# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 215033Orig1s000

# SUMMARY REVIEW

# Cross-Discipline Team Leader Review

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| **Date** | 5-Dec-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** | 7-Oct-2022 |
| **PDUFA Goal Date** | 7-Dec-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.<br>•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 (Madeline O'Connor, M.D.)
- 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 (Julie Nemecek, Ph.D.)
- Manufacturing Process and Facilities (Yifan Wang, 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 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. Bendamustine was originally approved under the brand name Treanda in 2009 (discontinued in 2016). This application presents a new formulation of bendamustine hydrochloride.

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) (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**

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. NDA215033 contains no clinical data but instead relies on the Agency's determination of safety and efficacy for the listed drug, BELRAPZO™. NDA 215033 was originally submitted to the agency in June of 2021 and received a tentative approval in March of 2022 as a result of 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 on December 7, 2022.

This submission includes minimal new data. This submission includes a request to extend the drug product expiry and a request for full approval.

**3. Product Quality**

Bendamustine is a small achiral molecule that is manufactured by MSN Laboratories Private Limited of India. 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 a multiple-dose vial. The drug product formulation is for the most part non-aqueous and contains no preservatives.

The proposed product, like the listed drug, is designed to be diluted with 0.9% Sodium Chloride Injection, USP, or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. The final admix is stable for up to 24 hours when stored refrigerated or up to 3 hour when stored at room temperature (see USPI). The Naming of Drug Products Containing Salt Drug Substances Guidance for Industry states that "…In such cases, when the monograph title contains the specific salt form of the active

moiety, the strength of the product or preparation also is expressed in terms of the specific salt form". The listed drug follows this exception. Accordingly, the proposed product will follow this exception as well.

NDA 215033 was recommended for approval at the end of the previous review cycle. The current submission does not include any significant new product quality data. **Instead, the primary purpose for this submission is the extension of shelf life for the drug product and a request for full approval.**

**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 **24-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. NDA 215033 remains approvable from a P/T perspective.

**8. Clinical/Statistical-Efficacy**

The clinical team confirmed that was no new data to preclude the approval of this application. Accordingly, NDA 215033 remains approvable from a clinical perspective.

**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 was finalized during the previous review cycle. There were nominal changes to the USPI (see labeling review dated 03/03/2022).

## 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.

NDA 215033 is eligible for full approval once orphan exclusivity granted to Eagle Pharmaceuticals Incorporation's product, Belrapzo expires on December 07, 2022. Accordingly, as there are no outstanding issue to precluding approval of this application, the CDTL recommends full **APPROVAL** of NDA 215033 for 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/

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