CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215331Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 6/13/22

To: David Bak, PharmD, BCNSP, Regulatory Project Manager, Division of Hematological Malignancies II (DHM2)

From: Jennifer Chen, PharmD, MBA, Regulatory Review Officer Office of Prescription Drug Promotion (OPDP)

CC: Jina Kwak, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for BORTEZOMIB injection, for intravenous use

NDA: 215331

In response to DHM2's consult request dated November 19, 2021, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for BORTEZOMIB injection, for intravenous use.

Labeling: OPDP's comments on the proposed PI are based on the draft labeling received by electronic mail from DHM2 (David Bak) on June 3, 2022, and we have no additional comments at this time.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 17, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Jennifer Chen at (301) 796-9398 or Jennifer.Chen@fda.hhs.gov.

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/s/

JENNIFER W CHEN
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 19, 2022
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 215331
Product Name and Strength:	Bortezomib Injection, 3.5 mg/3.5 mL (1 mg/mL) and 3.5 mg/1.4 mL (2.5 mg/mL)
Applicant/Sponsor Name:	MAIA Pharmaceuticals, Inc.
OSE RCM #:	2021-1906-1
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on May 17, 2022 for Bortezomib Injection. We reviewed the revised container labels and carton labeling for Bortezomib Injection (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Iverson, N. Label and Labeling Review for Bortezomib Injection (NDA 215331). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 APR 12. RCM No.: 2021-1906.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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05/19/2022 10:11:08 AM

HINA S MEHTA
05/23/2022 10:32:26 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 12, 2022
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 215331
Product Name, Dosage Form, and Strength:	Bortezomib Injection, 3.5 mg/3.5 mL (1 mg/mL) and 3.5 mg/1.4 mL (2.5 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	MAIA Pharmaceuticals, Inc.
FDA Received Date:	September 27, 2021, October 14, 2021, and March 21, 2022
OSE RCM #:	2021-1906
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the approval process for Bortezomib Injection, this review evaluates the proposed Bortezomib Prescribing Information, container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

MAIA Pharmaceuticals, Inc. submitted a 505(b)(2) NDA to obtain marketing approval for Bortezomib Injection. The Listed Drug (LD) for this product is Velcade (bortezomib) for Injection. Velcade for Injection is currently approved as a 3.5 mg lyophilized powder for intravenous or subcutaneous use for the treatment of adult patients with multiple myeloma and mantle cell lymphoma. The recommended starting dose of Velcade is 1.3 mg/m^2, it is available in a 3.5 mg vial for injection, and it can be administered intravenously at a concentration of 1 mg/mL and subcutaneously at a concentration of 2.5 mg/mL.

We note that the proposed Bortezomib Injection has the same dosage regimen (1.3 mg/m^2 dose) as the LD Velcade. However, there are differences in the proposed presentation as Bortezomib Injection will be available as a solution in 3.5 mg/1.4 mL and 3.5 mg/3.5 mL single

dose vials; unlike the listed drug Velcade which is a 3.5 mg lyophilized powder requiring reconstitution. Both Bortezomib Injection and Velcade (when reconstituted) have the same final concentration (1 mg/mL and 2.5 mg/mL). However, the proposed Bortezomib Injection will be for intravenous use only and administered at a concentrations of 1 mg/mL and 2.5 mg/mL, whereas the LD Velcade is only administered intravenously at a concentration of 1 mg/mL and subcutaneously at a concentration of 2.5 mg/mL. See Appendix A for product characteristics comparison of the LD Velcade (NDA 021602) and the proposed Bortezomib Injection product (NDA 215331).

From a medication error perspective, the introduction of a solution of Bortezomib Injection that can be administered intravenously at a concentration of 1 mg/mL and 2.5 mg/mL, may result in administration errors if the product is inadvertently administered subcutaneously using a concentration of 2.5 mg/mL as the LD Velcade. We sent an Information Request to clarify the risk mitigation strategies the Applicant will utilize to address the risk of medication error due to inappropriate product substitution. MAIA Pharmaceuticals, Inc. responded on March 21, 2022 that the proposed labels and labeling include prominence of the route of administration, cautionary statements, strength, and important product information.[a] See Appendix F for full information request.

We also note the proposed Bortezomib Injection labeling does not include sticker labels for the route of administration that can be applied after preparation. We performed a risk assessment of the proposed container label, carton labeling, and Prescribing Information to determine whether there are significant concerns in terms of safety related to preventable medication errors. We note areas of the proposed labels and labeling that could be revised to improve clarity and readability of important information. For the Division, we note the Dosage and Administration section lacks clarity, incorrect terminology for hazardous drugs, and the product strength is not in accordance with USP General Chapter <7>, Labeling. For the Applicant, we note missing handling information, lack of prominence between the strength statement and route of administration, and increased prominence of the net quantity statement. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

[a] Bortezomib (b) (4) Injection 1 mg/mL, 2.5 mg/ mL. NDA Number: 215331, Sequence Number: 0006. DMEPA INFORMATION REQUEST. Princeton (NJ): MAIA Pharmaceuticals Inc. 2022 MAR 21. Available from \\CDSESUB1\evsprod\nda215331\0006\m1\us\12-cover-letters\cover-letter-0006.pdf

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed container labels, carton labeling, and PI that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for MAIA Pharmaceuticals, Inc. to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 2 (DHM 2)

A. Highlights of Prescribing Information

1. Dosage and Administration Section

a. The Dosage and Administration section lacks clarity; therefore we recommend the following revisions:

i. Revise the statement, [redacted] (b) (4) to "For intravenous use only."

ii. Revise the statement, [redacted] (b) (4) to "The recommended starting dose of Bortezomib Injection is 1.3 mg/m^2 administered as a 3 to 5 second bolus intravenous injection." as this product is indicated for intravenous use only."

2. Dosage Forms and Strengths

a. As currently presented, the statement does not contain the strength. We recommend revising to:

Injection:

- 3.5 mg/3.5 mL (1 mg/mL) in a single-dose vial
- 3.5 mg/1.4 mL (2.5 mg/mL) in a single-dose vial

B. Prescribing Information

1. Dosage and Administration Section

a. Section 2.1 Important Dosing Guidelines

i. The Dosage and Administration section lacks clarity; therefore we recommend the following revisions:

a. Revise the statement, [redacted] (b) (4) to "Administer Bortezomib

Injection as a 3 to 5 second bolus intravenous injection." as this product is indicated for intravenous use only."

b. Section 2.9 Administration Precautions

i. We recommend revising the statement, [redacted] to "Bortezomib Injection is a hazardous drug." to align with current terminology used in labeling.

ii. We recommend revising the statement, [redacted] to "The drug quantity contained in one vial may exceed the usual dose required. " for added clarity.

c. Section 2.10 Instructions for Administration

i. Bortezomib Injection should be administered intravenously, therefore, we recommend revising the title of Section 2.10 to "Instructions for Intravenous Administration" for added clarity.

ii. We recommend revising the bulleted statements, [redacted] to "1 mg/mL concentration vial" and "2.5 mg/mL concentration vial" for clarity.

iii. We recommend clarifying room temperature stability for storage of unopened vials as follows, "Unopened vials may be stored room temperature at 20° to 25°C (68° to 77°F) for up to [redacted] prior to use."

2. Dosage Forms and Strengths

a. As currently presented, the statement does not contain the strength. We recommend revising to:

Injection: Bortezomib Injection is a clear, colorless to slightly yellow sterile solution available as:

- 3.5 mg/3.5 mL (1 mg/mL) in a single-dose vial
- 3.5 mg/1.4 mL (2.5 mg/mL) in a single-dose vial

3. How Supplied/Storage and Handling

a. The product strength is not expressed as a total quantity per total volume followed by the concentration per mL. The product strength should be expressed as the quantity per total volume followed by the quantity per milliliter (mL), as described in USP General Chapter <7>, Labeling. We

recommend revising the statement, (b) (4) [redacted] to "Bortezomib Injection is a clear, colorless to slightly yellow ready-to-use, sterile solution supplied as individually cartoned 5 mL vials containing 3.5 mg/3.5 mL (1 mg/mL) or 2 mL vials containing 3.5 mg/1.4 mL (2.5 mg/mL) of Bortezomib Injection." in accordance with USP General Chapter <7>.

b. We recommend revising the statement, (b) (4) [redacted] to "Follow guidelines for handling and disposal for hazardous drugs, including the use of gloves and other protective clothing to prevent skin contact." to align with current terminology used in labeling.

4.2 RECOMMENDATIONS FOR MAIA PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. Since Bortezomib Injection is a hazardous drug and requires special handling and disposal procedures. We recommend adding the statement, "CAUTION: Hazardous Agent" in bold red font on the principal display panel of the container labels and carton labeling.

2. We recommend relocating the statement, "Ready-to-use Vial" beneath the route of administration as this information appears more prominent than the strength.

3. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date.

4. There is lack of adequate differentiation between the colors utilized for the 3.5 mg/1.4 mL strength [redacted]. The listed drug uses [redacted] to highlight the subcutaneous route of administration. As the proposed product is for intravenous administration only using [redacted] color may cause confusion. . Therefore, we recommend revising the color scheme of 3.5 mg/1.4 mL strength to appear in its own unique color.

5. The strength statements (3.5 mg/3.5 mL and 3.5 mg/1.4 mL) lack prominence as the concentration per mL does not appear in the colored box (e.g. [redacted]). Lack of prominence of the entire strength statement may contribute to product selection medication errors. We recommend including the concentration per mL in the colored box directly beneath the total strength per total concentration statement for increased prominence.

6. The net quantity statement, "One Single-Dose Vial. Discard Unused Portion." is in close proximity to the product strength. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. We recommend relocating the net quantity statement away from the product strength beneath the route of administration on the principal display panel.

7. We recommend bolding the storage statement "Store refrigerated at 2 to 8°C (36° to 46°F)." to bring prominence to this important information.

8. The Rx Only statement appears prominent on the principal display panel. Decrease the prominence by debolding the Rx Only statement.

B. Container label for 3.5 mg/3.5 mL

1. We recommend revising the statement, [redacted] to "Contents: Each mL of Bortezomib Injection contains 1 mg of bortezomib, 10 mg mannitol, 0.82 mg sodium acetate, 20 mg dimethyl sulfoxide, and Water for Injection."

2. As currently presented, the placeholder, [redacted] is located in close proximity to the lot number, which could lead to confusion. Numbers or codes located in close proximity to the lot number may be mistaken as the lot number. We recommend deleting or relocating the placeholder, [redacted]

elsewhere so that the placeholder, [redacted] (b) (4) is not located in close proximity to the lot number.

C. Carton labeling 3.5 mg/1.4 mL

1. We recommend revising the statement, [redacted] (b) (4) to "Contents: Each mL of Bortezomib Injection contains 2.5 mg of bortezomib, 25 mg mannitol, 0.82 mg sodium acetate, 22 mg dimethyl sulfoxide, and Water for Injection."

D. Carton labeling 3.5 mg/3.5 mL

1. See C.1 and revise the carton labeling accordingly.

E. Sticker label

1. The LD Velcade has stickers that indicates the route of administration which are provided with each bortezomib for injection vial. These stickers should be placed directly on the syringe once the product is prepared to help alert practitioners of the correct route of administration. Due to postmarket reports of incorrect route of administration with bortezomib for injection, we recommend that you include similar stickers indicating the route of administration (intravenous) with each vial of Bortezomib Injection.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bortezomib received on October 14, 2021 from MAIA Pharmaceuticals, Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Bortezomib and the Listed Drug		
Product Name	Bortezomib For Injection	Velcade[b]
Initial Approval Date	N/A	May 13, 2003
Active Ingredient	bortezomib	bortezomib
Indication	• For the treatment of patients with multiple myeloma • Treatment of adult patients with mantle cell lymphoma	• For the treatment of patients with multiple myeloma • For the treatment of patients with mantle cell lymphoma
Route of Administration	Intravenous	Subcutaneous and intravenous
Dosage Form	Injection	For Injection
Strength	3.5 mg/1.4 mL (2.5 mg/mL), 3.5 mg/3.5 mL (1 mg/mL)	3.5 mg/vial

[b] Velcade [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2021 NOV 04. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021602s046lbl.pdf

Dose and Frequency	The recommended starting dose of Bortezomib for Injection is 1.3 mg/m^2. Untreated Multiple Myeloma Bortezomib Injection is administered in combination with oral melphalan and oral prednisone for 9, six-week treatment cycles. In Cycles 1 to 4, Bortezomib for Injection is administered twice weekly (Days 1, 4, 8, 11, 22, 25, 29, and 32). In Cycles 5 to 9, Bortezomib for Injection is administered once weekly (days 1, 8, 22, and 29). At least 72 hours should elapse between consecutive doses of Bortezomib Injection. Untreated Mantle Cell Lymphoma Bortezomib Injection is administered intravenously in combination with intravenous rituximab, cyclophosphamide, doxorubicin, and oral prednisone (VcR-CAP) for 6, three week treatment cycles. Bortezomib Injection is administered first followed by rituximab. Bortezomib Injection is administered twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a ten day rest period on Days 12 to 21. For patients with a response first documented at cycle 6, two additional VcR-CAP cycles are recommended. At least 72 hours should elapse between consecutive doses of Bortezomib Injection. Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma Bortezomib Injection (1.3 mg/m^2/dose) is administered twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a ten-day rest period (Days 12 to 21). For extended therapy of more than eight cycles, Bortezomib Injection may be administered on the standard schedule, or, for relapsed multiple myeloma, on a maintenance schedule of once weekly for four weeks (Days 1, 8, 15, and 22) followed by a	The recommended starting dose of Velcade is 1.3 mg/m^2. Untreated Multiple Myeloma Velcade is administered in combination with oral melphalan and oral prednisone for 9, six-week treatment cycles. In Cycles 1 to 4, Velcade is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29, and 32). In Cycles 5 to 9, Velcade is administered once weekly (days 1, 8, 22, and 29). At least 72 hours should elapse between consecutive doses of Velcade. Untreated Mantle Cell Lymphoma Velcade is administered intravenously in combination with intravenous rituximab, cyclophosphamide, doxorubicin, and oral prednisone (VcR-CAP) for 6, three week treatment cycles. Velcade is administered first followed by rituximab. Velcade is administered twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a ten day rest period on Days 12 to 21. For patients with a response first documented at cycle 6, two additional VcR-CAP cycles are recommended. At least 72 hours should elapse between consecutive doses of Velcade. Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma Velcade (1.3 mg/m^2/dose) is administered twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a ten day rest period (Days 12 to 21). For extended therapy of more than eight cycles, Velcade may be administered on the standard schedule or, for relapsed multiple myeloma, on a maintenance schedule of once weekly for four weeks (Days 1, 8, 15, and 22) followed by a 13 day rest period (Days 23 to 35). At least 72 hours should elapse between consecutive doses of Velcade. Patients with multiple myeloma who have previously responded to treatment with Velcade (either alone or in combination) and who have relapsed at least six months after their prior Velcade therapy may be started

	13-day rest period (Days 23 to 35). At least 72 hours should elapse between consecutive doses of Bortezomib Injection. Patients with multiple myeloma who have previously responded to treatment with Bortezomib Injection (either alone or in combination) and who have relapsed at least six months after their prior bortezomib therapy may be started on Bortezomib Injection at the last tolerated dose. Retreated patients are administered Bortezomib Injection twice weekly (Days 1, 4, 8, and 11) every three weeks for a maximum of eight cycles. At least 72 hours should elapse between consecutive doses of Bortezomib Injection. Bortezomib Injection may be administered either as a single agent or in combination with dexamethasone.	on Velcade at the last tolerated dose. Retreated patients are administered Velcade twice weekly (Days 1, 4, 8, and 11) every three weeks for a maximum of eight cycles. At least 72 hours should elapse between consecutive doses of Velcade. Velcade may be administered either as a single agent or in combination with dexamethasone .
How Supplied	Bortezomib Injection is supplied as individually cartoned 5 mL vials containing 3.5 mg/mL (1 mg/mL) or 2 mL vials containing 3.5 mg/1.4 mL (2.5 mg/mL) of Bortezomib Injection.	Velcade (bortezomib) for Injection is supplied as individually cartoned 10 mL vials containing 3.5 mg of bortezomib as a white to off-white cake or powder.
Instructions for Reconstitution	N/A	See Table A
Storage	Store Bortezomib Injection in a refrigerator at 2 to 8°C (36° to 46°F) in the original package to protect from light. Once removed from refrigeration, Bortezomib Injection may be stored at room temperature 20° to 25°C (68° to 77°F) for up to (b) (4).	Unopened vials may be stored at controlled room temperature 25°C (77°F); excursions permitted from 15° to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. Retain in original package to protect from light.

Table A: Instruction for Reconstitution of listed drug, Velcade

Route of Administration	Bortezomib Injection(mg/vial)	Diluent (0.9% Sodium Chloride)	Final Bortezomib Concentration (mg/mL)
Intravenous	3.5 mg	3.5 mL	1 mg/mL
Subcutaneous	3.5 mg	1.4 mL	2.5 mg/mL

APPEARS THIS WAY IN ORIGINAL

APPENDIX F. INFORMATION REQUEST

FDA Information Request: We note the proposed Bortezomib Injection will be administered intravenously at a concentration of 1 mg/mL and 2.5 mg/mL. We note this differs from the listed drug, Velcade for Injection, as the 2.5 mg/mL concentration is for subcutaneous administration only. We are concerned about the risk of medication errors if the proposed Bortezomib Injection 2.5 mg/mL is inadvertently substituted for Velcade for Injection and administered subcutaneously. We request you submit your risk mitigation strategies to address the risk of medication error due to inappropriate product substitution.

Applicant Response received on March 21, 2022: See
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APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Bortezomib labels and labeling submitted by MAIA Pharmaceuticals, Inc..

- Container labels received on October 14, 2021
- Carton labeling received on October 14, 2021
- Prescribing Information (Image not shown) received on October 14, 2021, available from \\CDSESUB1\evsprod\nda215331\0002\m1\us\114-labeling\draft\labeling\bortezomib(b) (4)-pi.pdf

G.2 Label and Labeling Images

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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