CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215331Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	10-Jun-2022
From	Sherita D. McLamore, Ph.D.
Subject	Cross-Discipline Team Leader (CDTL) Memo
NDA	215331
Type of Application	505(b)(2)
Applicant	MAIA Pharmaceuticals, Inc.
Date of Receipt	27-Sept-2021
PDUFA Goal Date	27-Jul-2021
Proposed Proprietary/Established Names	Bortezomib Injection
Dosage forms / Strength	Injection/3.5mg/3.5 mL and 3.5mg/1.4mL
Route of Administration	Intravenous (IV)
Proposed Indication(s)	•Indicated for the treatment of treatment of adult patients with multiple myeloma •Indicated for the treatment of adult patients treatment of adult patients with mantle cell lymphoma
Recommended:	**Approval**

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

- Clinical (Candis Morrison, Ph.D., CRNP)
- Clinal Pharmacology (Nan Zheng, Ph.D.)
- Pharmacology/Toxicology (Shwu-Luan Lee, Ph.D.)
- DEMPA (Nicole Iverson, Pharm. D., BCPS)
- Drug Product (William Adams, Ph.D.)
- Drug Substance (Rajan Pargani, Ph.D.)
- Microbiology (Jason God, Ph.D.)
- Manufacturing Process and Facilities (Caryn McNab, Ph.D.)
- Biopharmaceutics (Anitha Govada, Ph.D.)
- Labeling (Elizabeth Everhart)

1. Introduction

NDA 215331 was submitted for Bortezomib Injection 3.5mg/3.5mL and 3.5mg/1.4mL (1 mg/mL and 2.5 mg/mL) in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act. Bortezomib is a modified dipeptidyl boronic acid proteasome inhibitor. It is an antineoplastic agent that was originally approved under the brand name VELCADE® (bortezomib) 3.5mg/vial for the treatment of multiple myeloma and for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy under NDA 021602 in 2003. It is presented as a sterile lyophilized powder packaged in a clear single-use vial that must be reconstituted in either 1.4 mL of 0.9% sodium chloride injection for a nominal concentration of 3.5 mg/1.4 mL (2.5 mg/mL) for subcutaneous (SC) administration or 3.5 mL of 0.9% sodium chloride injection for a nominal concentration of 3.5 mg/3.5 mL (1 mg/mL) for intravenous (IV) administration.

The proposed, Bortezomib Injection, product is supplied as a refrigerated, ready-to-use (RTU), sterile solution in an (b) (4) single-dose vial for intravenous administration only. It is available in two presentations: 3.5 mg/1.4 mL (2.5 mg/mL) and 3.5 mg/3.5 (1 mg/mL) and is designed for intravenous administration without the need to reconstitute. The MAIA product is considered a "Pharmaceutical Alternative" as it is not pharmaceutically equivalent to the LD. The proposed product will differ from the LD in terms of its excipients and its RTU (ready to use) formulation. The active ingredient and strengths are the same as those of the LD upon reconstitution, which may reconstituted to either 1 mg/mL (intravenous or subcutaneous) or 2.5 mg/mL (subcutaneous). The proposed drug product will have the same indications, route of administration (IV only) and dosing regimen as the LD.

Unlike the LD which is approved for both intravenous (IV) and subcutaneous (SC) administration, the proposed product is only seeking approval for the IV route of administration.

The MDD for bortezomib is 1.3 mg/m^2 to be administered intravenously at a concentration of 1 mg/mL for nine 6-week treatment cycles. The bortezomib dosing regimen includes dosing weekly (days 1, 4, 8, 11, 22, 25 29 and 32) in cycles 1-4 and once weekly (days 1, 8, 22 and 29) in cycles 5-9.

No clinical studies were performed with the Accord formulation. Instead, this NDA relies on VELCADE® (bortezomib) for Injection, 3.5 mg/vial (NDA 021602) for safety and efficacy.

2. Background

This application presents a new formulation of bortezomib. Bortezomib is the first therapeutic proteasome inhibitor to be used in humans. Bortezomib is currently approved for initial treatment of patients with multiple myeloma, the retreatment of adult patients with multiple myeloma and the treatment of mantle cell lymphoma. The current application contains no clinical data but instead relies on the Agency's determination of safety and efficacy for the listed drug, VELCADE® which was previously approved for marketing under NDA 021602.

The new ready-to-use (RTU) formulation allows for an easier, less time-consuming preparation for practitioners. Accordingly, the focus of this new formulation was to develop stable ready-to-use liquid product.

3. Product Quality

Bortezomib is a modified dipeptidyl boronic acid proteasome inhibitor. It is a small chiral molecule that exists in its cyclic anhydride form as a trimeric boroxine; however, the boroxine is hydrolyzed to the monomeric boronic acid when exposed to an aqueous system. Bortezomib has a very low aqueous solubility and degrades in aqueous media. Bortezomib drug substance is manufactured and release tested (b) (4). applicant references DMF (b) (4) for all aspects pertaining to the manufacture and control of bortezomib drug substance; accordingly, limited information was included in the NDA. DMF (b) (4) was reviewed in conjunction with this application and deemed adequate to support the approval of the NDA.

Based on the information contained in the referenced DMF, a (b) (4) retest period has been established for the drug substance by the drug substance manufacturer.

The drug product, Bortezomib Injection 3.5 mg/1.4 mL (2.5 mg/mL) and 3.5 mg/3.5 mL (1 mg/mL) is supplied as a ready-to-use sterile solution. It is a presented as a clear, colorless solution filled in a clear, single-dose, glass vial. Each single dose vial contains the active together with Mannitol USP, Dimethyl Sulfoxide USP, Sodium Acetate USP, Water for Injection USP and Sodium Hydroxide NF/Hydrochloric Acid NF for pH adjustment. The drug product formulation does not contain antimicrobial preservatives, novel excipients, or overages and all excipients are compendial and within the IIG limits for the proposed route of administration.

The drug product is manufactured (b) (4) by Gland Pharma Limited of India (US agent listed) at a commercial batch sizes (b) (4) for the 3.5 mg/1.4 mL (2.5 mg/mL and 3.5 mg/3.5 mL (1 mg/mL) presentations, respectively. The manufacturing process was designed to ensure the sterility of the final product and the conformity to the release specifications. The manufacturing process is straight forward (b) (4) The validation information supporting the (b) (4) manufacturing demonstrates that the sterilization processes are controlled and are suitable for (b) (4) processing at the drug product manufacturing facilities.

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 information provided (formulation and physiochemical comparison) the review team concluded that the proposed product has the same indication and route of administration as the LD with comparable physicochemical properties. The pH and osmolality of the proposed drug product and the LD, after dilution (with 0.9 % sodium chloride injection, 1 mg/ml), are similar for the intravenous route of administration. Thus, the review team concluded that the disposition kinetics of bortezomib should be similar from the two products. 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 (b) (4) included 6 manufacturing, testing, and packaging facilities. At the time of review, all facilities associated with this application were considered adequate to perform the responsibilities listed in the NDA and are acceptable to support approval of this NDA.

Overall Product Quality Recommendation: The Office of Pharmaceutical Quality (drug substance, drug product, drug process, microbiology, biopharmaceutics and facilities) recommends APPROVAL of NDA 215331. Based on the available stability data, the applicant proposed, and the OPQ accepts the expiration dating period of **24-months** for the drug product when stored at stored under refrigerated conditions (i.e. 2°C and 8°C) and protected from light.

6. Clinical Pharmacology

The Applicant did not include any clinical pharmacology data to support this application but instead conducted an *in vitro* study to bridge formulation differences and requested a waiver for *in vivo* bioavailability and bioequivalence studies as per 21 CFR 320.22. As the biowaiver was granted a clinical pharmacology review was not warranted.

7. Non-Clinical Pharmacology/Toxicology

This NDA included one new toxicology study that was designed to investigate the hemolysis effect of the proposed product. Additionally, the formulation and the chemical evaluation of the drug product were reviewed, including the contents and levels of specified impurities and excipients, and the level of the (b) (4) dimethyl sulfoxide were evaluated.

The pharmacology/toxicology team concluded that there are no safety concerns identified with the related substances, residual solvents, excipients, vehicle and/or elemental impurities. The in vitro study was reviewed and demonstrated that the proposed product was void of hemolytic potential in human whole blood. As such, there are no outstanding pharmacology/toxicology issues and NDA 215331 is recommended from approval from a pharmacology/toxicology perspective.

8. Clinical/Statistical-Efficacy

The Applicant did not conduct human clinical studies in conjunction with NDA 215331 as this NDA relied on the safety and efficacy of the drug of the listed drug, VELCADE®. Based on the information provided, the clinical team recommends APPROVAL of NDA 215331.

9. Safety

Safety was based on the Prescribing Information for the listed drug VELCADE® (bortezomib) for Injection, 3.5 mg/vial.

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

11. Pediatrics N/A

12. Other Relevant Regulatory Issues N/A

13. Labeling

Overall Labeling Recommendation:

The label of this product is comparable to that of the LD. Labeling negotiations are ongoing at the time of this review.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

The review of this NDA was primarily based on product quality data. This product relies on the safety and effectiveness for the listed drug, VELCADE®, as there were no new clinical or nonclinical studies conducted for this 505(b)(2) application. The proposed product has the same active pharmaceutical ingredient, concentration, dosing regimen and indications but differs from the LD in terms of excipient profile and dosage form (ready-to-use solution vs. lyophilized powder).

Because all disciplines have recommended approval and because there are no outstanding issues precluding the approval of this application, the CDTL recommends full **APPROVAL** of NDA 215331.

- **Risk Benefit Assessment**

Please refer to NDA 021602

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/s/

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