and on the Agency's determination of safety and efficacy for the listed drug, Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, which was previously approved for marketing under NDA 205580.

2. Background

NDA 212209 has been issued two Complete Responses (CRs) due to issues related to product quality.

1st Review Cycle: August 31, 2018

NDA 212209 was originally submitted to the Agency in August 2018 (PDUFA Date: 30-Jun-19). This submission was issued a Complete Response on June 17, 2019 for matters related to product quality. Specifically, the drug substance manufacturing site ((b) (4) had an unacceptable compliance history and the field investigator observed objectionable conditions at the facility. As a result a OPF recommended WITHHOLD and the application was issued a Complete Response (CR).

2nd Review Cycle: July 1, 2019

This submission represents the Applicant's response to the Agency's June 16, 2019 Complete Response (PDUFA Date: 1-Jan-20). In this submission, the Applicant responded to the facility issue; however, the status of (b) (4) remained unchanged from the 1st review cycle and this

submission was issued a Complete Response in July of 2019 as a result of a WITHHOLD recommendation from OPF.

3rd Review Cycle: February 14, 2020

This submission represents the Applicant's response to the Agency's July 1, 2019 Complete Response Letter (PDUFA Date: August 14, 2020). In this submission, the Applicant addressed the outstanding facility issue.

3. Product Quality

There nominal new CMC information included in this submission (updated stability and new site). NDA 212209 was recommended for a CR from a product quality in the previous review cycles due to a WITHHOLD recommendation from the facilities reviewer. 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 listed facilities' inspectional history and compliance status (see CDTL memo dated 6/03/2019). (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. In this submission, (b) (4) and the associated testing facilities for (b) (4) content analysis; namely (b) (4) and (b) (4) were withdrawn per Applicant request due to the non-compliance status of the drug substance manufacturer (b) (4) and new facilities are proposed.

At the time of review, all facilities associated with the application are adequate or remain adequate from previous cycle reviews and the proposed facilities are currently acceptable to support approval of this NDA.

In addition to the facility changes, the applicant provided updated stability data. 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.

Overall Product Quality Recommendation: The Office of Pharmaceutical Quality (drug substance, drug product, drug process, microbiology, biopharmaceutics and facilities) recommends **APPROVAL** of NDA 212209.

6. Clinical Pharmacology

There was no clinical phamrmacology information included in this resubmission.

7. Non-Clinical Pharmacology/Toxicology

The Slayback Pharam product is a reformulation of the Listed Drug, Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, and the applicant is relying on the Agency's previous finding of safety and effectiveness for Belrapzo, as described in the approved labeling for the LD. The non-clinical pharmacology/toxicology team confirms that there was no new clinical pharmacology information included in this application and recommends granting approval of NDA 212209.

8. Clinical/Statistical-Efficacy

Slayback Pharam did not conduct human clinical studies, and therefore efficacy was based on the Prescribing Information for Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, the relied-upon listed drug. The clinical team recommends granting approval of NDA 212209.

9. Safety

There was no new safety information included in this resubmission. Safety was based on the Prescribing Information for the Listed Drug, Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL.

10. Advisory Committee Meeting **N/A**

11. Pediatrics N/A

12. Other Relevant Regulatory Issues N/A

13. Labeling

Labeling negotiations are ongoing at the time of this review

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product relies on the safety and efficacy of the Listed Drug, the Slayback product is nearly identical to the LD, as the active product has the same active ingredient, is the same dosage form and has the same routes of administration and concentration of bendamustine prior to (b) (4) dilution as the Listed Drug. There were no new clinical or nonclinical studies conducted for this 505(b)(2) application.

While all disciplines recommended approval of NDA 212209, the CDTL recommends **TENATIVE APPROVAL** of NDA 212209 Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL) for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established and for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. NDA 212209 is not eligible for full approval due to the orphan exclusivity granted to Eagle Pharmaceuticals Incorporation's product, Bendeka and may be granted full approval once the exclusivity period has expired.

- **Risk Benefit Assessment**

Please refer to NDA 205580.

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/s/

SHERITA D MCLAMORE
07/02/2020 11:11:42 AM

Cross-Discipline Team Leader Review

Date	30-Jun-2020
From	Sherita D. McLamore, Ph.D.
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA	212209
Type of Application	505(b)(2)
Applicant	Slayback Pharma, LLC
Date of Receipt	14-Feb-2020
PDUFA Goal Date	14-aUG-2020
Proposed Proprietary/Established Names	Bendamustine HCl
Dosage forms / Strength	Injection/ 100 mg/4 mL
Route of Administration	Intravenous
Proposed Indication(s)	•Indicated for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established. •Indicated for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.
Recommended:	**TENATIVE APPROVAL**

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Clinical (Candis Morrison, M.D.)
- Pharmacology/Toxicology (Michael Manning, Ph.D.)
- DEMPA (Nicole Garrison, Pharm. D.)
- Drug Product (Tefsit Bekele, Ph.D.)
- Drug Substance (Mohd Kabir, Ph.D.)
- Microbiology (Christine Craig, Ph.D.)
- Manufacturing Process and Facilities (Djelila Mezaache, Ph.D.)
- Biopharmaceutics (Joan Zhao, Ph.D.)
- OPDP Consult (Trung-Hieu Tran)

1. Introduction

NDA 212209 was submitted for Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL) in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act by Slayback Pharma LLC. This application presents a new formulation of bendamustine hydrochloride. Bendamustine hydrochloride is a small molecule, antitumor, alkylating agent that exhibits unique activity. Bendamustine was originally approved under the brand name Treanda (discontinued in 2016) for the treatment of 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. Most recently, Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, manufactured by Eagle Pharmaceuticals was approved under NDA 205580 (May 2018). Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL is the listed drug (LD) for this application.

Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, is presented as a multiple-dose, ready-to-dilute, non-aqueous solution containing the active (bendamustine hydrochloride), monothioglycerol and propylene glycol in polyethylene glycol 400. The proposed 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 non-aqueous formulation includes the active, monothioglycerol, dehydrated alcohol and sodium hydroxide in polyethylene glycol 400. The selection of excipients was based on the excipients listed in PI of the LD with the exception of the presence of dehydrated alcohol which replaced propylene glycol.

The proposed drug product and the LD are both (b) (4) and sterile. Like the listed drug, the proposed drug product must be diluted prior to use. Dilution was designed to be accomplished with either 0.9% Sodium Chloride Injection USP or with a 2.5% Dextrose/0.45% Sodium Chloride Injection admixture prior to intravenous administration. The recommended dosing regimen for the (b) (4) the Slayback formulation 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 for CLL and 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 for NHL.

The proposed drug product has the same indications, dosage form, route of administration, and (b) (4) as Eagle's formulation but differs in the excipient profile (i.e. dehydrated alcohol used in the Slayback formulation replaced propylene glycol in the LD). For that reason, NDA 212209 contained no clinical data, but instead relied upon information in the public domain, and on the Agency's determination of safety and efficacy for the listed drug, Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, which was previously approved for marketing under NDA 205580.

2. Background

NDA 212209 has been issued two Complete Responses (CRs) due to issues related to product quality.

1st Review Cycle: August 31, 2018

NDA 212209 was originally submitted to the Agency in August 2018 (PDUFA Date: 30-Jun-19). This submission was issued a Complete Response on June 17, 2019 for matters related to product quality. Specifically, the drug substance manufacturing site ((b) (4) had an unacceptable compliance history and the field investigator observed objectionable conditions at the facility. As a result a OPF recommended WITHHOLD and the application was issued a Complete Response (CR).

2nd Review Cycle: July 1, 2019

This submission represents the Applicant's response to the Agency's June 16, 2019 Complete Response (PDUFA Date: 1-Jan-20). In this submission, the Applicant responded to the facility issue; however, the status of (b) (4) remained unchanged from the 1st review cycle and this

submission was issued a Complete Response in July of 2019 as a result of a WITHHOLD recommendation from OPF.

3rd Review Cycle: February 14, 2020

This submission represents the Applicant's response to the Agency's July 1, 2019 Complete Response Letter (PDUFA Date: August 14, 2020). In this submission, the Applicant addressed the outstanding facility issue.

3. Product Quality

There nominal new CMC information included in this submission (updated stability and new site). NDA 212209 was recommended for a CR from a product quality in the previous review cycles due to a WITHHOLD recommendation from the facilities reviewer. 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 listed facilities' inspectional history and compliance status (see CDTL memo dated 6/03/2019). (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. In this submission, (b) (4) and the associated testing facilities for (b) (4) content analysis; namely (b) (4) and (b) (4) were withdrawn per Applicant request due to the non-compliance status of the drug substance manufacturer (b) (4) and new facilities are proposed.

At the time of review, all facilities associated with the application are adequate or remain adequate from previous cycle reviews and the proposed facilities are currently acceptable to support approval of this NDA.

In addition to the facility changes, the applicant provided updated stability data. 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.

Overall Product Quality Recommendation: The Office of Pharmaceutical Quality (drug substance, drug product, drug process, microbiology, biopharmaceutics and facilities) recommends **APPROVAL** of NDA 212209.

6. Clinical Pharmacology

The Slayback Pharam product is a reformulation of the Listed Drug, Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, and the applicant is relying on the Agency's previous finding of safety and effectiveness for Belrapzo, as described in the approved labeling for the LD. The clinical pharmacology team confirms that there was no new clinical pharmacology information included in this application and recommends granting approval of NDA 212209.

7. Non-Clinical Pharmacology/Toxicology

The Slayback Pharam product is a reformulation of the Listed Drug, Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, and the applicant is relying on the Agency's previous finding of safety and effectiveness for Belrapzo, as described in the approved labeling for the

LD. The non-clinical pharmacology/toxicology team confirms that there was no new clinical pharmacology information included in this application and recommends granting approval of NDA 212209.

8. Clinical/Statistical-Efficacy

Slayback Pharam did not conduct human clinical studies, and therefore efficacy was based on the Prescribing Information for Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, the relied-upon listed drug. The clinical team recommends granting approval of NDA 212209.

9. Safety

There was no new safety information included in this resubmission. Safety was based on the Prescribing Information for the Listed Drug, Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL.

10. Advisory Committee Meeting **N/A**

11. Pediatrics N/A

12. Other Relevant Regulatory Issues N/A

13. Labeling

Labeling negotiations are ongoing at the time of this review

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product relies on the safety and efficacy of the Listed Drug, the Slayback product is nearly identical to the LD, as the active product has the same active ingredient, is the same dosage form and has the same routes of administration and concentration of bendamustine prior to (b) (4) dilution as the Listed Drug. There were no new clinical or nonclinical studies conducted for this 505(b)(2) application.

While all disciplines recommended approval of NDA 212209, the CDTL recommends **TENATIVE APPROVAL** of NDA 212209 Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL) for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established and for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. NDA 212209 is not eligible for full approval due to the orphan exclusivity granted to Eagle Pharmaceuticals Incorporation's product, Bendeka and may be granted full approval once the exclusivity period has expired.

- **Risk Benefit Assessment**

Please refer to NDA 205580.

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/s/

SHERITA D MCLAMORE
06/30/2020 05:00:22 PM

Cross-Discipline Team Leader Review

Date	10-Sept-2019
From	Sherita D. McLamore, Ph.D.
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA	212209
Type of Application	505(b)(2)
Applicant	Slayback Pharma, LLC
Date of Receipt	01-Jul-2019
PDUFA Goal Date	01-Jan-2020
Proposed Proprietary/Established Names	Bendamustine HCl
Dosage forms / Strength	Injection/ 100 mg/4 mL
Route of Administration	Intravenous
Proposed Indication(s)	•Indicated for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established. •Indicated for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.
Recommended:	**COMPLETE RESPONSE**

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Clinical (Angelo de Claro, M.D.)
- Pharmacology/Toxicology (Michael Manning, Ph.D.)
- DEMPA (Nicole Garrison, Pharm. D.)
- Drug Product (Tefsit Bekele, Ph.D.)
- Drug Substance (Mohd Kabir, Ph.D.)
- Microbiology (Christine Craig, Ph.D.)
- Manufacturing Process and Facilities (Djelila Mezaache, Ph.D.)
- Biopharmaceutics (Joan Zhao, Ph.D.)
- OPDP Consult (Trung-Hieu Tran)

1. Introduction

NDA 212209 was submitted for Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL) in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act by Slayback Pharma LLC. Bendamustine is a small molecule, alkylating agent. It is a nitrogen mustard derivative and is active against resting as well as dividing cells. Bendamustine was originally approved under the brand name Treanda (discontinued in 2016) for the treatment of 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. Most recently, Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, manufactured by Eagle Pharmaceuticals was approved under NDA 205580 (May 2018). Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL is the listed drug (LD) for this application.

Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, is presented as a multiple-use, ready-to-dilute, non-aqueous solution containing the active (bendamustine hydrochloride), monothioglycerol and propylene glycol in polyethylene glycol 400. The proposed 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 non-aqueous formulation includes the active, monothioglycerol, dehydrated alcohol and sodium hydroxide in polyethylene glycol 400. The selection of excipients was based on the excipients listed in PI of the LD with the exception of the presence of dehydrated alcohol which replaced propylene glycol.

The proposed drug product and the LD are both (b) (4) and sterile. Like the listed drug, the proposed drug product must be diluted prior to use. Dilution was designed to be accomplished with either 0.9% Sodium Chloride Injection USP or with a 2.5% Dextrose/0.45% Sodium Chloride Injection admixture prior to intravenous administration. The recommended dosing regimen for the the (b) (4) the Slayback formulation 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 for CLL and 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 for NHL.

The active moiety, pharmaceutical form, strength, route of administration, (b) (4), drug content and proposed indications of the Slayback formulation is same as the LD. For that reason, no clinical studies were performed with Slayback formulation. Instead, this NDA relies on Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL (NDA 205580) for safety and efficacy.

2. Background

This application presents a new formulation of bendamustine hydrochloride. Bendamustine hydrochloride is an alkylating antitumor agent that exhibits unique activity. The antitumor effects of bendamustine hydrochloride have been demonstrated by multiple *in vitro* studies in multiple tumor cell lines including breast cancer, non-small cell and small cell lung cancer and ovarian carcinoma.

The proposed drug product has the same indications, dosage form, route of administration, and (b) (4) as Eagle's formulation but differs in the excipient profile. NDA 212209 contains no clinical data, but instead relies upon information in the public domain, and on the Agency's determination of safety and efficacy for the listed drug which was previously approved for marketing under NDA 205580. The original submission of this NDA was issued a COMPLETE RESPONSE (CR) in June of 2019 due to a withhold recommendation from product quality. This submission represents a response to the June 2019 CR.

3. Product Quality

There was no new product quality information included in this submission. NDA 212209 was recommended for a CR from a product quality due to a WITHHOLD recommendation from the facilities reviewer. 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 (see CDTL memo dated 6/03/2019). (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. This submission is the applicant's response to the June 2019 Complete Response Letter; however, the status of (b) (4) (b) (4) remained unchanged from the 1st review cycle with an Official Action Indicated (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 can be recommended for approval.

Overall Product Quality Recommendation: The Office of Pharmaceutical Quality (drug substance, drug product, drug process, microbiology, biopharmaceutics and facilities) recommends a **COMPLETE RESPONSE** for NDA 212209.

6. Clinical Pharmacology

No new clinical/pharmacology information provide in the resubmission

7. Non-Clinical Pharmacology/Toxicology

There was no new non-clinical pharmacology/toxicology information included in this resubmission.

8. Clinical/Statistical-Efficacy

There was no new clinical/statistical information included in this resubmission. Slayback Pharama did not conduct any human clinical studies in conjunction with NDA 212209. As such, efficacy was based on the Prescribing Information for the LD, Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL.

9. Safety

There was no new safety information included in this resubmission. Safety was based on the Prescribing Information for the Listed Drug, Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL.

10. Advisory Committee Meeting **N/A**

11. Pediatrics N/A

12. Other Relevant Regulatory Issues N/A

13. Labeling

There were no labeling negotiations during this review cycle due to the anticipated CR recommendation. Labeling reviews were suspended and will resume when the sponsor provides an acceptable response to the CR deficiencies. Accordingly, the overall labeling recommendation is pending at this time.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product relies on the safety and efficacy of the Listed Drug, the Slayback product is nearly identical to the LD, as the active product has the same active ingredient, is the same dosage form and has the same routes of administration and concentration of bendamustine prior to (b) (4) dilution as the Listed Drug. There were no new clinical or nonclinical studies conducted for this 505(b)(2) application.

With the exception of Facilities (OPF), all disciplines recommended approval of this NDA. The Facilities reviewer entered a withhold recommendation for this NDA as it was determined that the drug substance manufacturing site is not in compliance with CGMPs. Accordingly, the CDTL recommendation for this NDA is a **COMPLETE RESPONSE** and a satisfactory response to the deficient conditions is required in order for the firm to be given an acceptable recommendation from a compliance perspective.

CR Comment to be Conveyed to the applicant:
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.

- **Risk Benefit Assessment**

Please refer to NDA 205580.

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/s/

SHERITA D MCLAMORE
09/09/2019 05:06:18 PM

Cross-Discipline Team Leader Review

Date	3-June-2019
From	Sherita D. McLamore, Ph.D.
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA	212209
Type of Application	505(b)(2)
Applicant	Slayback Pharma, LLC
Date of Receipt	31-Aug-18
PDUFA Goal Date	30-Jun-19
Proposed Proprietary/Established Names	Bendamustine HCl
Dosage forms / Strength	Injection/ 100 mg/4 mL
Route of Administration	Intravenous
Proposed Indication(s)	•Indicated for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established. •Indicated for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.
Recommended:	**COMPLETE RESPONSE**

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Clinical (Angelo de Claro, M.D.)
-
- Pharmacology/Toxicology (Michael Manning, Ph.D.)
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NDA 212209 was submitted for Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL) in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act by Slayback Pharma LLC. Bendamustine is a small molecule, alkylating agent. It is a nitrogen mustard derivative and is active against resting as well as dividing cells. Bendamustine was originally approved under the brand name Treanda (discontinued in 2016) for the treatment of 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. Most recently, Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, manufactured by Eagle Pharmaceuticals was approved under NDA 205580 (May 2018). Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL is the listed drug (LD) for this application.

Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL, is presented as a multiple-use, ready-to-dilute, non-aqueous solution containing the active (bendamustine hydrochloride), monothioglycerol and propylene glycol in polyethylene glycol 400. The proposed 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 non-aqueous formulation includes the active, monothioglycerol, dehydrated alcohol and sodium hydroxide in polyethylene glycol 400. The selection of excipients was based on the excipients listed in PI of the LD with the exception of the presence of dehydrated alcohol which replaced propylene glycol.

The proposed drug product and the LD are both (b) (4) and sterile. Like the listed drug, the proposed drug product must be diluted prior to use. 0.9% Sodium Chloride Injection USP or with a 2.5% Dextrose/0.45% Sodium Chloride Injection admixture are proposed as diluents. The recommended dosing regimen for the (b) (4) the Slayback formulation 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 for CLL and 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 for NHL.

The active moiety, pharmaceutical form, strength, route of administration, (b) (4), drug content and proposed indications of the Slayback formulation is same as the LD. For that reason, no clinical studies were performed with Slayback formulation. Instead, this NDA relies on Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL (NDA 205580) for safety and efficacy.

2. Background

This application presents a new formulation of bendamustine hydrochloride. Bendamustine hydrochloride is an alkylating antitumor agent that exhibits unique activity. The antitumor effects of bendamustine hydrochloride have been demonstrated by multiple *in vitro* studies in multiple tumor cell lines including breast cancer, non-small cell and small cell lung cancer and ovarian carcinoma.

The proposed drug product has the same indications, dosage form, route of administration, and (b) (4) as Eagle's formulation but differs in the excipient profile. NDA 212209 contains no clinical data and relies upon information in the public domain and on the Agency's determination of safety and efficacy for the listed drug which was previously approved for marketing under NDA 205580.

3. Product Quality

Bendamustine is a small, achiral, BCS class 4 molecule. It is a white to off-white, non-hygroscopic, crystalline solid that is soluble in water (12.5 g/L) and soluble to sparingly soluble in ethanol. Bendamustine drug substance is manufactured and release tested by (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 NDA and was deemed adequate to support the approval of this NDA. 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 (b) (4) in the formulation. The drug product contains no antimicrobial preservatives; (b) (4) (b) (4) (b) (4) (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 applicant requested a waiver of *in vivo* bioequivalence of the drug product. The biopharmaceutics reviewer concluded that a waiver of the requirement to conduct *in vivo* bioequivalence studies is not applicable for the drug product as the proposed drug product contains excipients that are not present in the LD. Upon further review biopharmaceutics reviewer concluded that a bridge between the proposed Bendamustine HCl Injection and the LD could be established based on the information provided in the application.

The drug product is manufactured at the Corden pharma Latina S.p.A of Italy at a commercial batch size of (b) (4) The manufacturing process includes (b) (4) (b) (4). The drug product is sterilized by (b) (4)

The applicant proposed a 24-month expiration dating period for the drug product and a 24h refrigerated/ 3h room temperature in-use period for the diluted product. In support of the proposed expiries, the applicant provided 12 months of long term (5°C) and 6 months of accelerated (25ºC/60%RH) data together with data from a multi-puncture study, a photo stability study, a thermal cycling studies and in-use stability data to demonstrate compatibility and stability of drug product when co-mixed with either 0.9% Sodium Chloride Injection USP or 2.5% Dextrose/0.45% Sodium Chloride Injection USP.

Based on the data submitted, the *FDA rejects the proposed 24-month expiry and recommends a 15-month expiry* for the drug product when stored under refrigerated conditions in the original carton as per recommendations of ICH Q1E and Q1A (R2). Since the OPQ review team is recommending a CR action, no expiry will be granted during this review cycle. The agency accepts the proposed in-use time (i.e. 24 h under refrigeration and 3 h at room temperature) for dilution with 0.9% NaCl 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. Dilution with 2.5% dextrose/0.45% Sodium Chloride Injection USP infusion solution was not adequately supported. Accordingly, the proposed in-use period was rejected and this admixture was removed from all labeling.

NDA 212209 includes 2 manufacturing, testing, and packaging facilities:

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

Following completion of review of this application, it was determined that the drug substance site ((b) (4) 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.

Overall Product Quality Recommendation: The Office of Pharmaceutical Quality (drug substance, drug product, drug process, microbiology, biopharmaceutics and facilities) recommends a **COMPLETE RESPONSE** for NDA 212209.

6. Clinical Pharmacology

n/a

7. Non-Clinical Pharmacology/Toxicology

The Slayback product is a reformulation of the LD, Belrapzo and the applicant is relying on the Agency's previous findings of safety and efficacy as described in the approved labeling for the LD. The Applicant conducted a three-part, GLP-compliant in vitro blood compatibility study to assess the hemolytic potential, plasma compatibility, and platelet aggregation potential of the proposed formulation. It was concluded that the Slayback bendamustine formulation did not exhibit any unexpected effects on hemolysis, plasma compatibility or platelet aggregation under the conditions tested. Additionally, the applicant provided toxicological assessments for three individual impurities ((b) (4)) with proposed acceptance criteria (b) (4). The applicant completed forced degradation studies for those three impurities and it was concluded that the proposed acceptance criteria were adequately justified and therefore acceptable. The proposed bendamustine HCl formulation is recommended for approval for the proposed indications from the nonclinical pharmacology and toxicology perspective.

8. Clinical/Statistical-Efficacy

Slayback Pharama did not conduct any human clinical studies in conjunction with NDA 212209. As such, efficacy was based on the Prescribing Information for the LD, Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL.

9. Safety

Safety was based on the Prescribing Information for the Listed Drug, Belrapzo (bendamustine hydrochloride) Injection 100 mg/4 mL.

10. Advisory Committee Meeting **N/A**

11. Pediatrics N/A

12. Other Relevant Regulatory Issues N/A

13. Labeling

The review of the label was completed by DMEPA, OPDP, Clinical, Non-Clinical and CMC.

OPDP Consult:
In response to DHP's consult request OPDP reviewed the proposed product labeling (PI) for the NDA 212209. submission for Bendamustine Hydrochloride. OPDP's comments on the proposed labeling were based on the draft PI (see Nisha Patel's review dated 4/11/19).

Clinical Recommendations:
The clinical reviewer referenced the ADL's January 31, 2019 review.

DMEPA Recommendations:
The applicant was asked 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). The reviewer also notes that the applicant removed the option of using the diluent 2.5% dextrose/0.45% Sodium Chloride Injection, USP from the PI, container label and carton labeling in response to an inquiry from product quality. The revised container labels and carton labeling for the Slayback Pharma Bendamustine formulation are acceptable from a medication error perspective.
Non-Clinical Recommendations:
The non-clinical reviewer notes that with the exception of Pregnancy and Lactation Labeling Rule (PLLR) compliance, the label is comparable to that of the Listed Drug.

CMC Recommendations:

The following IRs were conveyed during the review cycle.

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 was also requested to remove the option of using the diluent 2.5% dextrose/0.45% Sodium Chloride Injection, USP from the PI, container label and carton labeling as a result of the deficient in-use stability data for this diluent. The applicant complied with all requests and the labels comply with all regulatory requirements and it is recommended for approval from a CMC perspective.

ADL Recommendations:

See review dated 1/31/19 and Pre-decisional Agency Information Memo dated 4/11/19

Overall Labeling Recommendation:

A final recommendation of the label was not made during this review cycle due to the facility issue and the anticipated CR recommendation. Labeling reviews were suspended and will resume when the sponsor responds to the CR. The overall labeling recommendation pending at this time.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product relies on the safety and efficacy of the Listed Drug, the Slayback product is nearly identical to the LD, as the active product has the same active ingredient, is the same dosage form and has the same routes of administration and concentration of bendamustine prior to (b) (4) dilution as the Listed Drug. There were no new clinical or nonclinical studies conducted for this 505(b)(2) application.

With the exception of Facilities (OPF), all disciplines recommended approval of this NDA. The Facilities reviewer entered a withhold recommendation for this NDA because it was determined that the drug substance manufacturing site is not in compliance with CGMPs. Accordingly, the CDTL recommendation for this NDA is a **COMPLETE RESPONSE.** A satisfactory correction of the deficient conditions is required in order for the firm to be given an acceptable recommendation from a compliance perspective.

CR Comment to be Conveyed to the applicant:
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.

- **Risk Benefit Assessment**

Please refer to NDA 205580.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHERITA D MCLAMORE
06/03/2019 09:00:11 AM