CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216078Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	216078
Applicant Name	Celerity Pharmaceuticals, LLC
Drug Product Name	Bendamustine Hydrochloride Injection
Dosage Form.	Injectable
Proposed Strength(s)	100 mg/4 mL (25 mg/mL)
Route of Administration	Intravenous
Maximum Daily Dose	207.6 mg/day (120 mg/m^2)
Rx/OTC Dispensed	Rx
Proposed Indication	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.
Drug Product Description	The drug product, Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL) is a sterile, clear, and colorless to yellow ready-to-dilute solution in a multiple-dose clear glass vial. Bendamustine is in the alkylating agent family of medication and it behaves as an alkylating agent causing intra-strand and inter-strand crosslinks 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. The proposed product contains the same active ingredient, in the same concentration as the LD. It has the same dosage form, route of administration and dosing regimen as the LD but differs from the LD in terms of its excipients (LD contains propylene glycol as (b) (4) whereas the proposed product contains alcohol). Akin to the LD, the proposed product is designed to be diluted with 0.9% Sodium Chloride Injection, USP or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. When 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° to 8°C or 36° to 46°F) or for 3 hours when stored at room temperature. The current submission does not include any new data. **Instead, the primary purpose for this submission is the request for full approval.**		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	2 – 8 °C and protect from light		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Paresma Patel	Paresma Patel
	Drug Product/ Labeling	Rajiv Agarwal	Sherita McLamore
	Manufacturing	Diane Goll	Daniel Obrzut
	Biopharmaceutics	Qi Zhang	Qi Zhang
	Microbiology	Jason God	Julie Nemecek
	Other (specify):	N/A	N/A
	RBPM	Dahlia Waters	
	ATL	Sherita McLamore	
Consults			

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: 18-months when stored under USP refrigerated conditions (i.e. 2°C and 8°C) and protected from light

b. Additional Comments for Action: n/a

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends APPROVAL of NDA 216078 for commercialization of Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/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	**-**	**Adequate**
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

Additional Lifecycle Comments: N/A

Sherita McLamore

Digitally signed by Sherita McLamore
Date: 11/28/2022 09:55:57AM
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Recommendation: APPROVAL

NDA 216078
Review #1

Drug Name/Dosage Form	Bendamustine hydrochloride Injection
Strength	100 mg/4 mL (25 mg/mL)
Route of Administration	IV
Rx/OTC Dispensed	R_x
Applicant	Celebrity Pharmaceuticals, LLC
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	09/14/2021	All
SN-002	11/10/2020	DS Process
SN-003	12/09/2021	Process
SN-004	12/14/2021	DS, DP , Process
SN-006	01/31/2022	DS, DP , Process and Micro
SN-007	02/07/2022	DS, DP, Process
SN-008	02/17/2022	DP, Process
SN-009	03/10/2022	DP and Process
SN-0010	02/07/2022	DS, DP, Process
SN-0012	04/01/2022	DP, Process
SN-0013	05/04/2022	DP, Process

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Kabir Shahjahan	Haripada Sarker
Drug Product	Rajiv Agarwal	Sherita McLamore
Microbiology	Jason God	Julie Nemecek
Process and Facility	Diana Goll	Daniel Obrzut
Biopharmaceutics	Qi Zhang	Qi Zhang
Regulatory Business Process Manager	Dahlia Waters	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a

Environmental	Rajiv Agarwal	Sherita McLamore

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)	N/A	02/04/2022	Adequate
	Type III			N/A	No Review	Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information provided in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

2. CONSULTS

N/A

NDA Executive Summary

1. Application/Product Information

NDA Number.	216078
Applicant Name	Celerity Pharmaceuticals, LLC
Drug Product Name	Bendamustine Hydrochloride Injection
Dosage Form.	Injectable
Proposed Strength(s)	100 mg/4 mL (25 mg/mL)
Route of Administration	Intravenous
Maximum Daily Dose	207.6 mg/day (120 mg/m^2)
Rx/OTC Dispensed	Rx
Proposed Indication	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.
Drug Product Description	The drug product, Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL) is a sterile, clear, and colorless to yellow ready-to-dilute solution in a multiple-dose clear glass vial. The drug product 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. Bendamustine is in the alkylating agent family of medication and it behaves as an alkylating agent causing intra-strand and inter-strand crosslinks 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. The proposed product contains the same active ingredient, in the same concentration as the LD. It has the same dosage form, route of administration and dosing regimen as the LD but differs from the LD in terms of its

	excipients (LD contains propylene glycol as (b) (4) whereas the proposed product contains alcohol). The product is designed to be diluted with 0.9% Sodium Chloride Injection, USP or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. When 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° to 8°C or 36° to 46°F) or for 3 hours when stored at room temperature. Target product profile was clearly identified and the CQAs for the drug product include assay, osmolality, extractables and leechables and particulate matter.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	2 – 8 °C and protect from light		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Kabir Shahjahan	Haripada Sarker
	Drug Product/ Labeling	Rajiv Agarwal	Sherita McLamore
	Manufacturing	Diane Goll	Daniel Obrzut
	Biopharmaceutics	Qi Zhang	Qi Zhang
	Microbiology	Jason God	Julie Nemecek
	Other (specify):	N/A	N/A
	RBPM	Dahlia Waters	
	ATL	Sherita McLamore	

Consults	

2. Final Overall Recommendation - *APPROVAL*

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends APPROVAL of NDA 216078 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	**-**	**Adequate**
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

Additional Lifecycle Comments: N/A

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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 HCl
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: 100 mg/4 mL (25 mg/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	**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 HCl
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	Provided
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	(b) (4)
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)

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	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:** Baxter Oncology GmbH 33790 Halle/Westfalen Germany **Manufactured for (Distributed by):** (b) (4)

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

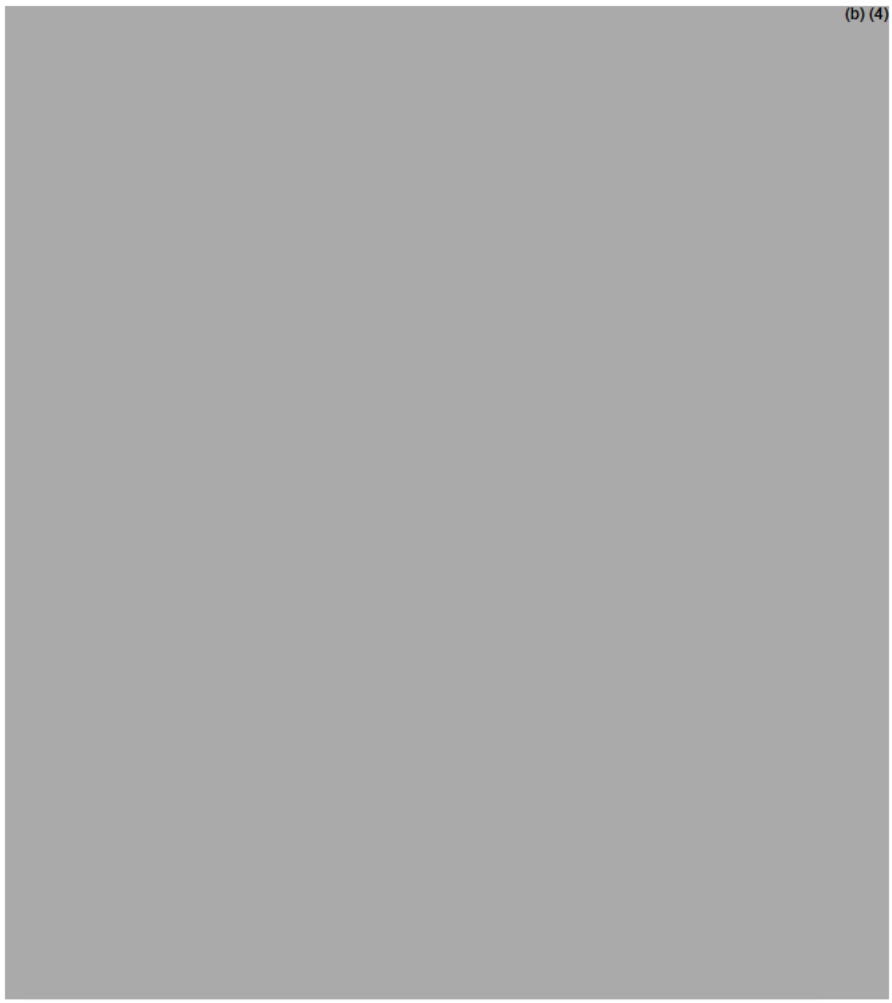
Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

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

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

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



3.2 Carton Labeling

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

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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)	Adequate	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 is on carton
Net contents (e.g., tablet count, volume of liquid)	Adequate	4 mL multiple-dose vial
"Rx only" displayed on the principal display	Adequate	Yes
NDC	Adequate	Yes
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	Multiple-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 (equivalent to 22.7 mg bendamustine free base),** 0.1 g alcohol, USP (equivalent to 0.1 g absolute ethanol), 5 mg monothioglycerol, NF in polyethylene glycol 400, NF, sodium hydroxide, NF to adjust acidity 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	(b) (4)
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 }***
- ***ATL, once the labelling is finalized, will add the final labelling and labels to their assessment.***
- ***Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."***

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

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 three Information Requests were communicated to the applicant on 3/1/2022 and applicant responded satisfactorily on 3/10/2022 and 5/4/2022. Provided information is Adequate from an ONDP-DP standpoint. Edits are also made to the labeling USPI/Carton to reflect the following comments and they are included.

- 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.
- Provide the amount of alcohol in terms of “absolute ethanol”.

Primary Labeling Assessor Name and Date: Rajiv Agarwal 5/10/2022

Secondary Assessor Name and Date: Sherita McLamore

Rajiv Agarwal

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Sherita McLamore

Digitally signed by Sherita McLamore
Date: 5/31/2022 01:06:49PM
GUID: 5032579500004157554 92db5bb8b1a5c

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CHAPTER VII: MICROBIOLOGY

Product Information	Solution for injection
NDA Number	216078
Assessment Cycle Number	1
Drug Product Name/ Strength	Bendamustine Hydrochloride Injection / 100 mg/4 mL
Route of Administration	IV
Applicant Name	Celerity Pharmaceuticals, LLC
Therapeutic Classification/ OND Division	OOD/DHM2
Manufacturing Site	Baxter Oncology GmbH Kantstrasse 2 Halle, North Rhine-Westphalia Germany 33790
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: This review covers sterility assurance for initial marketing of the sterile drug product. All deficiencies have been adequately addressed and the submission is adequate from the perspective of Quality Microbiology.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
eCTD 0001	**9/14/2021**
eCTD 0006	**1/31/2022**

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

Remarks: An IR was issued by the Agency, dated 18 November 2022. The Applicant requested clarification regarding Deficiencies #1 and #2 on 11/30/2021 and a response was issued was via email on 12/2/2022. The Applicant's responses to the IR were received 31 January 2022 and are addressed in the appropriate sections of this review.

Concise Description of Outstanding Issues: None

Supporting Documents:
(b) (4).docx, dated 15 February 2019 is referenced for (b) (4) (LOA: 19 April 2021).

[redacted]

S DRUG SUBSTANCE

N/A. Drug substance is supplied non-sterile.

Assessment: *Adequate*

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** Clear, colorless to yellow, ready to dilution solution in multiple-dose glass vials.

- **Drug product composition –**

Table 1: Drug product composition

Component	Quality Standard	Function	Component Quantity 100 mg/4 mL (PPE HA 42856)
Bendamustine Hydrochloride[a]	In house	Active ingredient	100 mg
Alcohol	EP/USP/JP	(b) (4)	400 mg
Monothioglycerol	NF		20 mg
Polyethylene Glycol 400	EP/USP/JP		q.s.
Sodium Hydroxide	EP/USP/JP	pH Adjuster	as needed to adjust pH of polyethylene glycol 400
(b) (4)	EP/USP/JP	(b) (4)	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

- **Description of container closure system –**
  - Vial: 6 mL (b) (4)
  - Stopper: 20 mm (b) (4)
  - Seal: 20 mm (b) (4)

Assessment: *Adequate*

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	216078; 505(b)(2) Type 5-New Formulation
Assessment Cycle	1
Drug Product	Bendamustine Hydrochloride Injection, for intravenous (IV) use
Dosage Form	100 mg/4 mL (25 mg/mL) in a multiple-dose vial
Indication	Treatment of Chronic lymphocytic leukemia (CLL) and Indolent B-cell non-Hodgkin lymphoma (NHL)
Dosage and Administration	For CLL: 100 mg/m2 infused intravenously over 10 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles. For NHL: 120 mg/m2 infused intravenously over 10 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles.
Applicant Name	Celerity Pharmaceuticals, LLC (Celerity)
OND Division	OND/OOD/DHM2
Associated INDs	PIND 151515 dated 08/13/2020
Listed Drug	NDA 205580 BELRAPZO® (bendamustine hydrochloride) injection, 100 mg/4 mL (25 mg/mL), (b) (4)
Biopharmaceutics Assessor	Qi Zhang, Ph.D.
Assessment Recommendation	***Adequate***

Assessment Summary

This 505(b)(2) application NDA 216078, for Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL), relies for approval on FDA's findings of safety and effectiveness of the LD approved under NDA 205580 BELRAPZO® Injection 100 mg/4 mL (25 mg/mL). The proposed drug product (DP)'s formulation contains alcohol as a (b) (4) vs. propylene glycol for the LD; therefore, a biowaiver under 21 CFR 320.22(b)(1) does not apply. The Applicant established a bridge to the LD under 21 CFR 320.24(b)(6). The Biopharmaceutics review is focused on evaluation of the provided data/information supporting the bridging between the proposed DP and the LD.

Overall, the scientific bridge between the proposed Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL), is adequately established to the LD, based on the following criteria: (1) The proposed DP and the LD have same indication, and both are intended for administration by intravenous infusion with the same rate of administration. (2) The proposed DP and the LD have the same active ingredient, same drug concentration (before and after dilution), and same dosing regimen. (3) The proposed DP has comparable physiochemical properties as the LD. Both, the proposed DP and the LD are sterile, clear, and colorless to yellow Ready-to-Dilute solutions in multiple-dose vials and have comparable pH (3.4-3.8) and osmolarities (321-452 mOsm/kg) after dilution with the same

dilution procedures. (4) The inclusion of alcohol in place of propylene glycol (b) (4) is not anticipated to impact the in vivo physiological disposition of bendamustine, relative to the LD in human subjects. Therefore, an in-vivo bioavailability study, comparing the LD to the proposed DP, is not needed.

Recommendation: From a Biopharmaceutics perspective, NDA 216078 for Bendamustine HCl Injection 100 mg/4 mL (25 mg/mL) is recommended for **APPROVAL**.

List of Submissions Being Assessed:

Document(s) Assessed	Sequence	Date Received
Original Submission	0001	09/14/2021

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

B.1 BCS DESIGNATION

Assessment: *Not Applicable for parenteral drug products*

Solubility: Bendamustine hydrochloride drug substance is a crystalline (b) (4) with pKa being 4.6 and 6.3, and pH 3.5 (in water, 5.4 mg/mL). The solubility of bendamustine hydrochloride in alcohol is reported ~78 mg/mL mg/mL at 25°C.

Permeability: Not provided in the submission, and it is not needed.

Following a single dose of 120 mg/m^2 of bendamustine hydrochloride the mean C_{max} is stated to achieve typically at the end of infusion. The dose proportionality of bendamustine has not been studied. The protein binding of bendamustine ranged from 94 to 96% and was concentration independent from 1 to 50 µg/mL. The blood to plasma concentration ratios in human blood ranged from 0.84 to 0.86 over a concentration range of 10 to 100 µg/mL. The intermediate half-life (t½) of the parent compound is approximately 40 minutes. The mean terminal elimination t½ of two active metabolites, γ-hydroxybendamustine (M3) and N-desmethylbendamustine (M4) are approximately 3 hours and 30 minutes, respectively.

Dissolution/Drug Release: Not applicable for parenteral drug products.

B.13 BRIDGING

Assessment: *Adequate*

There are two Listed Drugs (LDs) for Bendamustine Hydrochloride Injection 100 mg/4 mL (25 mg/mL) in the Orange Book, BENDEKA (NDA 208194 approved on 12/07/2015) and BELRAPZO (NDA 205580 approved on 05/15/2018). The two LDs only differ in the volume of diluents resulting in different final drug concentrations, e.g., 1.85 mg/mL to 5.6

mg/mL by 50 mL dilution for BENDEKA vs. 0.2 mg/mL to 0.7 mg/mL by 500 mL dilution for BELRAPZO[1].

The current 505(b)(2) application relies only on BELRAPZO. Unlike the LD, the proposed drug product contains ethyl alcohol as a (b) (4) vs. propylene glycol for the LD (Appendix **Table 1**). Because of the difference in the qualitative and quantitative compositions with respect to a (b) (4) a biowaiver under 21 CFR 320.22(b)(1) does not apply. The Applicant established a bridge between the proposed drug product and the LD under 21 CFR 320.24(b)(6). Refer to Request for Waiver of BA Study (SDN-001, Section 1.12.15.) for detailed information, supporting figures, tables, and literatures.

Summary of Key Findings in Support of the Bridging:

Physicochemical Properties

The comparative physicochemical properties of the proposed DP (3 registration batches, #0B001, 0C002, and 0C003); and the LD (#A190023), prior to dilution and after dilution with different diluents (500 mL of 0.9% Sodium Chloride Injection, or 2.5% Dextrose/0.45% Sodium Chloride Injection) are provided.

The pH data confirmed that there is no difference in pH; before dilution, the pH for both, the proposed DP and the LD, is approximately 3.4-3.5; after dilution with different diluents, the pH of both products is consistently similar (approximately 3.5-3.8) measured at final drug concentrations of 0.2 mg/mL and 0.7 mg/mL.

The osmolality data showed that the proposed DP and the LD have comparable osmolality in the diluted solution and no significant difference between two products (refer to Tables 6-10 of Section 1.12.15)). At a final drug concentration of 0.2 mg/mL the osmolality for the proposed DP is 325-341 vs. 321-334 mOsm/Kg for the LD; at a final drug concentration of 0.7 mg/mL the osmolality for the proposed DP is 434-452 vs. 417-436 mOsm/Kg for the LD.

The reported viscosity of undiluted proposed DP is 48 mPos vs. 94 mPos for the LD product (refer to Table 5 of Section 1.12.15). The difference in viscosity is expected since the proposed drug product substitutes alcohol (viscosity of 11 mP) for propylene glycol (viscosity of 420 mP); however, this difference is minimized because both products are diluted to 500 mL prior to use, and it has been demonstrated no significant difference in

[1] The final drug concentrations in labeling of the two LDs have been revised based on all dose scenarios (25 to 120 mg/m^2) and body surface areas (1 to 3 m^2), i.e., ~~1.85~~ 0.49 mg/mL to 5.6 mg/mL for BENDEKA, and ~~0.2~~ 0.05 mg/mL to 0.7 mg/mL for BELRAPZO. Refer to the ClinPharm Reviews for NDA 208194-Supplement-24 and NDA 205580-Supplement-10 for details. This Reviewer considers the drug concentrations of 1.85 mg/mL – 5.6 mg/mL and 0.2 mg/mL – 0.7 mg/mL (stated in the originally approved labels for BENDEKA® and TREANDA® [NDA 022249 approved on 03/20/2008]), acceptable for bridging purposes, as those concentrations represent the doses most patients would receive based on the clinical trial designs, and the physiochemical properties of the test product at the lower concentrations are likely to be similar to the LD.

the osmolarity after dilution. In addition, the proposed DP was found to be stable and comparable to LD, as all the critical parameters such as color of ready for dilution solution, assay, and impurities are found to be complying with proposed specifications at release and on stability. Refer to the Drug Product Reviews for additional CMC information.

Removal of Propylene Glycol and Inclusion of Alcohol as (b) (4)

Collectively, the following information support that the inlcusion of alcohol as (b) (4), in place of propylene glycol in the LD formulation, are not expected to affect the disposition kinetics of bendamustine from the proposed drug product:

1) The active ingredient for the proposed drug product is the same as that of the LD.
2) There are no changes proposed for the dosage form, strength, and mode of administration, indication and dosing regimen, and dilution procedures and storage conditions. Both, the proposed DP and the LD must be diluted in 500 mL of of 0.9% Saline or 0.45% Saline/2.5% Dextrose prior to administration. Both will have the same concentrations of the active ingredient before and after dilution at the time administration to the patients. Dosing is based on the intended indication and body surface area of the patient (refer to Table A of the labeling). A typical patient (120 mg/m^2 and 1.73 m^2) corresponds to an approximately 60-fold decrease in concentration of all excipients. For the largest dose and largest body surface area, this corresponds to a 35-fold decrease in concentration of all excipients.
3) Results of the comparative physiochemical data demonstrate that the proposed formulation resulted in a solution with similar physiochemical properties (e.g., pH and osmolarity) as compared to the LD after appropriate dilution prior to administration (refer to "Comparative Physicochemical Properties" above).
4) The removal of propylene glycol does not affect the dispostion, efficacy and safety of bendamustine injection, as no changes were evident following with the inclusion or exclusion of propylenen glycol in FDA approved bendamustaine drugs. Belrapzo and Treanda (both lyophilized powder and injectable solution) have same indication and same dosing regimen, despite having significant differences in formulations, drug concentrations and infusion rates.
5) The inclusion of alcohol in the proposed formulation is unlikely to impact potential protein binding of bendamustine compared to the LD. Results of published literature showed that that alcohol appears to competitively inhibit bovine serum albumin binding at concentrations of 25-200 mM. The maximum daily intake of alcohol from the proposed drug product is 830 mg, based on the maximum daily dose (MDD) of the drug product (207.6 mg [120 mg/m^2 and 1.73 m^2]). Using the assumption that a 70 kg human has 5.5 L of blood, the levels of alcohol at the maximum daily dose of bendamustine will be ~3 mM, which is at least 8 times lower than determined level in the published literature.
6) The inclusion of alcohol in the proposed formulation is not expected to affect any aspect of elimination kinetics of bendamustine or its metabolites, based on the metabolism rates of alcohol (7 g/hour). No clinical evidence and literature were found that alcohol would have an impact on metabolism, distribution or elimination, and safety of bendamustine in human subjects.

7) The quantity of alcohol used in the proposed formulation is within the recommendation of FDA's Inactive Ingredients Database (IIG) for IV route of administrion. The amount of alcohol present in the MDD of bendamustine is 830 mg vs. 4000 mg for the maximum daily exposure of alcohol of FDA approved drugs by IV administration. Refer to the Nonclinical Review for the supporting information.

In conclusion, the provided information and data including side-by-side comparison of the drug product and LD, and comparable physiochemical data (before and after dilution), as well as information available in the labeling and literature, justified the scientific appropriateness of reliance on the LD. The bridging between the proposed drug product and the LD is adequately established; therefore, an in-vivo bioavailability study, comparing the LD to the proposed DP, is not needed.

BIOPHARMACEUTICS LIST OF DEFICIENCIES CONVEYED TO THE APPLICANT DURING THE REVIEW

None.

APPENDIX

Table 1: Comparison of Qualitative and Quantitative Composition

[Before Dilution 100 mg/4 mL]

Component	BELRAPZO®	Proposed Drug Product
Strength	100 mg	100 mg
Fill Volume	4 mL	4 mL
Bendamustine Hydrochloride	25 mg/mL	25 mg/mL
Propylene Glycol	0.1 mL/mL	none
Alcohol	none	100 mg/mL
Monothioglycerol	5 mg/mL	5 mg/mL
Sodium Hydroxide[a]	as needed to adjust acidity of polyethylene glycol 400	as needed to adjust acidity of polyethylene glycol 400
Polyethylene Glycol 400	q.s.	q.s.

q.s. = quantity sufficient

[a] Sodium hydroxide is listed on the carton labeling as well as in the data elements section of the BELRAPZO® Prescribing Information (10/2019) found on DailyMed.

[After Dilution to 0.2 mg/mL]

Component	BELRAPZO®	Proposed Drug Product
Bendamustine Hydrochloride	0.2 mg/mL	0.2 mg/mL
Propylene Glycol	0.8 µL/mL	none
Alcohol	none	0.8 mg/mL
Monothioglycerol	0.04 mg/mL	0.04 mg/mL
Sodium Hydroxide[a]	as needed to adjust acidity of polyethylene glycol 400	as needed to adjust acidity of polyethylene glycol 400
Polyethylene Glycol 400	q.s.	q.s.

[After Dilution to 0.7 mg/mL]

Component	BELRAPZO®	Proposed Drug Product
Bendamustine Hydrochloride	0.7 mg/mL	0.7 mg/mL
Propylene Glycol	2.8 µL/mL	none
Alcohol	none	2.8 mg/mL
Monothioglycerol	0.14 mg/mL	0.14 mg/mL
Sodium Hydroxide[a]	as needed to adjust acidity of polyethylene glycol 400	as needed to adjust acidity of polyethylene glycol 400
Polyethylene Glycol 400	q.s.	q.s.

Qi Zhang

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