CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215033Orig1s000

CLINICAL REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research
Division of Hematologic Malignancies 2

MEMORANDUM

Date:	12/1/2022	**Tentative Approval**	4/8/2022
From:	M. OConnor, PhD, RN, Clinical Analyst E. Everhart, MSN, RN, ACNP, Associate Director for Labeling		
To:	Electronic Document Record		
Sponsor	Apotex, Inc	**Drug:**	Bendamustine Hydrochloride
Subject:	NDA 215033 505(b)(2) Bendamustine Class 1 Resubmission		
Resubmission Date	10/7/2022	**PDUFA Due Date:**	12/7/2022
Through:	Nicholas Richardson, DO, MPH - Clinical Team Lead		

There are no changes included in this resubmission that would alter the conclusion that this NDA can receive final clinical approval for the specified indications. For details regarding the initial submission, please see the clinical review submitted to DARRTs on 3/11/2022 and labeling review dated 3/3/2022. Because no clinical data was included in the application, no financial disclosure information was provided.

Labeling Recommendations

The following minor formatting edits were made:

- In the Highlights, the space between the HIGHLIGHTS OF PRESCRIBING INFORMATION and the Highlights Limitations Statement was removed to comply with PLR requirements.
- In the Highlights, the column heights were corrected to align.
- Other minor formatting changes were made throughout the USPI to align with PLR requirements, for example, italicizing cross references.

The USPI is acceptable with the changes described above and is recommended for approval.

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/s/

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12/02/2022 03:20:20 PM

Cross-Discipline Team Leader Review

Date	14-Mar-2022
From	Sherita D. McLamore, Ph.D.
Subject	Cross-Discipline Team Leader (CDTL) Review
NDA	215003
Type of Application	505(b)(2)
Applicant	Apotex Inc
Date of Receipt	8-Jun-2021
PDUFA Goal Date	4-Apr-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:	**Tentative Approval**

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

- Clinical (Candis Morrison, Ph.D, CRNP)
- ADL (Elizabeth Everhart, MSN, ACNP)
- Pharmacology/Toxicology (Moran Choe, Ph.D.)
- DEMPA (Nicole Iverson, Pharm. D.)
- Drug Product (Rajiv Agarwal, Ph.D., Ph.D)
- Drug Substance (Kabir Shahjahan, Ph.D.)
- Microbiology (Laura Wasil, Ph.D.)
- Manufacturing Process and Facilities (Yifan Wang, Ph.D.)
- Biopharmaceutics (Anitha Govada, Ph.D.)

1. Introduction

NDA 215033 was submitted by Apotex Inc. 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. Bendamustine was originally approved under the brand name Treanda in 2009 (discontinued in 2016). Bendamustine acts as an alkylating agent causing intra-strand and inter-strand cross-links between DNA bases.

The Listed Drug (LD) for this NDA is BELRAPZO™ (bendamustine hydrochloride) injection, 100 mg/4mL (25 mg/mL). BELRAPZO was approved under NDA 205580 in May of 2018. BELRAPZO is indicated for the treatment of (i) chronic lymphocytic leukemia (CLL) efficacy relative to first line therapies other than chlorambucil has not been established. and (ii) indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab containing regimen. It is an is an intravenous injection solution packaged in a multi-dose vial and is presented as a clear colorless to pale yellow, sterile solution. The proposed product has the same indications, dosage form, dose, route of administration, and dosing regimen as the LD. The proposed product differs from the LD in terms of the qualitative and quantitative composition of the excipients. Specifically, the Apotex formulation contains (b) (4) ethanol as the (b) (4) whereas the Listed Drug contains propylene glycol as (b) (4) Akin to the LD, the proposed product is designed to be diluted with 0.9% Sodium Chloride Injection, USP, or with 2.5% Dextrose/0.45% Sodium Chloride Injection, USP prior to intravenous administration with a final concentration ranging from 0.05 to 0.7 mg/mL. However, (b) (4)

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

2. Background

This application presents a new formulation of bendamustine hydrochloride. Bendamustine hydrochloride is an alkylating antitumor agent. 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 Applicant developed a 100 mg/4 mL (25 mg/mL) presentation which is consistent with the listed drug. Both the LD and the proposed product are supplied as sterile, clear, and colorless to yellow, RTD solutions packaged in multi-dose clear glass vials. The LD and the proposed product have the same indications, dosage form, route of administration, and dosing regimen but differ in terms of the qualitative and quantitative composition of the excipients. The current application contains no clinical data but instead relies on the Agency's determination of safety and efficacy for the listed drug, BELRAPZO™. Accordingly, approval of NDA 215033 from clinical, non-clinical and clinical pharmacology perspectives will be primarily based on publicly available information for BELRAPZO™.

3. Product Quality

Bendamustine is a small, achiral, BCS class 4 molecule. It is a white to off-white, non-hygroscopic powder that is soluble in water, freely soluble in methanol and slightly soluble in acetonitrile. (b) (4) exhibits polymorphic behaviour and has a melting range of (b) (4) The applicant references DMF (b) (4) for all aspects pertaining to the manufacture and control of the drug substance; accordingly, limited information was included in the NDA. DMF (b) (4) was reviewed in September 2021 and is adequate to support the approval of this NDA. Based on the information provided, a (b) (4) month retest period has been established by the drug substance manufacturer.

The drug product, Bendamustine HCl Injection,100 mg/4 mL (25 mg/mL) is supplied as a clear colorless to pale yellow, ready-to-dilute sterile solution in 5 mL clear multiple-dose vial. The drug product formulation is for the most part non-aqueous and includes the active, ethanol, monothioglycerol, polyethylene glycol 400 (PEG 400) and sodium hydroxide (as needed for pH modification). All excipients are compendial grades and commonly used in the proposed dosage form.

The drug product is manufactured and release tested by Apotex Corporation of India at a commercial batch size of (b) (4) The manufacturing process includes (b) (4) . During manufacture, (b) (4) (b) (4) . The applicant included appropriate in-process controls and operating parameters and demonstrated the suitability of the manufacturing process for the drug product at commercial scale. The manufacturing process ensures the sterility of the final product and the conformity to the release specifications. The container closure system for the drug product consists of three components: a glass vial, an (b) (4) closure and a flip off aluminum seal. The glass vials are comprised of USP (b) (4) 5 mL/20 mm tubular glass and the (b) (4) closures are described as 20mm (b) (4) rubber stoppers. Each container is sealed with a 20-mm aluminum flip-off seal. The aluminum seal does not have direct contact with the solution and is therefore not considered a primary packaging component. The primary container closure system was deemed suitable for the intended use and the rubber closure was demonstrated to be compatible with the drug product based on stability and leachable and extractable studies.

The biopharmaceutics review focused on bridging the proposed drug product to the LD to support the requested waiver for *in vivo* bioavailability. Based on the totality of the information provided, the proposed drug product is considered adequately bridged to the listed drug, under 21 CFR 320.24(b)(6), and therefore an in vivo pharmacokinetic study was not required.

NDA 215033 included 3 manufacturing, testing, and packaging facilities. At the time of review, both facilities associated with this application were considered adequate to perform the responsibilities listed in the NDA and are acceptable to support approval of this NDA.

Overall Product Quality Recommendation: The Office of Pharmaceutical Quality (drug substance, drug product, drug process, microbiology, biopharmaceutics and facilities) recommends APPROVAL of NDA 215033. Based on the available stability data, the applicant proposed, and the OPQ accepts the expiration dating period of **18-months** for the drug product when stored under refrigerated conditions (i.e. 2°C and 8°C) and protected from light. Analogous to the LD, the proposed product is formulated to be diluted with either 0.9% Sodium Chloride Injection, USP or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. The final admixture is stable for 24 hours when stored refrigerated (2-8°C or 36- 46°F) or for (b) (4) hours when stored at room temperature (15-30°C or 59-86°F) (see USPI Section 2: DOSAGE AND ADMINISTRATION for infusate in-use period and storage partially used vials).

6. Clinical Pharmacology

n/a

7. Non-Clinical Pharmacology/Toxicology

The non-clinical pharmacology/toxicology team confirms that there was no new nonclinical information included in this submission. Instead, this application relies on the FDA's previous finding of safety for the LD, Belrapzo, as described in the drug's approved labeling. Pharmacology/Toxicology has no concerns and recommends granting approval of NDA 215033.

8. Clinical/Statistical-Efficacy

No clinical data was submitted with this 505(b)2 NDA submission for bendamustine. 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 215033.

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

Labeling negotiations are ongoing at the time of this review

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

The evaluation of this NDA was primarily based on product quality information as this product relies on the safety and efficacy of the listed drug, Belrapzo. The proposed product has the same active ingredient, dosage form, dosing regimen, route of administration and concentration of bendamustine following dilution as the listed drug. There were no new clinical studies conducted for this 505(b)(2) application a n d the CDTL recommends **TENATIVE APPROVAL** (TA) of this NDA due to the unexpired patents and exclusivity on the relied-upon listed drug, Belrapzo.

The proposed product 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
03/14/2022 11:22:52 AM

Memorandum
Clinical Review 505(b)(2) NDA
Division of Hematologic Malignancies 2

Date	11 March 2022
NDA/BLA #	NDA 215033
Applicant	Apotex, Inc
Date of Submission	08 June 2021
PDUFA Goal Date	08 April 2022
Drug	Bendamustine Hydrochloride
Dosage form(s) / Strength(s)	100mg/4mL (25 mg/mL)
Clinical Reviewer	Candis Morrison, PhD, CRNP
Clinical Team Lead	Nicholas Richardson, DO MPH
Signatory	Nicole J. Gormley, MD
Applicant Proposed Indication(s)/Population(s)	• Treatment of patients with chronic lymphocytic leukemia • Treatment of patients with indolent B-cell NHL that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen
Recommendation on Regulatory Action	Tentative Approval
Recommended Indication(s)/Population(s) (if applicable)	• Treatment of patients with chronic lymphocytic leukemia • Treatment of patients with indolent B-cell NHL that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen

Summary

On 08 June 2021, DHM2 received a submission for New Drug Application pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for bendamustine hydrochloride by Apotex, Inc. The Listed Drug (LD) identified by the Applicant is BELRAPZO (bendamustine hydrochloride, NDA 205580) injection 100 mg/4mL (25mg/mL) in a multiple-dose vial. The

active pharmaceutical ingredient, dosage form, concentration, route of administration, dosing regimen and indications sought for the Apotex formulation are the same as the LD. The products differ on their excipient profile.

No clinical data was submitted with this 505(b)2 NDA submission for bendamustine. The proposed indications are the same as those for the listed drug, BELRAPZO. The label was updated to align with the label for the listed drug. Final agreed upon labeling was submitted on 03 March 2022.

Conclusion: Based on the clinical review, NDA 215033 for bendamustine for the *treatment of patients with chronic lymphocytic leukemia and treatment of patients with indolent B-cell NHL that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen* can be granted tentative approval.

See the CDTL Review for additional information for this application.

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/s/

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