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APPLICATION NUMBER:

216078Orig1s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

Date:	December 1, 2022
To:	File for NDA 216078
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 216078 Bendamustine Class 1 Resubmission
File:	NDA 216078
Applicant:	Baxter Healthcare Corporation
Drug:	Bendamustine Hydrochloride Injection 100 mg/4 mL

Background

On October 31, 2022, Baxter Healthcare Corporation submitted a class 1 resubmission to NDA 216078 (SDN 016). This resubmission was in response to the Agency's Tentative Approval Letter dated July 14, 2022, and requests final approval for the NDA. No new nonclinical information was included in SDN 016. NDA 216078 remains approvable from the nonclinical pharmacology and toxicology perspective.

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/s/

MICHAEL L MANNING
12/01/2022 03:49:02 PM

BRENDA J GEHRKE
12/01/2022 04:37:21 PM

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:	216078
Supporting document/s:	1, 7, 11
Applicant's letter date:	September 14, 2021
CDER stamp date:	September 14, 2021
Product:	Bendamustine Hydrochloride Injection (100 mg/4 mL)
Indication:	Same as listed drug product (NDA 205580, Belrapzo)
Applicant:	Celerity Pharmaceuticals, LLC
Review Division:	Division of Hematology Oncology Toxicology (DHOT) for Division of Hematologic Malignancies II (DHM2)
Reviewer:	Michael L Manning, PhD
Supervisor/Team Leader:	Brenda J Gehrke, PhD
Division Director:	John Leighton, PhD, DABT (DHOT)
Project Manager:	Wanda Nguyen, PharmD

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 216078 are owned by Celerity Pharmaceuticals, LLC or are data for which Celerity Pharmaceuticals, LLC has obtained a written right of reference. Any information or data necessary for approval of NDA 216078 that Celerity Pharmaceuticals, 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 applications is for descriptive purposes only and is not relied upon for approval of NDA 216078.

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1 Executive Summary

1.1 Introduction

The Applicant, Celerity Pharmaceuticals, 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 listed drug (LD) identified by the Applicant is Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL), approved on May 15, 2018 (NDA 205580), and marketed by Eagle Pharmaceuticals, Inc under the proprietary name Belrapzo. The active pharmaceutical ingredient (API), strength, dosage form, route of administration, dosing regimen, and indications sought for the proposed bendamustine HCl formulation and the LD are the same. The excipient profile of the proposed bendamustine HCl formulation and the LD differ.

1.2 Brief Discussion of Nonclinical Findings

The Applicant's proposed 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 provided justification to support the proposed level of the excipient Alcohol, which is not present in the LD, and to support the proposed acceptance criteria for impurities exceeding the ICH Q3B(R2) qualification threshold.

The Applicant referenced published articles to assess the impact of the reformulation on blood compatibility in lieu of conducting nonclinical studies. The Applicant cited clinical experience with approved products containing higher amounts of ethanol to assess the impact of the reformulation on local tolerance. At the pre-IND meeting, the Agency agreed with this strategy to assess the impact of the reformulation on blood compatibility and local tolerance.

The published literature cited by the Applicant indicates ethanol can destabilize the membranes of erythrocytes in vitro[1]; however, the ethanol concentration associated with the maximum daily dose (MDD) of the proposed formulation is expected to have negligible impact on erythrocyte stability[2]. Alcohol is present in higher amounts in approved products (i.e., Paclitaxel Injection [ANDA 76131] and Etoposide Injection [ANDA 74290]) compared to the proposed bendamustine HCl formulation. The label for Paclitaxel Injection contains a precaution for injection site reactions, and the label for Etoposide Injection mentions reports of extravasation with swelling. The label for the LD has a Warning and Precaution for extravasation injury and also mentions injection site reactions; however, the local irritation associated with the LD may be attributed to the API as the LD does not contain Alcohol. Because the proposed formulation is not

[1] Tyulina OV, Huentelman MJ, Prokopieva VD, Boldyrev AA, Johnson P. Does ethanol metabolism affect erythrocyte hemolysis?. *Biochim Biophys Acta*. 2000;1535(1):69-77. doi:10.1016/s0925-4439(00)00086-7

[2] Tyulina OV, Prokopieva VD, Dodd RD, et al. In vitro effects of ethanol, acetaldehyde and fatty acid ethyl esters on human erythrocytes. *Alcohol Alcohol*. 2002;37(2):179-186. doi:10.1093/alcalc/37.2.179

expected to cause hemolysis, there is minimal concern the proposed formulation would be associated with increased potential for local irritation relative to the LD.

The Applicant's justification for the proposed level of Alcohol is acceptable (see section 2.4 Comments on Novel Excipients).

The Applicant's justifications for the proposed acceptance criteria for impurities exceeding the ICH Q3B(R2) qualification threshold and the permitted daily exposure (PDE) of extractables/leachables from the container closure system are acceptable (see section 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 LD.

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

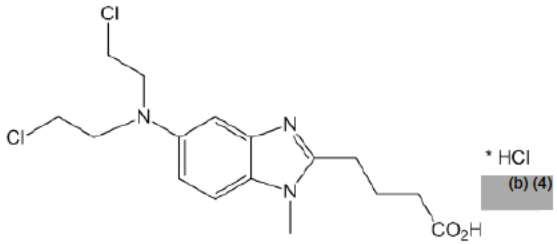
None

1.3.3 Labeling

The label is comparable to the label of the LD.

2 Drug Information

2.1 Drug

CAS Registry Number	(b) (4)
Generic Name	Bendamustine hydrochloride (b) (4)
Chemical Name	1*H*-Benzimidazole-2-butanoic acid, 5-(bis(2-chloroethyl)amino)-1-methyl-, hydrochloride, (b) (4)
Molecular Formula	$C_{16}H_{21}Cl_2N_3O_2 \cdot HCl \cdot$ (b) (4)
Molecular Weight	(b) (4) g/mol
Structure	 * HCl (b) (4)
Pharmacologic Class	Alkylating drug

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 151515

NDA 205580 (Belrapzo, Bendamustine Hydrochloride Injection)
ANDA 74290 (Etoposide Injection)
ANDA 76131 (Paclitaxel Injection)

2.3 Drug Formulation

The excipients in the proposed bendamustine HCl formulation and the LD differ (see Table 1).

Table 1: Comparative composition of the proposed bendamustine HCl formulation and the LD (quantities per 4 mL vial)

Product		Celerity Pharmaceuticals' bendamustine HCl injection, 100 mg/4 mL (25 mg/mL)	LD (NDA 205580): bendamustine HCl injection 100 mg/4 mL (25 mg/mL)
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
	Alcohol	400 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
	[redacted]	[redacted] (b) (4)	

q.s. - quantity sufficient

2.4 Comments on Novel Excipients

Alcohol is not present in the LD. The MDD of bendamustine (120 mg/m^2) in a typical patient (body surface area of 1.8 m^2) is 216 mg, or 8.64 mL of the proposed bendamustine HCl formulation (25 mg/mL). At the MDD of the proposed bendamustine HCl formulation, the maximum daily exposure (MDE) of Alcohol is 864 mg, which is less than the 4000 mg MDE of Alcohol described in the Inactive Ingredients Database for administration by the IV route. The Applicant's justification for the proposed level of Alcohol is acceptable.

2.5 Comments on Impurities/Degradants of Concern

The proposed acceptance criteria for four impurities exceed the ICH Q3B(R2) qualification threshold (see Table 2). The Applicant provided justification for the levels of these impurities. The proposed acceptance criteria are acceptable.

Table 2: Impurity acceptance criteria exceeding the ICH Q3B(R2) qualification threshold

Identity	Chemical Name	Proposed Limits (Release and Shelf-life)	Justification
(b) (4)		NMT (b) (4) %	• Known human metabolite ((b) (4)
		NMT (b) (4) %	• Known human metabolite (b) (4)
		NMT (b) (4) %	(b) (4)
		NMT (b) (4) %	

A leachables study was conducted to estimate the amounts of the compounds that may leach into the proposed bendamustine HCl formulation during storage contact with the container closure system. The study identified the levels of (b) (4) as exceeding the safety concern threshold (SCT) of 5 µg/day (see Table 3). The Applicant conducted a literature-based assessment to determine the PDE of (b) (4) The Agency agrees with the Applicant's determination of the PDE, and that the maximum exposures of (b) (4) are below the PDE.

Table 3: Potential leachable compounds exceeding the SCT of 5 µg/day

Identity	Maximum Daily Intake*	PDE	Justification for PDE
(b) (4)			• Based on publicly-available toxicology data
			• Based on publicly-available toxicology data

* Maximum daily intake in a typical patient (body surface area of 1.8 m^2)

(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

The indications sought for the proposed bendamustine HCl formulation are the same as those for the LD:

- Chronic lymphocytic leukemia
- Indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen

2.7 Regulatory Background

A pre-IND meeting was conducted under IND 151515. The Agency recommended the Applicant justify the levels of the excipient Alcohol in the proposed bendamustine HCl formulation, and the impact of Alcohol on blood compatibility and local tolerance. The Agency also indicated any new impurities or impurities at levels above the ICH Q3A/Q3B qualification thresholds or at levels higher than in the innovator's product may need to be qualified with nonclinical studies.

3 Studies Submitted

No nonclinical studies were submitted to NDA 216078.

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.

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

No special toxicology studies were submitted.

11 Integrated Summary and Safety Evaluation

See Executive Summary.

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/s/

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06/02/2022 11:30:31 AM

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06/02/2022 12:23:00 PM