CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212209Orig1s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

Date:	November 3, 2022
To:	File for NDA 212209
From:	Michael L Manning, PhD Pharmacology/Toxicology Reviewer Division of Hematology Oncology Toxicology (DHOT) Office of Oncologic Diseases (OOD)
Through:	Brenda J Gehrke, PhD Pharmacology/Toxicology Supervisor
Subject:	NDA 212209 Bendamustine Class 1 Resubmission
File:	NDA 212209
Applicant:	Slayback Pharma, LLC
Drug:	Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL)

Background

On October 7, 2022, Slayback Pharma, LLC submitted a class 1 resubmission to NDA 212209 (SDN 47). This resubmission was in response to the Agency's Tentative Approval Letter dated August 26, 2022, and requests final approval for the NDA. No new nonclinical information was included in SDN 47. NDA 212209 remains approvable from the nonclinical pharmacology and toxicology perspective.

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/s/

MICHAEL L MANNING
11/03/2022 09:00:41 AM

BRENDA J GEHRKE
11/03/2022 09:33:35 AM

MEMORANDUM

Date:	August 11, 2022
To:	File for NDA 212209
From:	Michael L Manning, PhD Pharmacology/Toxicology Reviewer Division of Hematology Oncology Toxicology (DHOT) Office of Oncologic Diseases (OOD)
Through:	Brenda J Gehrke, PhD Pharmacology/Toxicology Supervisor
Subject:	NDA 212209 Bendamustine Class 1 Resubmission
File:	NDA 212209
Applicant:	Slayback Pharma, LLC
Drug:	Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL)

Background

On June 27, 2022, Slayback Pharma, LLC submitted a class 1 resubmission to NDA 212209 (SDN 46). This resubmission was in response to the Agency's Tentative Approval Letter dated March 16, 2022. No new nonclinical information was included in SDN 46. NDA 212209 remains approvable from the nonclinical pharmacology and toxicology perspective.

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/s/

MICHAEL L MANNING
08/11/2022 05:01:13 AM

BRENDA J GEHRKE
08/11/2022 09:41:03 AM

MEMORANDUM

Date: February 17, 2022

To: File for NDA 212209

From: Michael L Manning, PhD
Pharmacology-Toxicology Reviewer
Division of Hematology Oncology Toxicology (DHOT)
Office of Oncologic Diseases (OOD)

Through: Brenda J Gehrke, PhD
Pharmacology-Toxicology Supervisor

Subject: Nonclinical review for NDA 212209 (SDN 33)

NDA: 212209

Applicant: Slayback Pharma, LLC

Drug: Bendamustine Hydrochloride Injection 100 mg/ 4 mL (25 mg/mL)

On June 16, 2021, Slayback Pharma, LLC submitted a class 2 resubmission to NDA 212209 (SDN 33). This resubmission was in response to the Agency's Tentative Approval Letter dated July 2, 2020. No new nonclinical information was included in SDN 33. NDA 212209 (SDN 33) is approvable from the perspective of nonclinical pharmacology and toxicology.

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/s/

MICHAEL L MANNING
02/17/2022 04:22:36 PM

BRENDA J GEHRKE
02/17/2022 04:41:58 PM

MEMORANDUM

Date: September 9, 2019
To: File for NDA 212209
From: Michael L Manning, PhD
Pharmacology-Toxicology Reviewer
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology and Oncology Products (OHOP)
Through: Christopher Sheth, PhD
Pharmacology-Toxicology Supervisor
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology and Oncology Products (OHOP)
Subject: Nonclinical review for NDA 212209 (SDN 20)
NDA: 212209
Applicant: Slayback Pharma, LLC
Drug: Bendamustine Hydrochloride Injection 100 mg/ 4 mL (25 mg/mL)

On July 1, 2019, Slayback Pharma, LLC submitted an NDA for Bendamustine Hydrochloride Injection 100 mg/ 4 mL (25 mg/mL). The current submission (SDN 20) was intended to be a full response to the Agency's Complete Response Letter dated June 17, 2019 regarding NDA 212209 (SDN 1). SDN 1 was approvable from the perspective of nonclinical pharmacology and toxicology, and no new nonclinical information was included in SDN 20. NDA 212209 (SDN 20) is approvable from the perspective of nonclinical pharmacology and toxicology.

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/s/

MICHAEL L MANNING
09/09/2019 10:16:24 AM

CHRISTOPHER M SHETH
09/09/2019 10:20:53 AM
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	212209
Supporting document/s:	1
Applicant's letter date:	August 31, 2018
CDER stamp date:	August 31, 2018
Product:	Bendamustine Hydrochloride Injection 100 mg/ 4 mL (25 mg/mL)
Indication:	Same as reference product Bendamustine Hydrochloride Injection 100 mg/ 4mL (25 mg/mL) (Belrapzo, NDA 205580)
Applicant:	Slayback Pharma LLC
Review Division:	Division of Hematology Oncology Toxicology (DHOT) for Division of Hematology Products (DHP)
Reviewer:	Michael L Manning, PhD
Supervisor/Team Leader:	Christopher M Sheth, PhD
Division Director:	John Leighton, PhD, DABT (DHOT) Ann Farrell, MD (DHP)
Project Manager:	Wanda Nguyen, PharmD

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 212209 are owned by Slayback Pharma LLC or are data for which Slayback Pharma LLC has obtained a written right of reference. Any information or data necessary for approval of NDA 212209 that Slayback Pharma LLC does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 212209.

TABLE OF CONTENTS

Table of Tables

1 Executive Summary

1.1 Introduction

The Applicant, Slayback Pharma LLC, is seeking marketing approval for a formulation of bendamustine hydrochloride (HCl) in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The reference listed drug (RLD) identified by the Applicant is Bendamustine Hydrochloride Injection 100 mg/4mL (25 mg/mL), approved on May 15, 2018 (NDA 205580), and marketed by Eagle Pharmaceuticals under the proprietary name Belrapzo. The active pharmaceutical ingredient (API), strength, dosage form, route of administration, (b) (4) and indications sought for the proposed bendamustine HCl formulation and the RLD are the same. The excipient profile of the proposed bendamustine HCl formulation and the RLD differ.

1.2 Brief Discussion of Nonclinical Findings

The Applicant's bendamustine HCl formulation is a reformulation of Belrapzo, and the current application is relying in part upon the Agency's previous findings of safety and efficacy for Belrapzo as described in the approved labeling. The Applicant also conducted a GLP-compliant in vitro blood compatibility study and provided toxicological assessments for individual impurities with proposed acceptance criteria (b) (4) the ICH Q3D qualification threshold.

The in vitro compatibility study was a three-part study to assess the hemolytic potential, plasma compatibility, and platelet aggregation potential of the proposed formulation. The concentration of test article and duration of incubation were considered to represent reasonable approximations of clinical use. In the hemolysis and plasma compatibility studies test article was mixed with human whole blood or citrated plasma, respectively, and incubated for 5 minutes at 37ºC. The degree of hemolysis was inferred from the amount of hemoglobin released from the red blood cells, while plasma compatibility was evaluated by macroscopic examination for changes in color, clarity, and presence of flocculation, precipitation, or coagulation. In the platelet aggregation study test article was mixed with platelet-rich human plasma and incubated for 15 minutes at 37ºC. Platelets were counted with an automatic hematology analyzer. The proposed bendamustine HCl formulation did not show any untoward effects on hemolysis, plasma compatibility, or platelet aggregation under the conditions tested.

Forced degradation studies identified (b) (4) impurities in the drug product with acceptance criteria at (b) (4) the ICH Q3D qualification threshold.

(b) (4)

(b) (4)

The Applicant's justification for the proposed acceptance criteria (b) (4) of the qualification threshold are acceptable (see 2.5 Comments on Impurities/Degradants of Concern).

The Applicant is relying on the in vitro and in vivo genotoxicity, carcinogenicity, and reproductive toxicity information described in the approved labeling for the RLD.

1.3 Recommendations

1.3.1 Approvability

From the perspective of nonclinical pharmacology and toxicology, the proposed bendamustine HCl formulation may be approved for the proposed indications.

1.3.2 Additional Nonclinical Recommendations

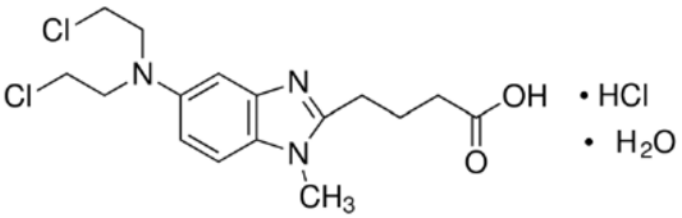
None

1.3.3 Labeling

The label is compliant with the Pregnancy and Lactation Labeling Rule (PLLR); otherwise, the label is comparable to the label of the RLD.

2 Drug Information

2.1 Drug

CAS Registry Number	1374784-02-7
Generic Name	Bendamustine HCl (monohydrate)
Chemical Name	1H-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-1-methyl-, monohydrochloride (monohydrate)
Molecular Formula	$C_{16}H_{21}Cl_2N_3O_2 \cdot HCl \cdot H_2O$
Molecular Weight	412.74 g/mol
Structure	
Pharmacologic Class	Alkylating drug

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 205580, Bendamustine Hydrochloride Injection 100 mg/ 4mL (25 mg/mL)

2.3 Drug Formulation

The excipients in the proposed bendamustine HCl formulation and the RLD differ (see Table 1). The proposed bendamustine HCl formulation should be diluted in (b) (4) mL of 0.9% Sodium Chloride Injection, USP.

Table 1: Comparative composition of the proposed bendamustine HCl formulation and the RLD

Product		Slayback Pharma's bendamustine HCl injection, 100 mg/4 mL (25 mg/mL)	RLD (NDA 205580): bendamustine hydrochloride injection 100 mg/4mL (25 mg/mL)
Dosage form		Injectable sterile solution	Injectable sterile solution
How supplied		Multiple-dose vial (100 mg/4 mL)	Multiple-dose vial (100 mg/4 mL)
Composition	Bendamustine HCl	100 mg	100 mg
	Monothioglycerol	20 mg	20 mg
	Propylene glycol	-	0.4 mL
	Dehydrated alcohol (b) (4) (b) (4))	157.8 mg	-
	Sodium hydroxide	q.s. to adjust pH	q.s. to adjust pH
	Polyethylene glycol 400	q.s. to 4.0 mL	q.s. to 4.0 mL
	(b) (4)		

q.s. - quantity sufficient

2.4 Comments on Novel Excipients

All excipients in the proposed bendamustine HCl formulation are present within limits described in the Inactive Ingredients Database by the intravenous route.

2.5 Comments on Impurities/Degradants of Concern

Proposed acceptance criteria for the (b) (4) impurities (b) (4) the ICH Q3D qualification threshold (see Table 2). The Applicant provided a toxicological assessment for each impurity. The proposed acceptance criteria for these impurities are acceptable.

Table 2: Impurities with acceptance criteria (b) (4) the ICH Q3D qualification threshold

Identity	Chemical Name	Proposed Limits	Applicant's Justification
(b) (4)			

Identity	Chemical Name	Proposed Limits	Applicant's Justification
(b) (4)			

* The RLD is not yet commercialized in the U.S. market; therefore, the sponsor evaluated their proposed drug product and commercially available Bendeka in a comparative dilution study.

2.6 Proposed Clinical Population and Dosing Regimen

The indications sought for the proposed bendamustine HCl formulation are the same as those for the RLD.

2.7 Regulatory Background

A pre-IND meeting was conducted. The Applicant proposed relying on the nonclinical data of Bendeka (NDA 208194), without right of reference, to support an NDA for the proposed bendamustine HCl formulation. In the meeting minutes sent to the Applicant on May 10, 2016, the Agency indicated the appropriateness of the information would be a review issue. In the current submission the Applicant has identified the RLD as Bendamustine Hydrochloride Injection 100 mg/4mL (25 mg/mL) (Belrapzo, NDA 205580).

3 Studies Submitted

3.1 Studies Reviewed

Study number	Study title	eCTD location
(b) (4) 3435	In Vitro Blood Compatibility Study of Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL) in Human Blood and Plasma	4.2.3.7.7.

4 Pharmacology

No pharmacology studies were submitted.

5 Pharmacokinetics/ADME/Toxicokinetics

No pharmacokinetic studies were submitted.

6 General Toxicology

No general toxicology studies were submitted.

[1] Dubbelman et al., Drug Metabolism and Disposition July 1, 2012, 40 (7) 1297-1307; DOI: https://doi.org/10.1124/dmd.112.045229

7 Genetic Toxicology

No genetic toxicology studies were submitted.

8 Carcinogenicity

No carcinogenicity studies were submitted.

9 Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies were submitted.

10 Special Toxicology Studies

Study title: In Vitro Blood Compatibility Study of Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL) in Human Blood and Plasma

Study no.:	(b) (4) 3435
Report date:	June 1, 2018
Study report location:	eCTD 4.2.3.7.7.
Conducting laboratory:	(b) (4)
GLP compliance:	Yes

Key study findings:

- The proposed bendamustine HCl formulation did not show any untoward effect on hemolysis, plasma compatibility, or platelet aggregation under the conditions tested.

The objective of the study was to assess the in vitro compatibility of the proposed bendamustine HCl formulation in human blood and plasma. The study was comprised of three parts: 1) hemolysis study, 2) plasma compatibility test (including macroscopic findings such as color change, flocculation, precipitation, or coagulation), and 3) platelet aggregation assay.

1) For the hemolysis study, freshly collected human whole blood was mixed with the proposed bendamustine HCl formulation (5.6 mg/mL) at formulation:blood ratios of 1:5, 1:10, and 1:20, and incubated for 5 minutes at 37ºC. The concentration of test article and duration of incubation were considered to represent reasonable approximations of clinical use. Human plasma and 1% saponin were used as negative and positive controls, respectively. Samples were centrifuged, and the degree of hemolysis was inferred by the optical density of the supernatant at 540 nm.

2) For the plasma compatibility test, freshly collected human citrated plasma was mixed with the proposed bendamustine HCl formulation (5.6 mg/mL) at formulation:plasma ratios of 1:5, 1:10, and 1:20, and incubated for 5 minutes at 37ºC. PBS (Ca^{2+} and Mg^{2+}

free), sodium chloride injection (0.9%), and homologous human plasma were used as blank control, vehicle control, and negative control, respectively. Samples were examined macroscopically for changes in color or clarity, and the presence of flocculation, precipitation, or coagulation. No microscopic examination was performed.

3) For the platelet aggregation assay, platelet-rich human plasma was mixed with the proposed bendamustine HCl formulation to obtain final test article concentrations of 50, 150, and 500 µg/mL, and incubated for 15 minutes at 37ºC. Sodium chloride injection (0.9%) and ADP (5 µM) and were used as negative and positive controls, respectively. Platelets were counted with an automatic hematology analyzer.

Results and Conclusions

1) The proposed bendamustine HCl formulation did not cause appreciable hemolysis of human blood under the conditions tested. The negative and positive controls performed as expected.

2) The proposed bendamustine HCl formulation did not cause any macroscopic changes to human plasma when compared to negative control under the conditions tested.

3) The proposed bendamustine HCl formulation did not cause any significant platelet aggregation under the conditions tested. The negative and positive controls performed as expected.

11 Integrated Summary and Safety Evaluation

See Executive Summary.

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/s/

MICHAEL L MANNING
05/15/2019 09:20:26 PM

CHRISTOPHER M SHETH
05/16/2019 07:10:42 AM
I concur