CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215033Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	215033
Applicant Name	Apotex Inc.
Drug Product Name	Bendamustine HCl
Dosage Form.	Injection
Proposed Strength(s)	100 mg/ 4mL (25 mg/mL)
Route of Administration	Intravenous
Maximum Daily Dose	(b) (4) mg/day
Rx/OTC Dispensed	Rx
Proposed Indication	Bendamustine is indicated for the treatment of Chronic Lymphocytic Leukemia (CLL) and Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen.
Drug Product Description	Bendamustine is a small achiral molecule that is manufactured by MSN Laboratories Private Limited of India (US agent Dr. Kondal Reddy Bairy). 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.

	The current submission does not include any significant new data. **Instead, the primary purpose for this submission is the extension of shelf life for the drug product and a request for full approval.**		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20°C to 25°C (68°F to 77°F) [redacted] (b) (4) 15°C and 30°C (59°F to 86°F).		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Kabir Shahjahan	Haripada Sarker
	Drug Product/ Labeling	Rajiv Agarwal	Sherita McLamore
	Manufacturing	Yifan Wang	Zhaoyang Meng
	Biopharmaceutics	N/A	N/A
	Microbiology	Julie Nemecek	Bryan Riley
	Other (specify):	N/A	N/A
	RBPM	Dahlia Walters	
	ATL	Sherita McLamore	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: 24 months when stored at 2-8°C

[redacted]

b. Additional Comments for Action: N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends APPROVAL of NDA 215033 for commercialization of Bendamustine Hydrochloride Injection, 100 mg/4 mL. Based on our evaluation of the available information, the applicant provided sufficient information to support an approval recommendation from the product quality perspective. The applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**N/A**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: N/A

Sherita McLamore

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Memo

From: Rajiv Agarwal, Ph.D., Ph.D., Expert Regulatory Review Scientist

Through: Sherita McLamore, Ph.D., Branch Chief

IND: NDA 215033 (Amendment 21 (10/07/2022))

Date: 10/11/2022

Re: Review of additional 6 months of stability data and extension of expiration dating period from 18 months to 24 months of **injection** Drug Product

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Background: Via amendment 21, a reference is made to an original New Drug Application (NDA 215033) for Bendamustine Hydrochloride Injection 25 mg/mL (4 mL) submitted on 10/7/2022.

Apotex Inc. submits product correspondence to notify the Agency of the following two changes to the NDA:

- Extension of shelf life for the drug product from 18 months to 24 months based on updated stability data.

- Update to materials specifications following excipient to align with current internal SOP's and to align with current USP-NF monographs:

  1. (b) (4) (ethanol Absolute (b) (4)
  2. Sodium Hydroxide (b) (4)
  3. (b) (4))

Discussion of extension of expiration dating period: During the review of the original NDA, it was noted that the product is not stable at Accelerated (25 ±2°C/60 ± 5 %) condition at 6 months (Compound I impurity is (b) (4) % at 6th month: Acceptance criterion: 0.4% for batch CSEA03001A) time point.

Per ICH Q1A, "if significant change occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The initial application should include a minimum of 6 months data from a 12-month study at the intermediate storage condition". Since there is no intermediate condition defined when accelerated condition is 25 ±2°C/60 ± 5 %, per ICH Q1A, if significant change

occurs between 3- and 6-months' testing at the accelerated storage condition, the proposed expiration dating period should be based on the real time data available at the long-term storage condition.

Impurities	In NDA Acceptance criterion): As approved	In USP (for drug substance)	In USP (For injection)	Ranges at stability (Long Term) Up to 24 months	Ranges at stability (Accelerated)
Compound C	NMT 0.20%	NMT 0.20%	-	ND-Less than LOD	ND
Compound D	NMT (b) (4) %	NMT 0.15%	NMT 0.6%	Less than LOQ (b) (4)	Less than LOQ
Compound E	NMT 0.45%	NMT 0.45%	NMT 1 5%	(b) (4)	(b) (4)
Compound G	NMT 0.35%	NMT 0.35%	-	ND- Less than LOD	ND
Compound H	NMT 0.30%	NMT 0.30%	NMT 0 9%	ND-Less than LOD	ND
Compound I	NMT 0.40%	NMT 0.40%	-	Less than LOD- (b) (4)	(b) (4)
Any unspecified impurity	NMT (b) (4) %	NMT 0.10%	NMT 0 2%	Less than LOQ – (b) (4)	Less than LOQ
Total impuri ies	NMT (b) (4) %	NMT 1 0%	NMT 3 5%	(b) (4)	(b) (4)

LOQ=Quantita ion Limit (b) (4) LOD=Detection Limit (b) (4)

Therefore, the proposed 24 months expiration dating period will only be granted if real time stability data at 2ºC to 8ºC (36ºF to 46ºF) is provided. Applicant reevaluated the shelf life and proposed 18- months (based on real time stability data via amendment dated 12/24/2021) instead of 24-month shelf life and 18 months of expiration dating period was granted.

Via this amendment Applicant submitted additional 6 months of stability data and requesting the extension of expiration dating period from 18 months to 24 months.

Evaluation: *Based on the satisfactory real time stability data on three primary stability batches (CSEA03001A, CSEA03003A, and CSEA03004A) in both upright and inverted positions, 24 months of expiration dating period may be granted.*

The storage condition remained unchanged, and it is " Store Bendamustine hydrochloride injection in refrigerator, 2° to 8°C (36° to 46°F). Retain in original carton until time of use to protect from light".

Discussion and evaluation of updated specifications of excipients: The originally proposed specifications of (b) (4) (ethanol Absolute (b) (4) Sodium Hydroxide (b) (4), and (b) (4) are updated per most current USP/NF compendial requirements, and they are adequate.

Overall evaluation: Adequate

Rajiv Agarwal

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Sherita McLamore

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	215033, resubmission
Assessment Cycle Number	MR02
Drug Product Name/ Strength	Bendamustine Hydrochloride Injection
Route of Administration	Intravenous infusion
Applicant Name	Apotex, Inc.
Therapeutic Classification/ OND Division	CDER/OOD/DHM2
Manufacturing Site	MSN Laboratories Private Limited Formulations Division, Unit-II Survey Nos. 1277, 1319 to 1324, Rangareddy District, Nandigama (Mandal), Telangana, India, 509228
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0021 (22)	10/07/2022

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: In this resubmission, the applicant proposes extending the shelf life from 18 months to 24 months based on additional stability data.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): N/A

Supporting Documents:
NDA 215033, NDA215033MR01.docx: review of the original submission, 10/29/2021, adequate.

The drug product is an intravenous solution for infusion which is (b) (4) multi-dose vials. In this resubmission, the applicant proposes several changes including updating the specifications for excipients to

align with current USP monographs and annual updates to the DMF for the API. The only change relevant to this product quality microbiology review is a request to extend the shelf life from 18 months to 24 months based on additional stability data.

A summary of changes is provided in module 1.2.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

The composition of the drug product is unchanged and is provided here solely for reference.

Table 1: Drug product composition

Component	Quality Standard	Function	Component Quantity 100 mg/4 mL (b) (4)
Bendamustine Hydrochloride[a]	In house	(b) (4)	100 mg
(b) (4)	EP/USP/JP		(b) (4)
Monothioglycerol	NF		(b) (4)
Polyethylene Glycol 400	EP/USP/JP		(b) (4)
Sodium Hydroxide	EP/USP/JP		as needed to adjust pH of polyethylene glycol 400
(b) (4)	EP/USP/JP		Not applicable[b]

Table 1 was reproduced from Table 2 in "Description and Composition of the Drug Product," located in Module 3.2.P.1

Assessment: *Not applicable*

(b) (4)

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Julie Nemecek

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Dahlia A. Walters

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Recommendation: **APPROVAL**

NDA 215003
Review #1

Drug Name/Dosage Form	Bendamustine HCl Injection
Strength	100 mg/4 mL (25 mg/mL)
Route of Administration	IV
Rx/OTC Dispensed	R_x
Applicant	Apotex Inc.
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	06/08/2021	All
Amendment 004	08/27/2021	DP, DS
Amendment 004	09/28/2021	Process
Amendment 004	10/19/2021	Micro
Amendment 004	10/28/2021	Biopharm
Amendment 0010	12/13/2021	DP, Biopharm
Amendment 0011	12/21/2021	DP
Amendment 0012	12/23/2021	DP
Amendment 0013	01/11/2022	DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Kabir Shahjahan	Paresma Patel
Drug Product	Rajiv Agarwal	Anamitro Banerjee
Process	Yifan Wang	Bogdan Kurtyka
Microbiology	Laura Wasil	Christine Craig
Facility	Yifan Wang	Bogdan Kurtyka
Regulatory Business Process Manager	Dahlia Waters	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	Rajiv Agarwal	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	9/17/2021	Adequate
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type V			n/a	No Review	Adequate information provided in the NDA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	205580	Listed Drug

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends APPROVAL of NDA 215033 for Bendamustine HCl Injection, 25 mg/mL. As part of this action, OPQ grants an 18-month expiration period for the drug product when stored at under refrigerated conditions (2-8ºC). There are no outstanding issues and no post-approval quality agreements to be conveyed to the applicant.

II. Summary of Quality Assessments

A. Product Overview

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 acts as an alkylating agent causing intra-strand and inter-strand cross-links between DNA bases. The proposed drug product, Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL) is indicated for the treatment of Chronic Lymphocytic Leukemia (CLL) and Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen. 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. The proposed product has the same indication, dosage form, dose, route of administration, and dosing regimen as the LD but differs from the LD in terms of the qualitative and quantitative composition of the excipients.

Bendamustine is a small achiral molecule that is manufactured by MSN Laboratories Private Limited of India (US agent Dr. Kondal Reddy Bairy). The drug product, Bendamustine HCl Injection,100 mg/4 mL (25 mg/mL) is an intravenous injection solution packaged in a multi-dose vial. It is cytotoxic drug that is supplied as a clear colorless to pale yellow, ready-to-dilute (RTD) sterile solution. Of note, there is no USP monograph for Bendamustine Hydrochloride Injection; however, there is a USP monograph for Bendamustine HCl for injection. 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.

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.

Based on the information provided in this application (original submission, responses to information requests and in the resubmission), OPQ considers all review issues adequately addressed and potential risks to patient safety and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 215033 and grants an 18-month drug product expiration period when stored at between 2–8 °C in the commercial packaging.

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of patients with 1. Chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established 2. Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.
Duration of Treatment	6- 28 day cycles for CLL and 8- (b) (4) day cycles for NHL
Maximum Daily Dose	(b) (4) mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance

Bendamustine is a small achiral molecule that is manufactured and release tested by MSN Laboratories Private Limited of India. Bendamustine is USP monographed. It is a white to off-white, non-hygroscopic powder that has a melting range of 155-159°C and is freely soluble in methanol and slightly soluble in acetonitrile. (b) (4) exhibits polymorphic behaviour and the Applicant states that the (b) (4) (b) (4) (b) (4) polymorph, which has been confirmed by (b) (4).

Complete chemistry, manufacturing, and control information for bendamustine drug substance is cross referenced in DMF (b) (4). DMF (b) (4) was reviewed last reviewed on September 17, 2021 and was deemed adequate to support the approval of the referenced NDA. There have been no updates to DMF (b) (4) since the last review therefore it is considered adequate to support the approval of NDA 215003. NDA 215033 is recommended for approval from a drug substance perspective.

Drug Product and Drug Process

The drug product, Bendamustine HCl Injection,100 mg/4 mL (25 mg/mL) is a cytotoxic drug that 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 and there are no novel excipients or overages in the formulation. The drug substance is bacteriostatic; hence, the drug product formulation is also devoid of antimicrobial preservatives.

The LD, BELRAPZO™ (Bendamustine Hydrochloride Injection) 100 mg/4 mL, is held by Eagle Pharmaceuticals Inc. The proposed product is intended for the same indications and has the same active ingredient, final admixture Bendamustine HCl concentration, dose, dosing regimen, and route of administration as the listed drug. The proposed formulation differs from the LD with respect to excipients. Specifically, the Apotex formulation contains a mixture of ethanol as the (b) (4) t whereas the LD contains propylene glycol as (b) (4). The applicant indicates that the selection of the excipient grade was based on the LD and the knowledge that the excipients have been used successfully in the approved injectable products. The product is packaged in 5 mL/20 mm clear tubular USP (b) (4) glass vial with 20 mm (b) (4) (b) (4) stoppers. (b) (4) is used to (b) (4) each container is sealed with a 20 mm aluminum flip-off seal with a (b) (4) top button. 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 USPI for the LD indicates that it is designed to be diluted with 0.9% Sodium Chloride Injection, USP, 2.5% Dextrose/0.45% Sodium Chloride Injection, USP (b) (4) The proposed product is designed to be diluted with either 0.9% Sodium Chloride Injection or a mixture of USP, 2.5% Dextrose/0.45% Sodium Chloride Injection, USP (b) (4) The resulting final concentration of bendamustine HCl in the infusion bag should be between 0.05 – 0.7 mg/mL (originally proposed range was (b) (4); see drug product review for details). The final infusates are stable for 24 hours under refrigerated conditions and for 3 hours when stored at room temperature. The partially used vials are stable for up to 28 days when stored in the original container closure system under refrigeration (2° to 8°C or 36° to 46°F); however, each vial is to be used for no more than six (6) dose withdrawals.

The drug product is manufactured and release tested by Apotex Corporation of India at a commercial batch size of (b) (4) which corresponds to (b) (4) vials. The manufacturing process ensures the sterility of the final product and the conformity to the release specifications. The manufacturing process includes (b) (4) The manufacturing process includes well

defined IPCs, CPPs and CQAs. The Applicant demonstrated the suitability of the manufacturing process for the drug product at commercial scale (no scale up proposed for commercial production).

The drug product specifications include controls for all critical quality attributes for the intended dosage form and comply with compendial standards. The drug product specifications are adequate to establish the drug product identity, potency, and purity, and provide adequate controls to ensure the quality of the drug product throughout the product expiry. The proposed specification and acceptance criteria for the drug product, together with controls for impurities in the drug substance are adequate to ensure that the critical quality attributes of this product are well controlled.

The Applicant initially proposed a 24-month shelf life for the drug product when stored between 2°C and 8°C. In support of the proposed 24-month expiry, 18 months of long-term primary stability data were provided for three registration batches of the drug product manufactured with the proposed commercial formula, by the proposed commercial process, and packaged in the aforementioned container closure system. The drug product was stored inverted, upright and in horizontal positions under long term (5°C) and accelerated conditions (25°C/60%RH). The results of the primary stability studies revealed stability excursions under accelerated conditions (OOS result at the 6-month time point under accelerated conditions). In addition to the data provided for the RTD solution, the Applicant provided stability data for the infusate in support of the label claims (i.e. final admixture is stable for 24 hours when stored refrigerated…and 3 when stored at room temperature).

Based on the available stability data and as a result of the stability failure, the OPQ rejects the proposed expiration dating period of 24-months. Per ICH Q1A and in the absence of data under intermediate storage conditions, the shelf life will be based the available real time data. Accordingly, the FDA proposed, and the Applicant accepted a reduced expiration dating period of **18-months** for the drug product when stored at stored under refrigerated conditions and protected from light. Additionally, the agency accepts the proposed in-use period (i.e. 24h under refrigeration and 3h at room temperature) 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.

NDA 215033 is recommended for approval from a drug product and drug process perspective with the following Life Cycle Management Consideration:

> *Drug product is unstable therefore, for added protection caution "Retain in original carton until time of use to protect from light" should be in place.*

Biopharmaceutics

The biopharmaceutics review is focused on evaluation of the provided data supporting the bridging of the proposed drug product to the LD. The review team concluded that a scientific bridge between the proposed formulation and the LD has been established in accordance with 21 CFR §320.24(b)(6) based on the following:

1. The proposed drug product is intended for intravenous administration upon dilution.
2. The proposed drug product contains the same active moiety, route of administration as the LD
3. The administered volumes are identical and the concentration range of active ingredient per mL upon dilution (with 0.9 % sodium chloride injection, USP; or 2.5% Dextrose+0.45% Sodium Chloride Injection, USP) 0.05 mg/mL to 0.7 mg/mL) is identical to the LD concentration after dilution.
4. The Applicant provided a comparison of the physicochemical properties of the proposed product and the LD, after dilution to 0.05 mg/mL, 0.2 mg/mL, 0.6 mg/mL and 0.7 mg/mL. The pH and osmolality of the proposed drug product, after dilution are similar to the pH and osmolality of the LD after dilution at the same concentrations.
5. The proposed and the LD products are intended to be used for the same indication, same route of administration and same dosing regimen at the same concentrations.
6. The differences in excipients quantitative and qualitative composition of the proposed product compared to the LD is justified to ensure the stability and solubility of the drug substance in the solution.
7. The minor differences in the excipient concentration (sodium hydroxide and polyethylene glycol 400) are not likely to affect the disposition kinetics of bendamustine hydrochloride.

Based on the information provided by the Applicant the proposed drug product is adequately bridged to the listed drug and an in-vivo bioavailability study comparing the LD to the proposed drug product is superfluous. NDA 215033 is recommended for APPROVAL from a biopharmaceutics perspective.

Quality Microbiology

The Quality Microbiology review focused on sterility assurance for the manufacturing process of the (b) (4) drug product. The drug product is a sterile solution that is (b) (4) 5mL vials. The validation information supporting (b) (4) .

The primary container closure system was deemed acceptable to maintain product sterility and the review team concluded that the Applicant provided adequate microbiology data pertaining to the product sterility and endotoxin levels. Bendamustine hydrochloride injection 25 mg/mL does not contain a preservative; however, the applicant stated that the drug product is self-preserving and was requested to perform antimicrobial effectiveness testing (AET). AET was performed with three product batches and the results met regulatory expectations for demonstrating the

antimicrobial effectiveness requirement for a multiple dose drug product. The manufacturing process is consistent with regulatory expectations for a sterile pharmaceutical product. Accordingly, based on the information provided, NDA 215033 is recommended for APPROVAL from a quality microbiology perspective.

Facilities

There were 3 facilities included in this application:

- **MSN Laboratories Private Limited (FEI 3011033544)**-– Drug substance and finished product analytical testing and release. Inactive ingredient, and packaging components analytical testing and release and storage.
- Manufacturing, packaging and labeling of finished product. Finished product storage and stability testing
- **MSN Laboratories Private Limited (FEI 3008656542)**-- Manufacturing and testing of drug substance
- **MSN Laboratories Private Limited (FEI 3005254981)** - Testing Facility for (b) (4) in drug substance

All facilities listed in NDA 215033 were deemed acceptable for the responsibilities listed in the application. Accordingly, NDA 215033 is recommended for approval from a compliance perspective.

Environmental Assessment

The categorical exclusion pursuant to at 21 CFR 25.31(a) and 21 CFR 25.15(d). The claim of categorical exclusion is acceptable and the request for categorical exclusion is granted.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment (see Attachment)

See attached drug product review

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	Bendamustine Hydrochloride
Route(s) of administration	Adequate	IV, Injection
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Dosage form: Injection Strength: 25 mg/ml (4 mL)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	Drug product is an injection
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	Multiple-dose
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	Adequate	Each mL contains 25 mg Bendamustine Hydrochloride, which is equivalent to 22.7 mg Bendamustine free base. **Comment:** This information is added to the USPI (in section 11) and carton label.

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	Yes, dilution instructions are in place
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	No specific instruction
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	Adequate	Observe the contents of the vial for any visible solid or particulate matter and discoloration. Do not use the product if solid or particulate matter is observed after reaching room temperature.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	There is no USP monograph for the drug product

Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	Not applicable
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	Not applicable

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Injection
Strength(s) in metric system	Adequate	100 mg/4 mL (25 mg/mL)
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	Strength is based on the weight of the salt. **Note:** An equivalency statement is added to the USPI (section 11) and carton label.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	Clear and colorless to yellow solution
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Drug product is an injection
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	Multiple-dose vial

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Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	Bendamustine Hydrochloride
Dosage form(s) and route(s) of administration	Adequate	Injection, IV
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	Adequate	Each mL contains 25 mg Bendamustine Hydrochloride, which is equivalent to 22.7 mg Bendamustine free base. **Comment:** This information is added to the USPI and carton label.
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	38 mg absolute ethanol, 5 mg monothioglycerol, NF in polyethylene glycol 400, and 0.08 mg sodium hydroxide
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Inadequate	Provided
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Adequate	38 mg (3.8%) absolute alcohol
Sterility statement (if applicable)	Adequate	Sterile vials
Pharmacological/Therapeutic class	Adequate	Alkylating agent
Chemical name, structural formula, molecular weight	Adequate	Yes
If radioactive, statement of important nuclear characteristics.	N/A	Not applicable

Other important chemical or physical properties (such as pKa or pH)	N/A	Not applicable

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	Not applicable
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	Not applicable
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	Not applicable

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

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Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Solution for injection
Strength(s) in metric system	Adequate	100 mg/4 mL
Available units (e.g., bottles of 100 tablets)	Adequate	Vials
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	A clear, and colorless to yellow solution
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not applicable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	Multiple-dose
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	Retain in original carton until contents are used to protect from light. **Comment:** This information is added to the USPI and carton label.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Store Bendamustine Hydrochloride Injection in refrigerator, 2ºC to 8ºC (36ºF to 46ºF).
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	Not applicable
Include information about child-resistant packaging	N/A	Not applicable

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Manufactured by: MSN Laboratories Private Limited, India Manufactured for: Apotex Corp. Weston, Florida 33326

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	N/A	No patient labeling
Special preparation instructions (if applicable)	N/A	No patient labeling
Storage and handling information (if applicable)	N/A	No patient labeling
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	No patient labeling
Active ingredient(s) (if applicable)	N/A	No patient labeling
Alphabetical listing of inactive ingredients (if applicable)	N/A	No patient labeling
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	N/A	No patient labeling

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

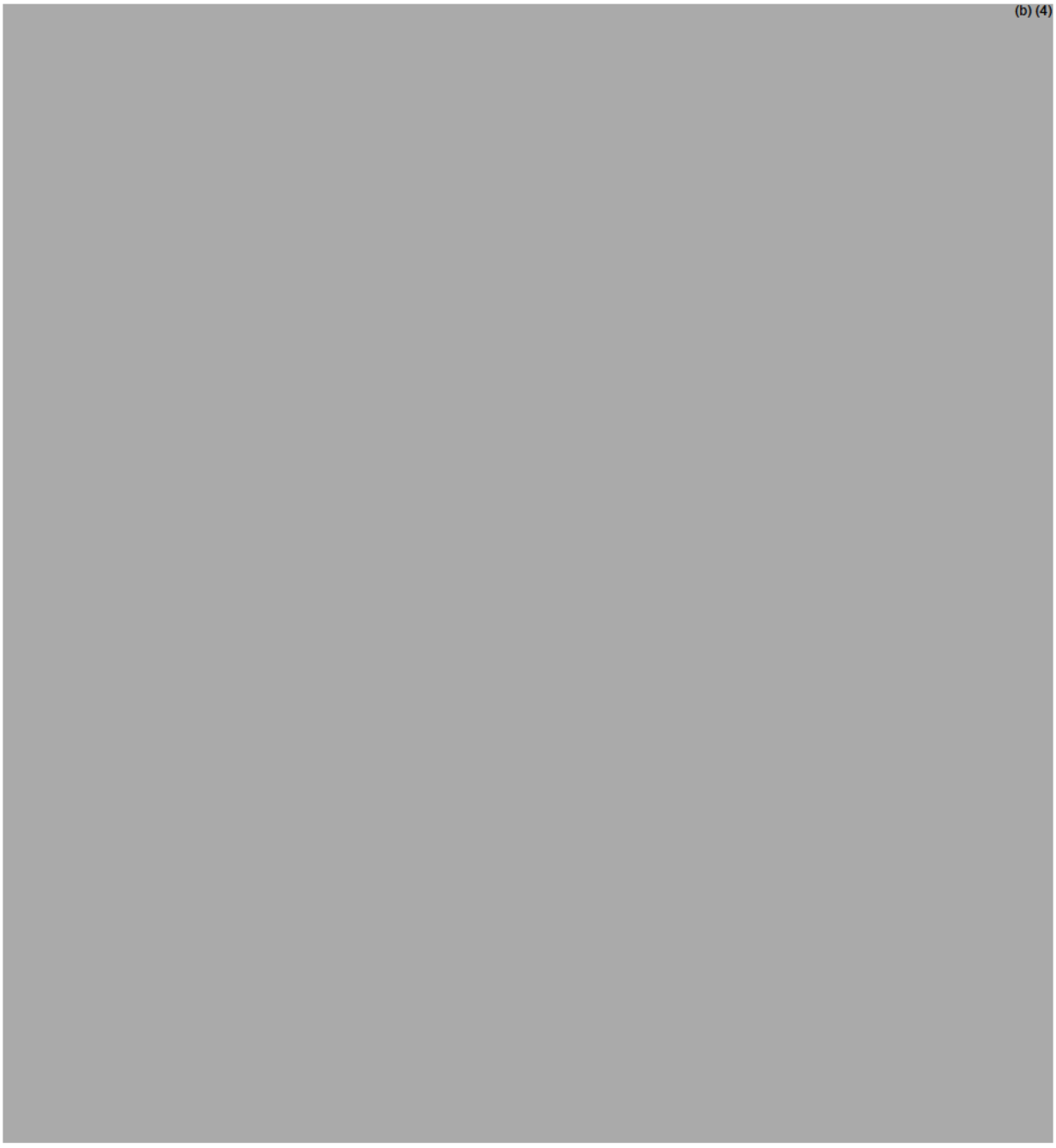
(b) (4)

[redacted]

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

3.2 Carton Labeling

(Copy/paste or refer to a representative example of a proposed carton labeling)



Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Inadequate	Bendmustine HCl
Strength(s) in metric system	Adequate	100 mg/4 mL (25 mg/mL)
Route(s) of administration	Adequate	For Intravenous infusion only
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	Due to the space restriction, this information will be on Carton. DMEPA is communicating it to the applicant.
Net contents (e.g., tablet count, volume of liquid)	Adequate	4 mL multi-dose vial
"Rx only" displayed on the principal display	Adequate	Yes
NDC	Adequate	60505-6228-0
Lot number and expiration date	Adequate	Space is provided
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Store in refrigerator, 2ºC to 8ºC (36ºF to 46ºF).
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	Adequate	Multi-dose vial
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	They are listed on carton: Each mL contains 25 mg bendamustine hydrochloride,USP, 38 mg absolute ethanol,5 mg monothioglycerol, polyethylene glycol 400, sodium hydroxide is used to adjust pH of polyethylene glycol 400.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Adequate	Provided on Carton
Linear Bar code	Adequate	Provided on both vial and carton labels

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	Both manufactured by and for are on the carton label **Manufactured by:** MSN Laboratories Private Limited, India ML No. 5/MN/TS/2014/F/G **Manufactured for:** Apotex Corp. Weston, Florida 33326
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	No medication guide
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	Not applicable
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Not applicable
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	Not applicable
And others, if space is available.	N/A	Not applicable

Assessment of Carton and Container Labeling: {*Adequate*}

The edits are made in the labeling (USPI) and will be communicated to the applicant by the clinical division.

ATL, once the labelling is finalized, will add the final labelling and labels to their assessment.

[3] Established name = [**Bendamustine HCl**] [IV] [injection]

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See Carton/Container Labeling Specific Resources for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these as deficiencies in this section.

Overall Assessment and Recommendation:

Following two Information Requests were communicated to the applicant on 1/19/2022 and applicant responded satisfactorily on 1/24/2022. Provided information is Adequate from an ONDP-DP standpoint. Edits are also made to the labeling (USPI) to reflect the following comments and will be conveyed to the Applicant by the Clinical Division.

Please add the following information to the carton label and provide a color mockup:

- Each mL contains 25 mg Bendamustine hydrochloride, which is equivalent to 22.7 mg Bendamustine free base.
- Retain vial in original carton until contents are used to protect from light.

Primary Labeling Assessor Name and Date: Rajiv Agarwal 1/24/2022

Secondary Assessor Name and Date: Anamitro Banerjee 1/25/2022

Rajiv Agarwal

Digitally signed by Rajiv Agarwal
Date: 1/25/2022 09:06:39AM
GUID: 504fa29c0000100b83d3aaa4905783c1

Anamitro Banerjee

Digitally signed by Anamitro Banerjee
Date: 1/25/2022 10:42:33AM
GUID: 5075764700003844b7bc89632228509f

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number/Type	NDA 215033-ORIG-1
Type of Submission	505(b)(2)
Assessment Cycle Number	1
Drug Product Name/ Strength	Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL)
Route of Administration	Injectable/Intravenous (Infusion)
Applicant Name	Apotex Inc.
Therapeutic Classification/ OND Division	OND/OOD/DHM2
Listed Drug	Belrapzo® (bendamustine hydrochloride) Injection 100 mg/4 mL (25 mg/mL); [NDA 205580, Eagle Pharmaceuticals Inc; Approved on May 15, 2018]
Proposed Indication	The treatment of patients with chronic lymphocytic leukemia (CLL)
Primary Reviewer	Anitha Palamakula Govada, Ph.D., R.Ph.
Secondary Reviewer	Om Anand, Ph.D.
Assessment Recommendation	**Adequate**

EXECUTIVE SUMMARY:

The proposed drug product, Bendamustine Hydrochloride for Injection, 25 mg/mL (100 mg/vial) is a solution for injection in a multi-dose vial, for intravenous (IV) administration. The proposed drug product has the same active ingredient (bendamustine hydrochloride), same indication and route of administration as the Listed Drug (LD), Belrapzo® (bendamustine hydrochloride) 100 mg/4mL (25 mg/mL) in a multiple-dose vial. The proposed product differs from the LD only in terms formulation (i.e. excipients). The pH and osmolality of the proposed drug product and the LD after dilution (with 0.9 % sodium chloride injection, USP; and 2.5% Dextrose+0.45% Sodium Chloride Injection, USP at the final diluted concentrations of 0.2 mg/mL, 0.6 mg/mL[1] and 0.05 mg/mL[2] and 0.7 mg/mL) is within the range of the LD, at final concentration of 0.05 mg/mL to 0.7 mg/mL.

[1] Revised label in SDN 0009 (submission date 10-28-2021) to reflect the LD label recent (10/2021) revisions. Note that Belrapzo label was revised in October 2021, includes major changes in section 2.3. Preparation for Intravenous Administration. Accordingly the proposed product label was revised for intravenous infusion using 25 mg/mL product in a 500 mL infusion bag of either 0.9% Sodium Chloride Injection, USP; or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP, the resulting final concentration of bendamustine HCl in the infusion bag should be within **0.05 to 0.7 mg/mL.**

[2] Physicochemical and osmolality data is provided in SDN 0010 (Submission date 12-13-2021) as part of Diluent Compatibility Study Report for the final concentration of 0.05 mg/mL and 0.7 mg/mL of bendamustine HCl in the infusion bag.

The Applicant established a scientific bridge under 21 CFR 320.24(b)(6) between the proposed drug product, Bendamustine Hydrochloride 100 mg/4 mL (25 mg/mL) for intravenous administration and the relied-upon listed drug, Belrapzo® (bendamustine hydrochloride) 100 mg/4mL (25 mg/mL) based on the following:

- The proposed drug product is intended for intravenous administration upon dilution.
- The proposed drug product contains the same active moiety (bendamustine), route of administration (IV) as the LD, Belrapzo® (bendamustine hydrochloride) 100 mg/4mL (25 mg/mL)).
- The administered volumes are identical and the concentration range of active ingredient per mL upon dilution (with 0.9 % sodium chloride injection, USP; or 2.5% Dextrose+0.45% Sodium Chloride Injection, USP) 0.05 mg/mL to 0.7 mg/mL) is identical to the LD concentration after dilution.
- The Applicant provided a comparison of the physicochemical properties of the proposed product and the LD, after dilution to 0.05 mg/mL, 0.2 mg/mL, 0.6 mg/mL and 0.7 mg/mL. The pH and osmolality of the proposed drug product, after dilution are similar to the pH and osmolality of the LD after dilution at the same concentrations.
- The proposed and the LD products are intended to be used for the same indication, same route of administration and same dosing regimen at the same concentrations.
- The differences in excipients quantitative and qualitative composition of the proposed product (Absolute Ethanol) compared to the LD (Propylene Glycol) is justified to ensure the stability and solubility of the drug substance in the solution.
- The minor differences in the excipient concentration (sodium hydroxide and polyethylene glycol 400) are not likely to affect the disposition kinetics of bendamustine hydrochloride.

Therefore, the disposition kinetics of bendamustine hydrochloride should be similar from these two products [Bendamustine Hydrochloride Injection, 25 mg/mL (100 mg/4 mL in each vial) and the LD Belrapzo® (bendamustine hydrochloride) product, 100 mg/4mL (25 mg/mL) in a multiple-dose vial].

The proposed Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL) formulation contains Absolute Ethanol at a concentration below the levels of currently approved products, therefore does not raise any safety concerns and is not expected to alter the pharmacokinetics of Bendamustine. The Applicant provided justification and published literature that supported the claim that the removal of Propylene Glycol[3] and addition of Absolute Ethanol does not alter the disposition kinetics of the drug substance.

[3] Note: As per the label description of a similar product for bendamustine hydrochloride approved under NDA 022249 as Treanda®, lyophilized powder for injection (25mg/mL or 100 mg/Vial) does not contain Propylene Glycol (PG) and therefore, bendamustine disposition kinetics are not expected to be impacted by removal of PG. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022249s025lbl.pdf (page 14, section 11 Description).

Therefore, based on the totality of the information provided, the proposed drug product, Bendamustine Hydrochloride, 25 mg/mL for intravenous administration is adequately bridged to the listed drug (LD), Belrapzo® (bendamustine hydrochloride)100 mg/vial (25 mg/mL) in accordance with 21 CFR §320.24(b)(6) and an in vivo pharmacokinetic study is not needed.

Recommendations: From a Biopharmaceutics perspective, NDA 215033 for Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL) in a multiple-dose vial is recommended for **APPROVAL**.

List of Submissions Being Assessed:

Document(s) Assessed	Sequence	Date Received
Original Submission	0002	06/08/2021
Minor Labeling Amendment	0009	10/28/2021
Response to Information Request	0010	12/13/2021

SUBMISSION:

Apotex Inc. submitted the current NDA[4] for Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL) intravenous infusion use under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. The 505(b)(2) application relies on FDA's findings of safety and effectiveness for the listed drug (LD), Belrapzo® (bendamustine hydrochloride) product, 25 mg/mL for injection, 100 mg/vial (for intravenous administration) marketed by Eagle Pharmaceuticals Inc. under the approved NDA 205580.

BIOPHARMACEUTICS REVIEW:

The LD, NDA 205580, Belrapzo® (bendamustine hydrochloride) is supplied as a sterile, clear, and yellow ready-to-dilute 100 mg/4 ml (25mg/mL) injection solution in a multiple dose glass vial. The LD is intended for intravenous infusion and specified in Belrapzo® product label, must be diluted in 500 mL of either 0.9% sodium chloride, USP; or 2.5% Dextrose+0.45% Sodium Chloride Injection, USP.

The LD final concentrations in the admixture were approved to be within the range of 0.2 mg/mL to 0.7 mg/mL, which is revised in October 2021 Label revision to a range of 0.05 mg/mL to 0.7 mg/mL of Bendamustine Hydrochloride in the infusion bag prior to intravenous administration over 30 minutes.

Apotex Inc. developed a ready to dilute liquid dosage form of Bendamustine Hydrochloride 100 mg/4 mL (25 mg/mL) injection solution in a multiple dose vial, which is intended to be used for the same indication, same route of administration and same dosing regimen at same concentrations. Apotex's proposed formulation differs from the LD in qualitative and quantitative composition of excipients. The proposed formulation contains Absolute Ethanol as (b) (4) and omits propylene glycol used in the LD formulation. The Applicant stated that the difference in excipients between the proposed formulation and LD does not impact the safety and efficacy of the proposed product. The Applicant provided supportive information and comparison between the proposed drug product and the LD along with additional justification/information to support their bridge request.

[4] In the Pre-NDA meeting preliminary comments conveyed on 10/09/2020 to the Applicant, the Agency indicated that a scientific bridge can be established between the proposed and (b) (4) (b) (4) the LD to Belrapzo® in the current NDA.

Table 1 below provides a side-by-side comparison, demonstrating that the conditions of use, active ingredient, route of administration, final dosage form, the total volume and method of dilution for administration, strength and physico-chemical properties of the proposed drug product are similar to those of the LD.

Table 1: The side-by- side comparison of the LD and proposed drug product before dilution

Formulation Composition	**<u>Listed Drug:</u> BELRAPZO® (bendamustine HCl) injection 25 mg/mL (100 mg/4 mL)**	**<u>Apotex Proposed Product:</u> Bendamustine Hydrochloride Injection 25 mg/mL (100 mg/4 mL)**
Ingredient	**Amount/vial**	**Amount/vial**
Bendamustine HCl	100 mg*	100 mg
Monothioglycerol, NF	20 mg*	20 mg
Propylene Glycol, USP	**0.4 mL***	***NONE***
Absolute Ethanol (100%), USP	***NONE***	**152 mg**
Sodium hydroxide **	QS	0.32 mg
Polyethylene Glycol 400 (PEG 400), NF	QS to 4 mL* (b) (4)	(b) (4)

* Information is from Label Claim
** As per DailyMed label information

The Applicant's proposed formulation of Bendamustine Hydrochloride Injection 25 mg/mL (100 mg/4 mL) differs from the Listed Drug Belrapzo® only in the comparative and qualitative composition of the excipients as summarized in the Table 2 below.

Table 2: Comparative qualitative and quantitative composition of LD, Belrapzo® vs. proposed test formulation product after dilution (Admixture)

Example 1: After dilution of single vial (containing 100 mg bendamustine HCl) – final drug concentration of 0.2 mg/mL in the infusion bag				
Total Volume	**504 mL (4 mL concentrate + 500 mL admixture)**		**504 mL (4 mL concentrate + 500 mL admixture)**	
Individual Ingredient Amount and Concentration	**Ingredient**	**Listed Drug**	**Ingredient**	**Apotex Proposed Product**
	Bendamustine HCl	100 mg (0.1984 mg/mL)	Bendamustine HCl	100 mg (0.1984 mg/mL)
	Propylene Glycol, USP	0.4 mL (0.0008 mL/mL)	Absolute Ethanol (100%)	152 mg (0.3016 mg/mL)
	Monothioglycerol, NF	20 mg (0.0396 mg/mL)	Monothioglycerol, NF	20 mg (0.0397 mg/mL)
	Polyethylene Glycol 400 (PEG 400), NF	~3.6 mL (0.0071 mL/mL)	Polyethylene Glycol 400 (PEG 400), NF	~3.7 mL (0.0073 mL/mL)
	Sodium hydroxide, NF*		Sodium hydroxide, NF	0.32 mg (0.0006 mg/mL)
Example 2: After dilution for a maximum recommended dose (120 mg/m^2 dose for NHL) prepared for an oversized patient with 2.7 m^2 body surface area requiring 324 mg of bendamustine HCl – final drug concentration of 0.6 mg/mL in the infusion bag				
Total Volume	**512.96 mL (12.96 mL concentrate + 500 mL admixture)**		**512.96 mL (12.96 mL concentrate + 500 mL admixture)**	
Individual Ingredient Amount and Concentration	**Ingredient**	**Listed Drug**	**Ingredient**	**Apotex Proposed Product**
	Bendamustine HCl	324 mg (0.6316 mg/mL)	Bendamustine HCl	324 mg (0.6316 mg/mL)
	Propylene Glycol, USP	1.296 mL (0.0025 mL/mL)	Absolute Ethanol (100%)	492.480 mg (0.9601 mg/mL)
	Monothioglycerol, NF	64.8 mg (0.1263 mg/mL)	Monothioglycerol, NF	64.8 mg (0.1263 mg/mL)
	Polyethylene Glycol 400 (PEG 400), NF	~11.664 mL (0.0227 mL/mL)	Polyethylene Glycol 400 (PEG 400), NF	~12.001 mL (0.0234 mL/mL)
	Sodium hydroxide, NF*	-	Sodium hydroxide, NF	1.0368 mg 0.0020 mg/mL)

Note: * - Quantity of sodium hydroxide not disclosed in BELRAPZO™ label

Physico-chemical characterization of the proposed product are provided. Table 3 a side-by-side comparison below between three lots of the proposed product and the LD before dilution shows that the pH and assay ranges of bendamustine are comparable. It is noted that osmolarity of the formulation before dilution was not provided by the Applicant. The Applicant reported that osmolality measurement before dilution was not possible due to the high viscosity. However, the concentration of the Bendamustine after dilution with above mentioned diluents (0.05 mg/mL to 0.7 mg/mL) is very low, the osmolality of the diluents would not be altered. Hence, it is acceptable that the Applicant did not test osmolality of the product before dilution.

Table 3: Comparative physicochemical data pH and assay sample ranges before dilution of the proposed product vs LD

Control or Test	Limits	Batch No.			Listed drug: BELRAPZO (Eagle Pharmaceutical Inc.) **
		CSEA03001	CSEA03003	CSEA03004	P000074 (Exp: 04/2023)
pH (Batch Release)	Between (b) (4)	3.48	3.50	3.47	3.51
Assay of Bendamustine Hydrochloride (Batch Release)	Not less than (b) (4)	102.2% (25.56 mg)	103.5% (25.87 mg)	103.2% (25.79 mg)	100.3%

A side-by-side comparation of pH, osmolarity and assay of final admixture solution after dilution is provided for all listed diluents as summarized in the Tables 4 to 7 below. Based on the data shown in Tables 4 and 5 below, the critical parameters (pH, osmolality of infusion solution and assay) are comparable between the proposed formulation and the LD at room temperature up to 3 hours and in the refrigerated storage conditions (5º±3ºC) up to 24 hours after dilution prior to administration.

Table 4: Comparison of pH and osmolality of the proposed Bendamustine injection RTU and LD products after dilution for infusion (Post dilution with 0.9 % Sodium chloride Injection to a concentration of 0.05, 0.2, 0.7 mg/mL):

Comparison of pH and osmolality of the proposed Bendamustine injection RTU and LD products after dilution with *0.9 % Sodium chloride Injection* to a concentration of 0.05, 0.2, 0.7 mg/mL				
	0.05 mg/mL			**LD**
Batch #	**CSEA03001**	**CSEA03003**	**CSEA03004**	**P000074**
pH	4.27	4.29	4.28	4.25
Osmolality (mOsm/kg)	304	301	302	303
Assay (% Bendamustine HCl)	98.1	96.1	95	98.9
	0.2 mg/mL			**LD**
Batch #	**CSEA03001**	**CSEA03003**	**CSEA03004**	**P000074**
pH	3.85	3.92	3.85	3.85
Osmolality (mOsm/kg)	319	319	314	318
Assay (% Bendamustine HCl)	103.9	103.2	99.8	100.9
	0.7 mg/mL			**LD**
Batch #	**CSEA03001**	**CSEA03003**	**CSEA03004**	**P000074**
pH	3.54	3.56	3.56	3.51
Osmolality (mOsm/kg)	420	418	422	429
Assay (% Bendamustine HCl)	101.9	104.1	102.7	99.7

Table 5: Comparison of pH and osmolality of the proposed Bendamustine injection RTU and LD products after dilution for infusion (Post dilution with 2.5% Dextrose + 0.45% Sodium Chloride Injection USP to a concentration of 0.05, 0.2, 0.7 mg/mL)

Comparison of pH and osmolality of the proposed Bendamustine injection RTU and LD products after dilution with **Diluent mixture of 2.5% Dextrose + 0.45% Sodium Chloride Injection to a final** concentration of 0.05, 0.2, 0.7 mg/mL				
	0.05 mg/mL			**LD**
Batch #	**CSEA03001**	**CSEA03003**	**CSEA03004**	**P000074**
pH	4.12	4.09	4.12	4.11
Osmolality (mOsm/kg)	306	307	306	307
Assay (% Bendamustine HCl)	103.4	103.6	100.5	100.6
	0.2 mg/mL			**LD**
	CSEA03001	**CSEA03003**	**CSEA03004**	**P000074**
pH	3.53	3.56	3.56	3.55
Osmolality (mOsm/kg)	407	413	405	418
Assay (% Bendamustine HCl)	103.5	102.4	101.2	99.4
	0.7 mg/mL			**LD**
Batch #	**CSEA03001**	**CSEA03003**	**CSEA03004**	**P000074**
pH	3.5	3.49	3.5	3.46
Osmolality (mOsm/kg)	430	427	424	440
Assay (% Bendamustine HCl)	103.7	102.5	101.7	99.5

Alcohol (Ethanol absolute): The function of absolute ethanol in the proposed drug product is as a (b) (4). The concentration of the ethanol in the proposed drug product is 38 mg/mL. The Applicant stated that the concentration of Absolute alcohol used in the proposed formulation is less than the maximum amount being currently administered to patients in USFDA approved products like Doxercaliferol Injection wherein (b) (4) mL/mL of Ethanol & MDV (Multi dose vial) formulation has (b) (4) mL/mL of Ethanol. (b) (4) The Applicant provided comparative human metabolism data of Bendamustine and Ethanol, which showed that metabolism of Ethanol and Bendamustine occurs through completely independent pathways. Although the level of ethanol included in the proposed formulation of Bendamustine HCl injection was found acceptable, the acceptability is

differed to the clinical and nonclinical reviewers to determine if safety information related to alcohol content should be included in Warnings and Precaution[5].

In addition, the Applicant performed a detailed evaluation in the available published literature and USFDA's previously approved NDA reviews with and without the addition of propylene glycol. As per the Label of NDA 022249, TREANDA is available in two formulations, a solution (TREANDA Injection) and a lyophilized powder (TREANDA for Injection). It is noted that lyophilized powder Treanda® formulation description section does not list propylene glycol[6] while Treanda® liquid formulation contains propylene glycol (162 mg/0.5 mL or 648 mg/ 2mL). Therefore, it can be concluded that presence or absence of propylene glycol (PG) in the formulation did not have impact on the disposition kinetics of bendamustine from these formulations and the distribution and elimination of bendamustine are expected to be the same for these two products.

Excerpt from the NDA 022249, TREANDA label:

TREANDA Injection (45 mg/0.5 mL or 180 mg/2 mL solution)

TREANDA (bendamustine HCl) Injection for intravenous use is supplied as a sterile clear colorless to yellow solution in a single-dose vial. Each 0.5 mL vial contains 45 mg of bendamustine hydrochloride, 162 mg of Propylene Glycol, USP and 293 mg of N,N-Dimethylacetamide, EP. Each 2 mL vial contains 180 mg of bendamustine hydrochloride, 648 mg of Propylene Glycol, USP and 1172 mg of N,N-Dimethylacetamide, EP. An overfill of 0.2 mL is included in each vial.

TREANDA for Injection (25 mg/vial or 100 mg/vial lyophilized powder)

TREANDA (bendamustine HCl) for Injection for intravenous use is supplied as a sterile non-pyrogenic white to off-white lyophilized powder in a single-dose vial. Each 25-mg vial contains 25 mg of bendamustine hydrochloride and 42.5 mg of mannitol, USP. Each 100-mg vial contains 100 mg of bendamustine hydrochloride and 170 mg of mannitol, USP. The pH of the reconstituted solution is 2.5 to 3.5.

Another example is Pfizer's Docetaxel which contained propylene glycol (b) (4) mg/mL) when compared to Taxotere®. In this latter review, the FDA concluded that the bioavailability of Pfizer's Docetaxel would be comparable to Taxotere® and clearly mentioned that "the differences in the inactive ingredients are not expected to impact the amount of drug delivered to the site of action based on comparable physical characteristics".

[5] Refer to the clinical and non-clinical comments for safety profile of the formulation with LD addressed in the pre-NDA meeting preliminary comments 10/15/2020.
[6] https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022249s025lbl.pdf

Formulation Composition	Listed Drug: BELRAPZO® (bendamustine HCl) injection 25 mg/mL (100 mg/4 mL)	Apotex Proposed Product: Bendamustine Hydrochloride Injection 25 mg/mL (100 mg/4 mL)
Ingredient	**Amount/mL**	**Amount/mL**
Bendamustine HCl	25 mg*	25 mg
Monothioglycerol, NF	5 mg*	5 mg
Propylene Glycol, USP	**0.1 mL***	***NONE***
Absolute Ethanol (100%), USP	***NONE***	**38 mg**
Sodium hydroxide **	QS	0.08 mg
Polyethylene Glycol 400 (PEG 400), NF	QS to 1 mL	(b) (4)

Reviewer's Assessment: Adequate

The Applicant submitted information to establish a scientific bridge between the proposed drug product, Bendamustine Hydrochloride liquid Injection 100 mg/4 mL (25 mg/mL) RTD intravenous administration and the listed drug (LD), in accordance with 21 CFR §320.24(b)(6), based on the following:

- The proposed drug product is intended for intravenous administration.
- The proposed drug product contains the same active moiety (Bendamustine Hydrochloride) and is the same dosage form (RTD liquid injection), route of administration (IV) as the LD, Belrapzo® (bendamustine hydrochloride) product for injection. The volumes administered are identical as the concentration of active ingredient per mL upon dilution with (0.9% Sodium Chloride Injection, USP or 2.5% Dextrose+0.45% Sodium Chloride Injection, USP) is identical to the LD concentration of 0.05 to 0.7 mg/mL after reconstitution.
- The Applicant provided a comparison of the physicochemical properties of the proposed for Bendamustine Hydrochloride liquid Injection and the LD, after reconstitution. The pH and osmolality of the proposed drug product and the LD, after reconstitution (0.9% Sodium Chloride Injection, USP or 2.5% Dextrose+0.45% Sodium Chloride Injection, USP) for a final concentration range of 0.05 to 0.7 mg/mL), are similar.
- The proposed product has comparable pH, final concentration, osmolality of infusion solution as that of the LD.
- The differences in excipients quantitative and qualitative composition of the proposed product (Absolute Ethanol) compared to the LD (Propylene Glycol) is justified to ensure the stability and solubility of API in the solution formulation. The minor differences in the composition of excipient concentration (sodium hydroxide and polyethylene glycol 400) are not likely to affect the disposition kinetics of bendamustine hydrochloride.

- Because the formulations for administration have similar physico-chemical properties upon dilution, the disposition kinetics of bendamustine hydrochloride should be similar from the proposed product Bendamustine Hydrochloride Injection 25 mg/mL (100 mg in 4 ml vial) and the LD product, Belrapzo® (bendamustine hydrochloride) Injection 25 mg/mL (100 mg in 4 ml vial).

Therefore, based on the totality of the information provided, the proposed drug product is adequately bridged to the listed drug, under 21 CFR 320.24(b)(6).

Om Anand

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Anitha Palamakula Govada

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	215033
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Bendamustine Hydrochloride Injection/ 25 g/mL (4 mL)
Route of Administration	Intravenous infusion
Applicant Name	Apotex Inc.
Therapeutic Classification/ OND Division	Oncology product/ Office of Oncologic Diseases/DHM2
Manufacturing Site	MSN Laboratories Private Limited, Formulations Division, Unit-II, Survey Nos. 1277, 1319 to 1324, Rangareddy District, Nandigama (Mandal), Telangana 509228, India
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
ECTD Sequence 0002	**6/8/2021**
ECTD Sequence 0008	**10/19/2021**

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: This 505(b)(2) NDA is for initial marketing of Bendamustine Hydrochloride Injection, 25 mg/mL (4 mL) in a multi-dose vial. The applicant references NDA 205580 for the drug product BELRAPZO®, which is Bendamustine Hydrochloride in 100 mg/4 mL (25 mg/mL) multi-dose vials. At the time of this submission, the applicant stated that the RLD has changed; the proposed product includes the same API in the same concentration, same dosage form, route of administration and dosing regimen. The only difference between the two products is the inactive ingredients included in the product formulation. An Information Request sent on 6 October 2021 and the responses received on 19 October 2021 are covered in this review.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): N/A

Supporting Documents:
DMF [redacted] The most recent relevant studies were reviewed and deemed adequate in review [redacted].doc on 16 June 2020.

S DRUG SUBSTANCE

The drug substance is received as [redacted] therefore, the drug substance is not reviewed.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

(Sequence 0002, Module 3.2.P.1, Description and Composition of the Drug Product)

- **Description of the drug product –** Clear colorless to yellow color, ready-to-dilute solution, filled in a 5 mL clear glass multi-dose vial stoppered with a 20 mm rubber stopper and sealed with an aluminum seal.

- **Drug product composition –**

Ingredient	Function	Quantity per mL	Quantity per vial
Bendamustine Hydrochloride, USP	Active ingredient	25.0 mg	100.0 mg
Alcohol (Ethanol absolute), USP	[redacted]	38 mg	152.0 mg
Monothioglycerol, USP-NF	[redacted]	5 mg	20.0 mg
Sodium Hydroxide, NF	[redacted]	0.08 mg	0.32 mg
Polyethylene glycol 400 (PEG 400), NF	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

- **Description of container closure system for the drug product–**

Component	Description	Supplier
Vial	5 mL clear tubular USP [redacted] glass vial with 20 mm neck	[redacted]
Rubber Stopper	20 mm [redacted]	
Seal	20 mm aluminum flip-off seal [redacted] color)	

Assessment: ***Adequate***

The applicant provided an adequate description of the drug product's composition and container closure system.

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/s/

SHERITA D MCLAMORE
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