CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216078Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	5-Dec-2022
From	Tefsit Bekele, Ph.D.
Subject	Cross-Discipline Team Leader (CDTL) Memo
NDA	216078
Type of Application	505(b)(2)
Applicant	Celebrity Pharmaceuticals, LLC.
Date of Receipt	31-Oct-2022
PDUFA Goal Date	31-Dec-2022
Proposed Proprietary/Established Names	Bendamustine HCl
Dosage forms / Strength	Injection/ 100 mg/4 mL
Route of Administration	Intravenous
Proposed Indication(s)	•Indicated for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established. •Indicated for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.
Recommended:	**APPROVAL**

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

- Clinical (Madeline O'Connor, PhD, RN)
- ADL (Elizabeth Everhart, MSN, RN, ACNP)
- Pharmacology/Toxicology (Michael Manning, Ph.D.)
- DEMPA (Nicole Iverson, PharmD., BCPS)
- Drug Product (Rajiv Agarwal, Ph.D.)
- Drug Substance (Kabir Shahjahan, Ph.D.)
- Microbiology (Jason God, Ph.D.)
- Manufacturing Process and Facilities (Diana Goll, Ph.D.)
- Biopharmaceutics (Qi Zhang, Ph.D.)

1. Introduction

NDA 216078 was originally submitted by Celebrity Pharmaceuticals, LLC 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 and was originally approved under the brand name Treanda in 2009 (discontinued in 2016).

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 and is

indicated for the treatment of (i) chronic lymphocytic leukemia (CLL) efficacy relative to first line therapies other than chlorambucil has not been established and (ii) indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab containing regimen. It is an intravenous injection solution packaged in a multi-dose vial and is presented as a clear colorless to pale yellow, sterile solution. The proposed product has the same indications, dosage form, dose, route of administration, and dosing regimen as the LD but differs from the LD in terms of the qualitative and quantitative composition of the excipients. In particular, the LD utilizes propylene glycol as (b) (4) and the proposed drug product utilizes alcohol as (b) (4). Akin to the LD, the proposed product is designed to be diluted with 0.9% Sodium Chloride Injection, USP or with 2.5% Dextrose/0.45% Sodium Chloride Injection, USP prior to intravenous administration.

The recommended dosing regimen for Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL) is 100 mg/m2 infused intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles for CLL and 120 mg/m2 infused intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles for NHL.

2. Background

NDA 216078 presents a new formulation of bendamustine hydrochloride. Bendamustine is an alkylating antitumor agent. The antitumor effects of bendamustine hydrochloride have been demonstrated by multiple *in vitro* studies in multiple tumor cell lines including breast cancer, non-small cell and small cell lung cancer and ovarian carcinoma.

The Applicant developed a 100 mg/4 mL presentation which is consistent with the listed drug, BELRAPZO™. Both the LD and the proposed product are supplied as sterile, clear, and colorless to yellow, RTD solutions packaged in multi-dose clear glass vials. The LD and the proposed product have the same indications, dosage form, route of administration, and dosing regimen but differ in terms of the qualitative and quantitative composition of the excipients. The current application contains no clinical data but instead relies on the Agency's determination of safety and efficacy for the listed drug, BELRAPZO™. Accordingly, approval of NDA 216078 from clinical, non-clinical and clinical pharmacology perspectives will be primarily based on publicly available information for BELRAPZO™.

NDA 216078 was originally submitted to the agency in September of 2021 and received a Tentative Approval (TA) in July of 2022. **The current submission includes no new data but instead only includes a request for full approval**.

3. Product Quality

This resubmission contains no CMC information but instead only includes a request for full approval. All facilities associated with this application remain adequate and are acceptable to support approval of this NDA. The previously accepted expiration dating period of **18-months** for the drug product remains unchanged.

Overall Product Quality Recommendation: The Office of Pharmaceutical Quality (drug substance, drug product, drug process, microbiology, biopharmaceutics and facilities) recommends APPROVAL of NDA 216078. Based on the available real-time stability data, the applicant proposed, and the **OPQ accepts the expiration dating period of 18-months for the drug product when stored under refrigerated conditions (i.e. 2°C and 8°C) and protected from light**. Analogous to the LD, the proposed product is formulated to be diluted with either 0.9% Sodium Chloride Injection, USP or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. The final admixture is stable for 24 hours when stored refrigerated (2-8°C or 36- 46°F) or for (b) (4) hours when stored at room temperature (15-30°C or 59-86°F) (see USPI Section 2: DOSAGE AND ADMINISTRATION for infusate in-use period and storage partially used vials).

6. Clinical Pharmacology

n/a

7. Non-Clinical Pharmacology/Toxicology

The non-clinical pharmacology/toxicology team confirmed that no new data was included in this submission. Accordingly, NDA 216078 remains approvable from a pharmacology/toxicology perspective.

8. Clinical/Statistical-Efficacy

The clinical team confirmed that no new data was included in this submission. Accordingly, NDA 216078 remains approvable from a clinical perspective.

9. Safety

Safety was based on the Prescribing Information for the Listed Drug BELRAPZO™.(bendamustine hydrochloride) Injection 100 mg/4 mL.

10. Advisory Committee Meeting N/A

11. Pediatrics N/A

12. Other Relevant Regulatory Issues N/A

13. Labeling

The USPI submitted by the Applicant was compared to and updated to align with the approved USPI for the listed drug, BELRAPZO™. The final agreed upon labeling was submitted on 11 May 2022 (see review dated 06/09/2022).

At the completion of labeling negotiations, the USPI was acceptable from the ADL and all review disciplines. The label was deemed to be compliant with Physician Labeling Rule (PLR) [including the Pregnancy and Lactation Labeling Rule (PLLR)] requirements; is consistent with labeling guidance recommendations and with CDER labeling policies; conveys the essential scientific information needed for safe and effective use of the drug; is clinically meaningful and scientifically accurate; is a useful communication tool for health care practitioners, and is consistent with other USPI with the same active moiety, drug class, or similar indication.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

The evaluation of this NDA was primarily based on product quality information as this product relies on the safety and efficacy of the listed drug, BELRAPZO™. The proposed product has the same active ingredient, dosage form, dosing regimen, route of administration and concentration of bendamustine following dilution as the listed drug.

NDA 216078 is eligible for full approval once orphan exclusivity granted to Eagle Pharmaceuticals Incorporation's product, Belrapzo expires on December 07, 2022. Accordingly, the CDTL recommends full **APPROVAL** of NDA 216078 for Bendamustine Hydrochloride Injection, 100 mg/4 mL (25 mg/mL) for the treatment of patients with chronic lymphocytic leukemia (efficacy relative to first line therapies other than chlorambucil has not been established) and for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

- **Risk Benefit Assessment**

Please refer to NDA 208850.

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/s/

SHERITA D MCLAMORE
12/05/2022 10:30:33 AM

Cross-Discipline Team Leader Review

Date	13-Jun-2022
From	Sherita D. McLamore, Ph.D.
Subject	Cross-Discipline Team Leader (CDTL) Memo
NDA	216078
Type of Application	505(b)(2)
Applicant	Celebrity Pharmaceuticals, LLC.
Date of Receipt	14-Sept-2021
PDUFA Goal Date	14-Jul-2022
Proposed Proprietary/Established Names	Bendamustine HCl
Dosage forms / Strength	Injection/ 100 mg/4 mL
Route of Administration	Intravenous
Proposed Indication(s)	•Indicated for the treatment of patients with chronic lymphocytic leukemia. Efficacy relative to first line therapies other than chlorambucil has not been established. •Indicated for the treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.
Recommended:	**TENTATIVE APPROVAL**

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

- Clinical (Pamela Seam, M.D.)
- ADL (Elizabeth Everhart, MSN, RN, ACNP)
- Pharmacology/Toxicology (Michael Manning, Ph.D.)
- DEMPA (Nicole Iverson, PharmD., BCPS)
- OPDP Consult (Jennifer Chen, Pharm.D)
- Drug Product (Rajiv Agarwal, Ph.D.)
- Drug Substance (Kabir Shahjahan, Ph.D.)
- Microbiology (Jason God, Ph.D.)
- Manufacturing Process and Facilities (Diana Goll, Ph.D.)
- Biopharmaceutics (Qi Zhang, Ph.D.)

1. Introduction

NDA 216078 was submitted by Celebrity Pharmaceuticals, LLC 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 and was originally approved under the brand name Treanda in 2009 (discontinued in 2016).

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 and is indicated for the treatment of (i) chronic lymphocytic leukemia (CLL) efficacy relative to first line therapies other than chlorambucil has not been established and (ii) indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab containing regimen. It is an intravenous injection solution packaged in a multi-dose vial and is presented as a clear colorless to pale yellow, sterile solution. The proposed product has the same indications, dosage form, dose, route of administration, and dosing regimen as the LD but differs from the LD in terms of the qualitative and quantitative composition of the excipients. In particular, the LD utilizes propylene glycol as (b) (4) and the proposed drug product utilizes alcohol as (b) (4) Akin to the LD, the proposed product is designed to be diluted with 0.9% Sodium Chloride Injection, USP or with 2.5% Dextrose/0.45% Sodium Chloride Injection, USP prior to intravenous administration.

The recommended dosing regimen for Bendamustine HCl Injection, 100 mg/4 mL (25 mg/mL) is 100 mg/m2 infused intravenously over 30 minutes on Days 1 and 2 of a 28-day cycle, up to 6 cycles for CLL and 120 mg/m2 infused intravenously over 60 minutes on Days 1 and 2 of a 21-day cycle, up to 8 cycles for NHL.

2. Background

This application presents a new formulation of bendamustine hydrochloride. Bendamustine is an alkylating antitumor agent. The antitumor effects of bendamustine hydrochloride have been demonstrated by multiple *in vitro* studies in multiple tumor cell lines including breast cancer, non-small cell and small cell lung cancer and ovarian carcinoma.

The Applicant developed a 100 mg/4 mL presentation which is consistent with the listed drug, BELRAPZO™. Both the LD and the proposed product are supplied as sterile, clear, and colorless to yellow, RTD solutions packaged in multi-dose clear glass vials. The LD and the proposed product have the same indications, dosage form, route of administration, and dosing regimen but differ in terms of the qualitative and quantitative composition of the excipients. The current application contains no clinical data but instead relies on the Agency's determination of safety and efficacy for the listed drug, BELRAPZO™. Accordingly, approval of NDA 216078 from clinical, non-clinical and clinical pharmacology perspectives will be primarily based on publicly available information for BELRAPZO™.

3. Product Quality

Bendamustine hydrochloride (b) (4) is a small, achiral, BCS class 4 molecule that is manufactured and release tested by Baxter Oncology GmbH. of Germany. It is a white to off-white, slightly hygroscopic powder that is freely soluble in methanol and slightly soluble in isopropyl alcohol, acetonitrile, and tetrahydrofuran. The drug substance exhibits polymorphic behaviour and has a melting range of 151-154°C. (b) (4)

The applicant references DMF (b) (4) for the manufacture and control (b) (4) DMF (b) (4) was reviewed in conjunction with this NDA and was deemed adequate. The (b) (4) was included in the NDA. Based on the information provided, a (b) (4)-month retest period has been established by the drug substance manufacturer.

The drug product, Bendamustine HCl Injection,100 mg/4 mL (25 mg/mL) is a sterile, clear, and colorless to yellow ready-to-dilute solution in a multiple-dose clear glass vial. The drug product formulation is for the most part non-aqueous with each multi-dose vial of containing 100 mg bendamustine hydrochloride, (b) (4) mg alcohol, (b) (4) mg monothioglycerol in polyethylene glycol 400 and sodium hydroxide as needed for pH modification. All excipients are compendial grades and commonly used in the proposed dosage form. The formulation contains no novel excipients, overages or antimicrobial preservatives in the formulation.

The drug product is manufactured, and release tested by Baxter Oncology GmbH of Germany at a commercial batch size of (b) (4) A complete description of the manufacturing process is included in the submission. (b) (4) The manufacturing process employs standard operating procedures for this dosage form and includes well defined IPCs, CPPs and CQAs.

The container closure system for the drug product consists of three components: a glass vial, an (b) (4) closure and a flip off aluminum seal. The glass vials are comprised of USP (b) (4) 6 mL/20 mm dark amber tubular glass vial. The (b) (4) closure is a 20mm (b) (4), (b) (4) rubber stopper. The aluminum seal does not have direct contact with the solution and is therefore not considered a primary packaging component. The primary container closure system was deemed suitable for the intended use and the rubber closure was demonstrated to be compatible with the drug product based on stability and leachable and extractable studies.

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

NDA 216078 included 5 manufacturing, testing and packaging facilities all of which were considered adequate to perform the responsibilities listed in the NDA.

Overall Product Quality Recommendation: The Office of Pharmaceutical Quality (drug substance, drug product, drug process, microbiology, biopharmaceutics and facilities) recommends APPROVAL of NDA 216078. Based on the available real-time stability data, the applicant proposed, and the **OPQ accepts the expiration dating period of 18-months for the drug product when stored under refrigerated conditions (i.e. 2°C and 8°C) and protected from light**. Analogous to the LD, the proposed product is formulated to be diluted with either 0.9% Sodium Chloride Injection, USP or 2.5% Dextrose/0.45% Sodium Chloride Injection, USP. The final admixture is stable for 24 hours when stored refrigerated (2-8°C or 36- 46°F) or for (b) (4) hours when stored at room temperature (15-30°C or 59-86°F) (see USPI Section 2: DOSAGE AND ADMINISTRATION for infusate in-use period and storage partially used vials).

6. Clinical Pharmacology

n/a

7. Non-Clinical Pharmacology/Toxicology

The proposed product is a reformulation of the LD and the applicant is relying in part on the Agency's previous findings of safety and efficacy as described in the approved labeling for the LD. The active pharmaceutical ingredient (API), strength, dosage form, route of administration, dosing regimen, and indications sought for the proposed bendamustine HCl formulation and the LD are the same. The excipient profile of the proposed bendamustine HCl formulation and the LD differ.

The Applicant referenced published articles to assess the impact of the reformulation on blood compatibility in lieu of conducting nonclinical studies.

The Applicant's justification for the proposed level of Alcohol is acceptable. The Applicant's justifications for the proposed acceptance criteria for impurities exceeding the ICH Q3B(R2) qualification threshold and the permitted daily exposure of extractables/leachables from the container closure system are acceptable. The Applicant's reliance on the in vitro and in vivo genotoxicity, carcinogenicity, and reproductive toxicity information described in the approved labeling for the LD is acceptable. From the perspective of nonclinical pharmacology and toxicology, the proposed bendamustine HCl formulation recommended for approval for the proposed indications.

8. Clinical/Statistical-Efficacy

No clinical data was submitted for this NDA and efficacy was based on the Prescribing Information for the LD, BELRAPZO™ (bendamustine hydrochloride) Injection 100 mg/4 mL. Accordingly. the clinical team recommends granting tentative approval of NDA 216078.

9. Safety

Safety was based on the Prescribing Information for the Listed Drug BELRAPZO™.(bendamustine hydrochloride) Injection 100 mg/4 mL.

10. Advisory Committee Meeting **N/A**

11. Pediatrics N/A

12. Other Relevant Regulatory Issues N/A

13. Labeling

The USPI submitted by the Applicant was compared to and updated to align with the approved USPI for the listed drug, BELRAPZO™. . The final agreed upon labeling was submitted on 11 May 2022.

At the completion of labeling negotiations, the USPI was acceptable from the ADL and all review disciplines. The label was deemed to be compliant with Physician Labeling Rule (PLR) [including the Pregnancy and Lactation Labeling Rule (PLLR)] requirements; is consistent with labeling guidance recommendations and with CDER labeling policies; conveys the essential scientific information needed for safe and effective use of the drug; is clinically meaningful and scientifically

accurate; is a useful communication tool for health care practitioners, and is consistent with other USPI with the same active moiety, drug class, or similar indication.

While USPI is acceptable from the ADL standpoint, because of marketing exclusivity of the listed drug, this application is recommended for a tentative approval and the revision date at the end of the Highlights will remain as X/XXXX until this product receives full approval.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

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

The proposed product may be granted full approval once the exclusivity period has expired

- **Risk Benefit Assessment**

Please refer to NDA 208194.

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/s/

SHERITA D MCLAMORE
06/13/2022 09:34:12 PM