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APPLICATION NUMBER:

215331Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	215331
Supporting document/s:	SDN 1
Applicant's letter date:	September 27, 2021
CDER stamp date:	September 27, 2021
Product:	Bortezomib (b) (4) Injection
Indication:	For the treatment of multiple myeloma and mantle cell lymphoma (MCL)
Applicant:	Maia Pharmaceuticals, Inc.
Review Division:	Division of Hematology Oncology Toxicology (DHOT) for Division of Hematologic Malignancies 2
Reviewer:	Shwu-Luan Lee, PhD
Supervisor/Team Leader:	Brenda Gehrke, PhD
Division Director:	John Leighton, DABT, PhD
Project Manager:	David Bac, PharmD

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1 Executive Summary

1.1 Recommendations

Recommending approval.

1.1.1 Approvability

There are no unresolved pharmacology/toxicology issues.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

The label of this product will be comparable to that of the listed drug, Velcade, for the pharmacology/toxicology related sections. See the approved label.

1.2 Brief Discussion of Nonclinical Findings

The efficacy and safety evaluation of Bortezomib (b) (4) Injection (Maia Pharmaceuticals, Inc.) relies on the FDA's previous finding of safety and effectiveness for the listed drug (LD), Velcade (NDA 021602), as described in the drug's approved labeling. One new toxicology study to investigate the hemolysis effect of Maia pharmaceutical's bortezomib was submitted to the current NDA.

Information regarding the formulation and the chemical evaluation of the drug product for Bortezomib (b) (4) Injection compared with the LD Velcade are summarized below. These items included the contents and levels of specified impurities and excipients, and the level of the (b) (4) dimethyl sulfoxide (DMSO). From a pharmacology/toxicology perspective, no safety concerns related to the specifications of the drug substance and drug product (related substances, residual solvents, excipients, and/or elemental impurities) have been identified. The in vitro study submitted and reviewed demonstrated that Maia's bortezomib injection was void of hemolytic potential in human whole blood.

There are no pharmacology/toxicology issues to preclude the approval of Bortezomib Injection.

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number

179324-69-7

2.1.2 Generic Name

Bortezomib

2.1.3 Code Name

ABZM

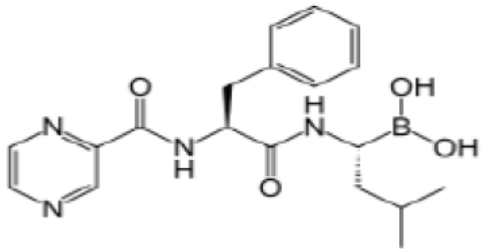
2.1.4 Chemical Name

[(1R)-3-Methyl-1-({(2S)-3-phenyl-2-[(pyrazin-2-yl carbonyl) amino]propanoyl} amino)butyl]boronic acid

2.1.5 Molecular Formula/Molecular Weight

$C_{19}H_{25}BN_4O_4$/384.24 (anhydrous); 402.24 (monohydrate)

2.1.6 Structure



2.1.7 Pharmacologic class

Proteasome inhibitor

2.2 Relevant IND/s, NDA/s, and DMF/s

NDA 021602 (Listed drug: Velcade, Millennium Pharmaceuticals, Inc)
DMF [redacted] (b) (4) for CMC of drug substance

Reviewer's note:
According to the Applicant, Maia's Bortezomib Injection 2.5 mg/mL has been developed as a generic equivalent to the LD Velcade (bortezomib) for injection (3.5 mg per vial), which is available as a lyophilized powder and manufactured by Millennium Pharmaceuticals, Inc; NDA 021602. The bortezomib drug substance was sourced (b) (4)

2.3 Drug Substance

The complete information for the drug substance is available in the DMF (b) (4) submitted to the FDA (b) (4).

Impurities

Table 1: Summary of Potential Impurities

(b) (4)

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Table 2: Summary of Specifications of Related Substance [redacted] Contents

[redacted] content by HPLC (% area)	In house	[redacted]	Not more than	[redacted]
Related substances by HPLC (% w/w)	In house	[redacted]	Not more than	[redacted]
		Any individual unspecified impurity	Not more than	
		Total impurities	Not more than	
Residual solvents by GC (ppm)	In house	[redacted]	Not more than	[redacted]

(Table from the Applicant, adapted based on Module 3, Section 3.2.S.4, Table 1)
Comment: The specifications are in line with the ICH Q3A and ICH Q3C guidance documents and are acceptable.

Residual solvents

Table 3: Residual Solvent Limit

[redacted]

Comment: The levels of the residual solvents are in line with ICH Q3C R(8).

Elemental impurities

The contents of elemental impurities in the drug substance (DS) batches were below the quantitation level (BOL) and in line with the ICH Q3D guidance. Due to the levels of elemental impurities in the DS being approximately [redacted]% lower than the control threshold (set as [redacted]% of Option 1 limits), and the amount of drug product administered per day is less than 10 grams (twice weekly at 1.3 [redacted] m^2/dose or 2.[redacted] dose based on

the body surface area of 2 m^2), the Applicant proposes that it is not necessary for the routine testing of the drug substance for elemental impurities.

2.4 Clinical Formulation

2.4.1 Drug Formulation

Drug product:
Bortezomib (b) (4) Injection is available in two dosage strengths: 3.5 mg/1.4 mL (2.5 mg/mL) and 3.5 mg/3.5 mL (1 mg/mL). The drug product is manufactured at Gland Pharma Ltd. (India).

A tabulated comparative summary of the ingredients and their functions for Maia's Bortezomib (b) (4) Injection, 1 and 2.5 mg/mL, is provided in the table below (from the Applicant; eCTD Module 3, Section 3.2.P.1).

Table 4: Quantitative Composition of Bortezomib (b) (4) Injection

Ingredient	Functions	2.5 mg/mL Presentation		1 mg/mL Presentation	
		Quantity/mL (mg)	Quantity/Vial (mg)	Quantity/mL (mg)	Quantity/Vial (mg)
Bortezomib	Active Ingredient	2.5	3.5	1.0	3.5
Mannitol USP	(b) (4)	25	35	10	35
Dimethyl Sulfoxide USP		22	30.8	20	70
Sodium Acetate (b) (4) USP		0.82	1.15	0.82	2.87
Hydrochloric acid NF		(b) (4)			
Sodium Hydroxide NF					
Water for Injection USP					
		(b) (4)			

(Table from the Applicant)

The evaluation of the excipients in the drug product was assessed by comparing with FDA's Inactive Ingredient Database (IID). As shown in the table below, the inactive

ingredients (excipients) are not the same as the listed drug Velcade (bortezomib) for Injection.

Table 5: Comparison of Ingredients in Maia's Product to the Listed Drug and FDA's IID

Ingredient	Quantity in Proposed 2.5 mg/mL Drug Product (mg)		Quantity in Proposed 1 mg/mL Drug Product (mg)		Quantity in Listed Drug Per Vial (mg)	IID Level (%)
	Per mL	Per Vial	Per mL	Per Vial		
Bortezomib	2.5	3.5	1.0	3.5	3.5	Not applicable
Mannitol USP	25	35	10	35	35	IV Injection, solution: (b) (4) mg/mL ((b) (4)% w/v)
Dimethyl Sulfoxide USP	22	30.8	20	70	-	No listing in IID for IV Injection, Solution*
Sodium Acetate (b) (4) USP	0.82	1.15	0.82	2.87	-	IV Injection, Solution: (b) (4) mg/mL ((b) (4)% w/v (b) (4) mg/mL (b) (4))
Hydrochloric Acid NF	q.s. for pH adjustment		q.s. for pH adjustment		-	IV Injection: ADJ PH
Sodium Hydroxide NF	q.s. for pH adjustment		q.s. for pH adjustment		-	IV Injection, solution: (b) (4) mg/mL ((b) (4)% w/v)
Water for Injection USP	(b) (4)				-	-

(Table from Applicant's Table 6, Section 3.2.P.2)

Specifications of Drug Product

Table 6: Justification of Specification (Drug Product)

Attribute	Specification (Shelf-Life)		Justification
Related Substances by HPLC (% w/w)	(b) (4)	NMT (b) (4)%	Based on ICH Q3B Qualification Threshold for a product with MDD (b) (4) mg. See Table 2 for a detailed comparison of the impurity specifications versus the USP PF monograph.
		NMT % NMT % NMT % NMT %	
	Any individual unspecified	NMT (b) (4)%	Based on ICH Q3B Identification Threshold for a product with MDD (b) (4) mg.

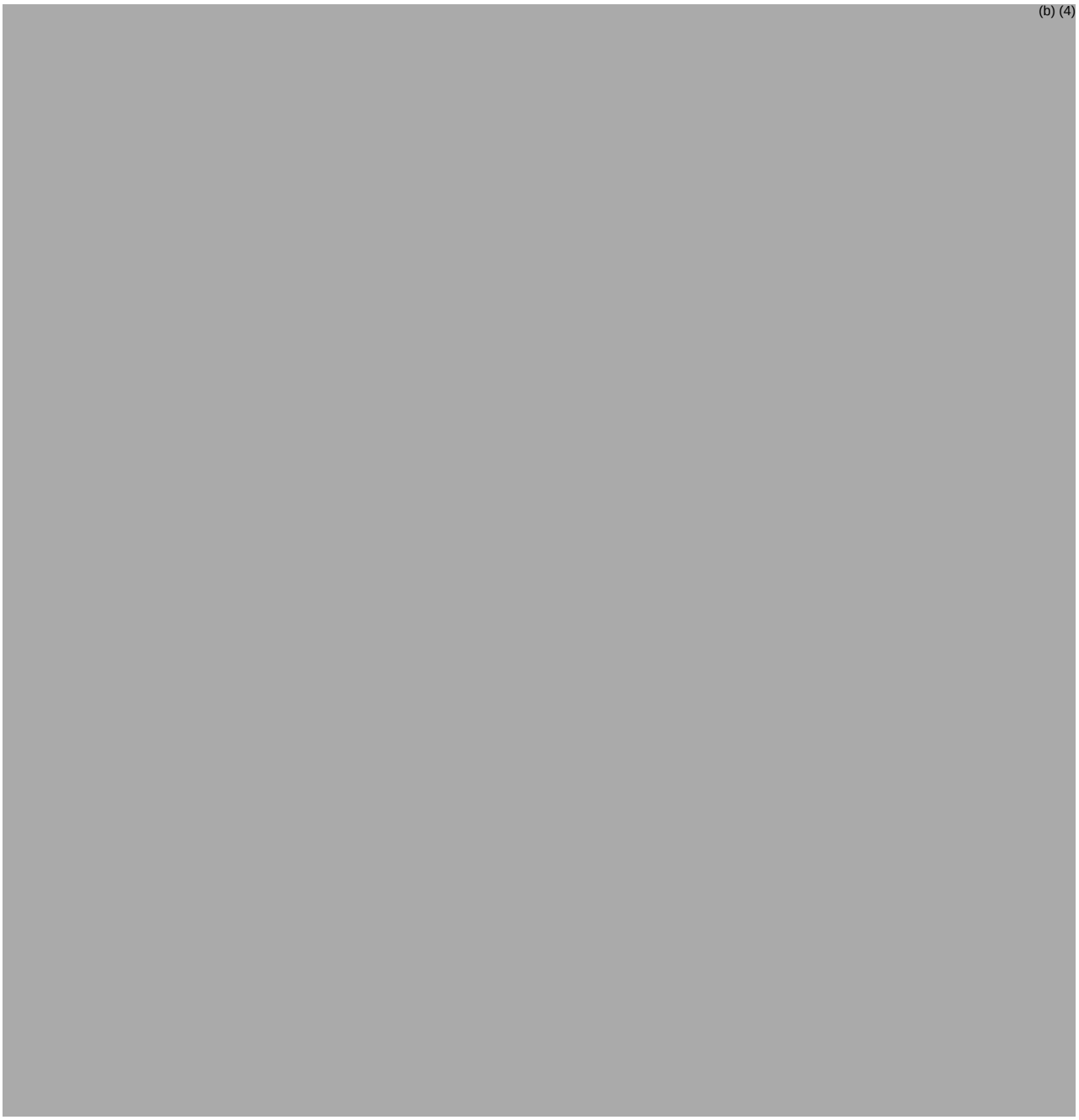
	Total	NMT (b) %	Based on USP PF monograph for the lyophilized drug product.
Osmolality*	2.5 mg/mL (b) (4) mOsmol/kg 1 mg/mL (b) (4) mOsmol/kg		Based on drug product development data
Elemental Impurities*	Complies with USP Requirements		Based on ICH Q3D/USP <232> requirements for parenteral product.
USP <1> for Injections*	Complies with USP Requirements		Based on USP <1> for Injections.
(b) (4)			

Table 2, as shown below Table 9 in the current NDA review.
(Table based on Applicant, excerpted from Table 1, Module 3, Section 3.2.P.5.1)

Comments on impurities:

Table 7: Bortezomib Injection Degradation Impurities

(b) (4)



Based on the recommended human dose of 1.3 mg/m^2, the maximum daily dose for bortezomib is 2.34 mg, using 1.8 m^2 as the body surface area. The proposed specification for an individual specified impurity in the drug product is NMT (b) (4) % and in line with the ICH Q3B threshold for the maximum daily dose at (b) (4) mg.

Elemental impurities
The elemental impurities content of the drug substance affects the elemental impurities content of the finished drug product. Since no detectable elemental impurities are in the drug substance, the content of elemental impurities in the drug product will not be remarkable.

According to the Applicant, no additive or colorant made of iron oxides is used in the formulation of Bortezomib (b) (4) Injection 1 mg/mL [3.5 mg/3.5 mL, 5mL vial] and 2.5 mg/mL [3.5 mg/1.4 mL, 2 mL vial], therefore, 21 CFR 73.1200 is not applicable.

Comments on excipients (b) (4):
Besides the API, the formulation contains mannitol (b) (4), dimethyl sulfoxide (DMSO) (b) (4), sodium acetate (b) (4), hydrochloric acid and/or sodium hydroxide for pH adjustment, and Water for Injection (b) (4).
(b) (4). Critical material attributes of the excipients employed in the formulation are controlled as per the relevant monographs in the USP/NF.

As summarized in Table 7 (above), the excipients (inactive ingredients) are at the same level as in the LD (where present in the LD) and/or below the levels indicated in FDA's IID. (b) (4)

(b) (4)

2.4.2 Comment on Novel Excipients

There are no novel excipients.

2.5 Proposed Clinical Population and Dosing Regimen

Clinical population: Identical to what has been described in the label for Velcade; briefly, for the treatment of adult patients with multiple myeloma (MM) and mantle cell lymphoma (MCL).

See the label of Bortezomib Injection for additional information.

2.6 Regulatory Background

Bortezomib has been well-studied and approved for multiple indications. The current NDA 215331 relies on the FDA's previous finding of safety for the listed drug Velcade (NDA 021602) and proposes similar indications as those for Velcade.

3 Studies Submitted

3.1 Studies Reviewed

- Special toxicology study:

Study #8441821 ((b) (4) Study #): Bortezomib (b) (4) injection: assessment of hemolytic potential using an in vitro test method with human whole blood (eCTD, Module 4)

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

Reviews Referenced

NDA 021602

Nonclinical supporting data
Pharmacology, pharmacokinetics/ADME/Toxicokinetics and toxicology studies of bortezomib were reviewed under NDA 021602.

10 Special Toxicology Studies

Study title: Bortezomib (b) (4) Injection: assessment of hemolytic potential using an in vitro test method with human whole blood

Study no.: (b) (4) Study No. 8441821
Study report location: eCTD, Module 4
Conducting laboratory and location: (b) (4)
Date of study initiation: June 16, 2020
*GLP compliance: Yes
*QA statement: Yes

Agents/Vehicles, lot #, and/or % purity

Agent	Batch/Lot Number	Purity
[a]Bortezomib (b) (4) Injection 1 mg/mL	BORDD1019	99.5%
[a]Bortezomib Injection 2.5 mg/mL	BORDD1019	100.9%
Reference article: Velcade (bortezomib) for Injection, 3.5 mg/vial	227919	Not available
Saline control (diluent for reference article) 0.9% sodium chloride for injection	05-139-DK	Not available

[a]The test article was provided as a pre-formulated solution at concentrations of 1 mg/mL and 2.5 mg/mL

Vehicle	Lot number	Composition
Vehicle 1: Placebo for Bortezomib (b) (4) Injection, 1 mg/mL	NB-20-008/66-B	10 mg/mL Mannitol, 20 mg/mL Dimethyl sulfoxide, 0.8 mg/mL Sodium Acetate Anhydrous; adjusted to pH (b) (4) with sodium hydroxide and/or hydrochloric acid, as applicable, q.s. to 1.0 mL with sterile water for injection (provided by the Sponsor)
Vehicle 2: Placebo for Bortezomib (b) (4) Injection, 2.5 mg/mL	NB-20-008/66-A	25 mg/mL Mannitol, 22 mg/mL Dimethyl sulfoxide, 0.8 mg/mL Sodium Acetate Anhydrous; adjusted to pH (b) (4) with sodium hydroxide and/or hydrochloric acid, as applicable, q.s. to 1.0 mL with sterile water for injection (provided by the Sponsor)

Key Study Findings

- At the bortezomib final concentration of 5000 ng/mL, the mean % hemolysis for Bortezomib (b) (4) Injection (1 mg/mL or 2.5 mg/mL product), Velcade (adjusted to 1 mg/mL or 2.5 mg/mL), and corresponding vehicles ranged between 0.17%-0.19% for the 1 mg/mL concentration and 0.15%-0.17% for the 2.5 mg/mL concentration.
- Under the study conditions, the Bortezomib (b) (4) Injection samples were considered negative for hemolysis.

Bortezomib (b) (4) Injection (1 mg/mL and 2.5 mg/mL bortezomib, test product), the reference product Velcade at corresponding concentrations, saline (negative control) and 1% saponin (positive control) were incubated with whole human blood (from a single donor) for 30-35 minutes at ~37 °C. To obtain the final concentration of bortezomib at 5000 ng/mL, 0.005 mL of 1 mg/mL Bortezomib (b) (4) Injection () or Velcade and 0.002 mL of 2.5 mg/mL Bortezomib (b) (4) Injection () or Velcade were each added to 0.5 mL of whole human blood and diluted to 1 mL (the final assay volume) with 0.9% saline.

The hemoglobin index (approximate hemoglobin content in mg/dL) of the supernatant was determined. The % hemolysis was calculated by comparing the hemoglobin content of the supernatant to that of the donor, after accounting for the sample dilution factor. Test samples were considered negative for hemolysis if the % hemolysis value was less than 10%, and positive for hemolysis if the % hemolysis value was greater than 25%.[5]

In the current study, the saline negative controls demonstrated % hemolysis values of less than 10%, while the Saponin positive controls resulted in >25% hemolysis, thus meeting the study acceptance criteria.

Results:

Table 9: Hemolytic Effects of Bortezomib (b) (4) Injections in Human Whole Blood

Treatment [Final bortezomib concentration in blood]	Hemoglobin (mg/dL) of Supernatant	% Hemolysis†
	Average ± Standard Deviation [Range]	Average ± Standard Deviation [Range]
Bortezomib Injection, 1 mg/mL [5000 ng/mL]	11.7 ± 3.2 [Range: 8 - 14]	0.18 ± 0.05 [Range: 0.13 – 0.22]
Bortezomib Injection Vehicle for 1 mg/mL presentation [Equivalent to 5000 ng/mL]	12.0 ± 0.0 [Range: All 12]	0.19 ± 0.00 [Range: All 0.19]
VELCADE, 1 mg/mL [5000 ng/mL]	11.0 ± 2.0 [Range: 9 - 13]	0.17 ± 0.03 [Range: 0.14 – 0.17]

[5] Amin and Dannenfelser, J Pharm Sci, 95(6), 1173-1176, 2006.

Treatment [Final bortezomib concentration in blood]	Hemoglobin (mg/dL) of Supernatant	% Hemolysis†
	Average ± Standard Deviation [Range]	Average ± Standard Deviation [Range]
Bortezomib Injection, 2.5 mg/mL [5000 ng/mL]	11.0 ± 0.0 [Range: All 11]	0.17 ± 0.00 [Range: All 0.17]
Bortezomib Injection Vehicle for 2.5 mg/mL presentation [Equivalent to 5000 ng/mL]	10.3 ± 0.6 [Range: 10 - 11]	0.16 ± 0.01 [Range: 0.16 – 0.17]
VELCADE, 2.5 mg/mL [5000 ng/mL]	9.7 ± 1.5 [Range: 8 - 11]	0.15 ± 0.02 [Range: 0.13 – 0.17]
0.9% Saline - Negative Control	9.3 ± 3.0 [Range: 9 - 10]	0.15 ± 0.01 [Range: 0.14 – 0.16]
1% Saponin - Positive Control	6359 ± 235.5 [Range: 6287 - 6428]	99.36 ± 1.1 [Range: 98.23 – 100.44]

† = Calculated using a dilution factor of 2 and Hb content of donor of 12,800 mg/dL.
(Table from the Applicant)

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