

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209191Orig1s000

OTHER REVIEW(S)

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:	April 8, 2022
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 209191
Product Name and Strength:	Bortezomib for Injection, 1 mg/vial, 2.5 mg/vial
Applicant/Sponsor Name:	Hospira, Inc.
OSE RCM #:	2021-1345-3
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

As part of the approval process for Bortezomib for Injection, 1 mg/vial and 2.5 mg/vial, this review evaluates the proposed Prescribing Information (PI), container labels, and carton labeling, and sticker labels. DMEPA had made recommendations during previous label and labeling reviews.^{a,b,c}

1.1 REGULATORY HISTORY

Hospira submitted Bortezomib for Injection (NDA 209191) on June 30, 2016. The application received a Tentative Approval letter on April 26, 2017 due to patent protection of the listed drug, Velcade (NDA 021602) upon which the application relies. Hospira submitted a request for final approval of Bortezomib for Injection (NDA 209191) on September 7, 2017. The application received a Complete Response on November 3, 2017 due to facility inspection issues. On December 22, 2017, Hospira submitted a Complete Response Amendment resubmission

^a Iverson N. Label and Labeling Review for Bortezomib (NDA 209191). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 OCT 14. RCM No.: 2021-1345.

^b Iverson N. Label and Labeling Review for Bortezomib (NDA 209191). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 NOV 22. RCM No.: 2021-1345-1.

^c Iverson N. Label and Labeling Review for Bortezomib (NDA 209191). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2017 OCT 12. RCM No.: 2021-1345-2.

request for full approval. However, the application received a Complete Response on February 22, 2018 due to product quality issues.

Hospira received final approval of Bortezomib for Injection (NDA 209191) on July 12, 2018 for the 2.5 mg/vial strength. Subsequently, Hospira received approval of supplemental NDA 209191/S-001 on December 28, 2018 which, included the addition of a new vial strength presentation of 1 mg/vial. Following a final judgement issued on October 10, 2019, the Agency converted the final approval of NDA 209191 to a tentative approval due to patent protection of the listed drug, Velcade (NDA 021602) upon which the application relies. On June 30, 2021, Hospira resubmitted Bortezomib for Injection (NDA 209191) and received tentative approval on December 17, 2021. Hospira submitted a request for final approval of Bortezomib for Injection (NDA 209191) on March 2, 2022.

2 CONCLUSION

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

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Office of Oncologic Diseases Associate Director for Labeling Review of the Prescribing Information

Product Title	Bortezomib For Injection
Applicant	Hospira Inc.
Application/Supplement Number	NDA 209191
Type of Application/Submission ¹	505(b)(2) NDA
Is Proposed Labeling in “Old” Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Proposed Indication(s)	<ul style="list-style-type: none"> • Treatment of adult patients with multiple myeloma • Treatment of adult patients with relapsed mantle cell lymphoma
Approved Indication(s)	N/A
Date FDA Received Application	March 2 2022
Review Classification (Priority/Standard)	Standard
PDUFA Goal Date	May 2, 2022
Review Date	April 11, 2022
Reviewer	Elizabeth Everhart, MSN, RN, ACNP

This Associate Director for Labeling (ADL) review provides recommendations on the content and format of the United States Prescribing Information (USPI) to help ensure that the USPI:

- Is compliant with Physician Labeling Rule (PLR) [including the Pregnancy and Lactation Labeling Rule (PLLR)] requirements,²
- Is consistent with labeling guidance recommendations³ and with CDER labeling policies, as appropriate,
- 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, as appropriate

The applicant submitted a 505(b)(2) NDA for Bortezomib for Injection; Velcade (bortezomib) NDA 021601 is the listed drug for this NDA; this product has the same active and inactive ingredients. The applicant received a Tentative Approval on 12/17/2021 due to unexpired patents and exclusivity of the listed drug. The applicant has resubmitted the application requesting full approval at this time due

¹ Examples include: Original Biologics License Application (BLA), New Molecular Entity (NME) NDA, Original NDA, NDA Efficacy Supplement, 505(b)(2) New Drug Application (NDA), New Chemical Entity (NCE) NDA, NDA Prior Approval Labeling Supplement, NDA CBE-0 Labeling Supplement

² See [January 2006 Physician Labeling Rule](#); 21 CFR [201.56](#) and [201.57](#); and [December 2014 Pregnancy and Lactation Labeling Rule](#) (the PLLR amended the PLR regulations). For applications with labeling in non-PLR “old” format, see 21 CFR [201.56\(a\) and \(e\)](#) and [201.80](#).

³ See [Prescription Drug Labeling Resources](#) website for PLR labeling guidances. When final, guidances represent the FDA’s current thinking on a topic. Applicants can use an alternative approach if it satisfies statutory and regulatory requirements.

to impending expiration of the patents and exclusivity.

The USPI submitted by the applicant was compared to the USPI attached to the tentative approval letter dated 12/17/2021. In the Highlights of the USPI, an extra space between the product title and initial year of approval was removed by the FDA. An edit to correct the subsection 6.1 title in the Table of Contents from "Clinical Trial Safety Experience" to "Clinical Trial Experience" was made by FDA, as well as the addition of a missing cross reference in section 5.5. The revision date at the end of the Highlights was also updated to reflect the month and year of full approval. No further edits were proposed by the applicant or the FDA.

After the conclusion of labeling negotiations, the USPI is acceptable from the ADL standpoint.

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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:	December 15, 2021
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 209191
Product Name and Strength:	Bortezomib for Injection, 1 mg/vial, 2.5 mg/vial
Applicant/Sponsor Name:	Hospira, Inc.
OSE RCM #:	2021-1345-2
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on December 10, 2021 for Bortezomib. We reviewed the revised container label and carton labeling for Bortezomib (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made for the 1 mg and 2.5 mg carton labeling and the 2.5 mg container label 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. We found the 1 mg container label and sticker labels acceptable in our last review.

^a Iverson, N. Label and Labeling Review for Bortezomib (NDA 209191). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 NOV 22. RCM No.: 2021-1345-1.

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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:	November 22, 2021
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 209191
Product Name and Strength:	Bortezomib for Injection, 1 mg/vial, 2.5 mg/vial
Applicant/Sponsor Name:	Hospira, Inc.
OSE RCM #:	2021-1345-1
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 November 19, 2021 for Bortezomib. We reviewed the revised container labels and carton labeling for Bortezomib (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 revised container label and carton labeling are unacceptable from a medication error perspective because they contain terminology inconsistent with the Prescribing Information.

3 RECOMMENDATIONS FOR HOSPIRA, INC.

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

A. Container label and carton labeling

1. We recommend revising the statement on the side panel, "Protect from light (b) (4)." to "Protect from light (see Prescribing Information)." to be consistent with the Prescribing Information.

^a Iverson, N. Label and Labeling Review for Bortezomib (NDA 209191). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 OCT 14. RCM No.: 2021.1345.

B. Carton labeling

1. We recommend revising the statement of the side panel of the carton labeling, “Reconstitution: See back of the carton [REDACTED] (b) (4)” to “Reconstitution: See back of the carton or Prescribing Information.” to be consistent with the Prescribing Information.

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Office of Oncologic Diseases Associate Director for Labeling Review of the Prescribing Information

Product Title	Bortezomib For Injection
Applicant	Hospira Inc.
Application/Supplement Number	NDA 209191
Type of Application/Submission ¹	505(b)(2) NDA
Is Proposed Labeling in “Old” Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Proposed Indication(s)	<ul style="list-style-type: none"> • Treatment of adult patients with multiple myeloma • Treatment of adult patients with relapsed mantle cell lymphoma
Approved Indication(s)	N/A
Date FDA Received Application	June 30, 2021
Review Classification (Priority/Standard)	Standard
PDUFA Goal Date	December 30, 2021
Review Date	November 10, 2021
Reviewer	Elizabeth Everhart, MSN, RN, ACNP; ADL (acting)

This Associate Director for Labeling (ADL) review provides recommendations on the content and format of the United States Prescribing Information (USPI) to help ensure that the USPI:

- Is compliant with Physician Labeling Rule (PLR) [including the Pregnancy and Lactation Labeling Rule (PLLR)] requirements,²
- Is consistent with labeling guidance recommendations³ and with CDER labeling policies, as appropriate,
- 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, as appropriate

The applicant submitted a 505(b)(2) NDA for Bortezomib for Injection; Velcade (bortezomib) NDA 021601 is the listed drug for this NDA; this product has the same active and inactive ingredients.

The applicant is seeking approval of the multiple myeloma and the relapsed mantle cell lymphoma indications and dosage regimens, but as there are

¹ Examples include: Original Biologics License Application (BLA), New Molecular Entity (NME) NDA, Original NDA, NDA Efficacy Supplement, 505(b)(2) New Drug Application (NDA), New Chemical Entity (NCE) NDA, NDA Prior Approval Labeling Supplement, NDA CBE-0 Labeling Supplement

² See [January 2006 Physician Labeling Rule](#); 21 CFR [201.56](#) and [201.57](#); and [December 2014 Pregnancy and Lactation Labeling Rule](#) (the PLLR amended the PLR regulations). For applications with labeling in non-PLR “old” format, see 21 CFR [201.56\(a\) and \(e\)](#) and [201.80](#).

³ See [Prescription Drug Labeling Resources](#) website for PLR labeling guidances. When final, guidances represent the FDA’s current thinking on a topic. Applicants can use an alternative approach if it satisfies statutory and regulatory requirements.

unexpired patents and exclusivity, and this NDA will receive a Tentative Approval at this time.

The USPI submitted by the applicant was compared to the approved USPI for the listed drug, Velcade. Edits were made to the title of this product since it does not have a proposed proprietary name. Throughout the USPI, when referring to this product, the title was changed to Bortezomib for Injection; when referring to the listed drug, the product was referred to as bortezomib. Additional updates to the USPI were made to align with recent updates to the listed drug, as well as to align with current labeling practices and to correct some formatting issues. Please see the attached label with tracked changes and edits/comments for further information.

After the conclusion of labeling negotiations, the USPI is acceptable from the ADL standpoint.

Attachment: Revised labeling with track changes edits and bubble comments explaining the revisions.

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

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

Memorandum

Date: November 4, 2021

To: Laura Wall, MS, APHN, Regulatory Project Manager
Division of Hematological Malignancies II (DHM2)

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

CC: Kathleen Klemm, PharmD, RAC, Deputy Director, OPDP

Subject: OPDP Labeling Comments for BORTEZOMIB FOR INJECTION, for
subcutaneous or intravenous use

NDA: 209191

In response to DHM2 consult request dated August 5, 2021, OPDP has reviewed the proposed product labeling (PI) for the NDA resubmission for BORTEZOMIB FOR INJECTION, for subcutaneous or intravenous use (Bortezomib), submitted pursuant to section 505(b)(2).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DHM2 (Laura Wall) on October 26, 2021, and we have no additional comments at this time.

Thank you for your consult. If you have any questions, please contact Adesola Adejuwon at (240) 402-5773 or Adesola.Adejuwon@fda.hhs.gov.

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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:	October 14, 2021
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 209191
Product Name, Dosage Form, and Strength:	Bortezomib for Injection, 1 mg/vial, 2.5 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Hospira, Inc.
FDA Received Date:	June 30, 2021
OSE RCM #:	2021-1345
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 of the 505(b)(2) NDA class II resubmission for Bortezomib for Injection, we reviewed the proposed Bortezomib Prescribing Information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Hospira received final approval of Bortezomib for Injection (NDA 209191) on July 12, 2018 for the 2.5 mg/vial strength. Subsequently, Hospira received approval of supplemental NDA 209191/S-001 on December 28, 2018 which, included the addition of a new vial strength presentation of 1 mg/vial. Following a final judgement issued on October 10, 2019, the Agency converted the final approval of NDA 209191 to a tentative approval due to patent protection of the listed drug, Velcade (NDA 021602) upon which the application relies.

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
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
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

Hospira, Inc. submitted a 505(b)(2) NDA to obtain marketing approval of Bortezomib for 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/m² and it can be administered intravenously at a concentration of 1 mg/mL and subcutaneously at a concentration of 2.5 mg/mL.

Both the proposed Bortezomib for Injection and LD Velcade (when reconstituted) have the same final concentration when administered intravenously (1 mg/mL) and subcutaneously (2.5 mg/mL), but differ in terms of how much diluent is required to prepare the final concentration (see Appendix A). We note that the proposed Bortezomib for Injection has the same concentration per mL of active ingredient upon reconstitution (intravenously at a concentration of 1 mg/mL and subcutaneously at a concentration of 2.5 mg/mL), same dosage form (for Injection), route of administration (intravenous and subcutaneous), and dosage regimen (1.3 mg/m² dose) as the LD Velcade. However, there are differences in the strength as Bortezomib for Injection is being proposed as 1 mg/vial strength and 2.5 mg/vial strength while the LD, Velcade is available as 3.5 mg/vial strength.

We acknowledge that approval of the 1 mg vial strength and 2.5 mg vial strength of Bortezomib for Injection will increase the reconstitution scenarios from two to six and may increase the potential for incorrect reconstitution errors. However, since Bortezomib products are reconstituted differently based on the route of administration, practitioners would rely on the reconstitution directions on both the carton labeling and Prescribing Information. Taking into consideration the risk of medication errors, the Applicant intends to mitigate the risk by providing reconstitution instructions on the carton labeling, sticker labels and in the PI. Of note, the LD also contains reconstitution directions on the carton labeling and Prescribing Information. Therefore, it is important to ensure that labels and labeling contain warning statements regarding further dilution and include prominent concentration information. The Applicant is also proposing additional risk mitigation strategies by utilizing a different background color (e.g. green background color for 1/vial mg strength and purple background color for 2.5 mg/vial strength vs. blue background color for LD Velcade) (b) (4)

[REDACTED]

[REDACTED]

We performed a risk assessment of the proposed container labels, carton labeling, sticker labels, and PI for Bortezomib for Injection to determine whether there are significant concerns in terms of safety related to preventable medication errors. For the Division and the Applicant, we note the use of incorrect terminology for the usual dosage statement, hazardous drugs statement, and diluent. For the Applicant, we note the final concentration of the subcutaneous route on the 1 mg/vial strength sticker label and carton labeling does not reflect the concentration after 0.4 mL of diluent is added. We have confirmed with the Office of

Pharmaceutical Quality that the amount extracted from the 1 mg/vial after dilution is 0.4 mL; therefore we recommend revisions of the final concentration on the label and labeling. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed container labels, carton labeling, sticker labels, 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 Hospira, Inc. to address our concerns.

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

A. Prescribing Information

1. Dosage and Administration Section

a. Section 2.7 Administration Precautions

- i. We recommend revising the statement, “Bortezomib for Injection is a (b) (4) drug.” to “Bortezomib for Injection is a hazardous drug.” to align with current terminology used in labeling.

b. Section 2.8 Reconstitution/Preparation for Intravenous and Subcutaneous Administration

- i. We recommend revising all instances of “0.9% sodium chloride” to the correct terminology, “0.9% Sodium Chloride Injection, USP”.
- ii. In Table 5 Reconstitution Volumes and Final Concentration for Intravenous and Subcutaneous Administration, we recommend including an asterisk beneath the table to denote the actual vial content for subcutaneous preparation of the 1 mg/vial is 1 mg/0.4 mL to reflect the concentration after the diluent is added. For example, “*Actual vial content results in a final concentration of 1 mg/0.4 mL.”.

2. How Supplied/Storage and Handling Section

- a. We recommend revising the statement, “Follow guidelines for handling and disposal for (b) (4) drugs, including the use of gloves and other protective clothing to prevent skin contact.” 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 HOSPIRA, INC.

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

A. Container Label for 1 mg/vial

1. We recommend revising the word, “(b) (4)” to “hazardous” on the container label for the 1 mg/vial to reflect alignment with current terminology recommended in labeling for hazardous drugs. Revise “CAUTION: (b) (4) Agent” to “CAUTION: Hazardous Agent” in bold red font.

B. Container Label for 2.5 mg/vial

1. To ensure consistency with the terminology in the Prescribing Information, we recommend revising the recommended dosage statement “(b) (4)” to read, “Recommended Dosage: See Prescribing Information.”
2. We recommend revising the word, “(b) (4)” to “hazardous” on the container label for the 2.5 mg/vial to reflect alignment with current terminology recommended in labeling for hazardous drugs. Revise “CAUTION: (b) (4) Agent” to “CAUTION: Hazardous Agent” in bold red font.

C. Carton Labeling

1. We recommend revising all instances of “0.9% sodium chloride” to the correct terminology, “0.9% Sodium Chloride Injection, USP”.
2. See B.1 and revise the carton labeling accordingly.
3. Bortezomib is a hazardous drug; however the principal display panel of the carton labeling does not convey this information. Hazardous drugs require special handling procedures. Add the statement, “CAUTION: Hazardous Agent” in bold red font on the principal display panel of the carton labeling.
4. We recommend revising the final concentration of the subcutaneous route on the 1 mg/vial strength carton labeling to “1 mg/0.4 mL” to reflect the actual concentration after the diluent is added.

D. Sticker Labels

1. See C.1 and revise the sticker labels accordingly.
2. To ensure consistency with the terminology in the Prescribing Information, we recommend revising the statement “See (b) (4) for full instructions” to “See Prescribing Information for full instructions”.

3. See C.4 and revise the sticker labels accordingly.
4. Since there are two strengths of Bortezomib for Injection that require different preparation instructions, we recommend including the strength following the product name in the first line of the sticker labels as follows:
“Bortezomib for Injection 1 mg/vial” and “Bortezomib for Injection 2.5 mg/vial”

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bortezomib received on June 30, 2021 from Hospira, Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Bortezomib and the Listed Drug		
Product Name	Bortezomib For Injection	Velcade ^a
Initial Approval Date	N/A	May 13, 2003
Active Ingredient	bortezomib	bortezomib
Indication	<ul style="list-style-type: none"> For the treatment of patients with multiple myeloma Treatment of adult patients with mantle cell lymphoma who have received at least 1 prior therapy. 	<ul style="list-style-type: none"> For the treatment of patients with multiple myeloma For the treatment of patients with mantle cell lymphoma
Route of Administration	Subcutaneous and intravenous	
Dosage Form	for Injection	
Strength	1 mg/vial, 2.5 mg/vial	3.5 mg/vial
Dose and Frequency	The recommended starting dose of Bortezomib for Injection is 1.3 mg/m ² .	The recommended starting dose of Velcade is 1.3 mg/m ² .

^a Velcade [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 APR 25. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021602s044lbl.pdf

	<p><u>Untreated Multiple Myeloma</u></p> <p>Bortezomib for 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 for Injection.</p> <p><u>Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma</u></p> <p>Bortezomib for Injection (1.3 mg/m²/dose) is administered twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a ten-day rest period (Days 12-21). For extended therapy of more than eight cycles, Bortezomib for 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 13-day rest period (Days 23 to 35). At least 72 hours should elapse between consecutive doses of Bortezomib for Injection.</p> <p>Patients with multiple myeloma who have previously responded to treatment with Bortezomib for Injection (either alone or in combination) and who have relapsed at least six months after their prior Bortezomib for Injection therapy may be started on Bortezomib for Injection at the last tolerated dose. Retreated patients are administered Bortezomib for Injection twice weekly (Days 1, 4, 8, and 11) every three weeks for a maximum of eight cycles. At least 72</p>	<p><u>Untreated Multiple Myeloma</u></p> <p>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.</p> <p><u>Untreated Mantle Cell Lymphoma</u></p> <p>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.</p> <p><u>Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma</u></p> <p>Velcade (1.3 mg/m²/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.</p> <p>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 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</p>
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	hours should elapse between consecutive doses of Bortezomib for Injection. Bortezomib for Injection may be administered either as a single agent or in combination with dexamethasone.	consecutive doses of Velcade. Velcade may be administered either as a single agent or in combination with dexamethasone .
How Supplied	Bortezomib for Injection is supplied as individually cartoned 5 mL or 10 mL vials containing 1 mg or 2.5 mg of bortezomib, respectively, as a white to off-white cake or powder.	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	See Table A	See Table B
Storage	Unopened vials may be stored at controlled room temperature 20° to 25°C (68° to 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.	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 Bortezomib for Injection

Route of Administration	Bortezomib Injection(mg/vial)	Diluent (0.9% Sodium Chloride)	Final Bortezomib Concentration (mg/mL)
Intravenous	1 mg	1 mL	1 mg/mL
Subcutaneous	1 mg	0.4 mL	2.5 mg/mL
Intravenous	2.5 mg	2.5 mL	1 mg/mL
Subcutaneous	2.5 mg	1 mL	2.5 mg/mL

Table B: 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

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 9, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, bortezomib. Our search identified 28 previous reviews (see Table 3 below), and we considered our previous recommendations to see if they are applicable for this current review.

Table 3. Comparison of Bortezomib for Injection and Bortezomib Injection Products						
Application	Product Name	Applicant	Strength	Route	NDA Status	OSE Review
NDA 021602 (Listed drug)	Velcade (bortezomib) for Injection	Millennium Pharms	3.5 mg/vial	Intravenous Subcutaneous	Approved 5/13/2003	2018-1491 ^b 2014-1549 and 2014-1550 ^c 2014-380 ^d 2011-1669 and 2007-1769 ^e 2012-38 ^f 2011-203-1 ^g 2011-203 ^h
(b) (4)						
NDA 206927	Bortezomib for Injection	Dr. Reddy's Laboratories	3.5 mg/vial	Intravenous	Approved 10/04/2019	2019-974-1 ^j 2019-974 ^k 2014-879 ^l

^b Garrison, N. Label and Labeling Review for Velcade (Bortezomib) for Injection (NDA 021602/S-044). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Dec 17. RCM No.: 2018-1491.

^c Rutledge, M. Label and Labeling Review MEMO for Velcade (NDA 021602/S-040). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 Sept 18. RCM No.: 2014-1549 and 2014-1550.

^d Rutledge, M. Label and Labeling Review MEMO for Velcade (NDA 021602/S-038). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 June 18. RCM No.: 2014-380.

^e Wood-Cummings, T. Label, Labeling, Usability and Postmarket Medication Error Review for Velcade (NDA 021602/S-027). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 Jan 13. RCM No.: 2007-1769 and 2011-1669.

^f Oleszczuk, Z. Postmarket Medication Errors Review for Velcade (NDA 021602 and TSI 001293). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2012 Jan 13. RCM No.: 2012-38.

^g Tu, CM. Label and Labeling Review. Velcade (NDA 021602). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 Mar 29. RCM No.: 2011-203-1

^h Tu, CM. Label and Labeling Review. Velcade (NDA 021602). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2011 Mar 29. RCM No.: 2011-203
(b) (4)

^j Garrison, N. Label and Labeling Review for Bortezomib for Injection (NDA 206927). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Sept 6. RCM No.: 2019-974-1.

^k Garrison, N. Label and Labeling Review for Bortezomib for Injection (NDA 206927). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Aug 19. RCM No.: 2019-974.

^l Rutledge, M. Label and Labeling Review MEMO for Bortezomib for Injection (NDA 206927). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 Sept 25. RCM No.: 2014-879.

Table 3. Comparison of Bortezomib for Injection and Bortezomib Injection Products						
Application	Product Name	Applicant	Strength	Route	NDA Status	OSE Review
NDA 205004	Bortezomib for Injection	Fresenius Kabi	3.5 mg/vial	Intravenous	Approved 11/06/2017	2018-651 ^m 2017-1836 ⁿ 2014-2238 ^o 2014-2237 ^p 2012-2862 ^q
NDA 208645	Bortezomib Injection	Actavis	2.5 mg/mL and 3.5 mg/1.4 mL	Intravenous	(b) (4)	
(b) (4)						
NDA 215441	Bortezomib Injection	Accord Healthcare	2.5 mg/mL and 3.5 mg/1.4 mL	Intravenous	Tentative Approval on 8/20/2021	2020-2295 ^u 2020-2295-1 ^v 2020-2295-2 ^w
NDA 209191	Bortezomib for Injection	Hospira	2.5 mg/vial 1 mg/vial	Intravenous Subcutaneous	Subject of this review	2018-1030 ^x 2017-2639 ^y 2017-1845 ^z 2016-1533-1 ^{aa} 2016-1533 ^{bb} 2021-1345

^m Rychlik, I. Label and Labeling Review for Bortezomib for Injection (NDA 205004/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Apr 6. RCM No.: 2018-651.

ⁿ Rahimi, L. Label and Labeling Review MEMO for Bortezomib for Injection (NDA 205004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 19. RCM No.:2017-1836.

^o Rutledge, M. Label and Labeling Review for Bortezomib for Injection (NDA 205004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 SEPT 02. RCM No.:2014-2238.

^p Rutledge, M. Label and Labeling Review for Bortezomib for Injection (NDA 205004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 FEB 03. RCM No.:2014-2237.

^q Wright, K. Label and Labeling Review MEMO for Bortezomib for Injection (NDA 205004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 May 8. RCM No.:2012-2862.

(b) (4)

^u Gao, T. Label and Labeling Review for Bortezomib for Injection (NDA 215441). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 21. RCM No.: 2020-2295.

^v Gao, T. Label and Labeling Review for Bortezomib for Injection (NDA 215441). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAY 07. RCM No.: 2020-2295-1.

^w Gao, T. Label and Labeling Review for Bortezomib for Injection (NDA 215441). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAY 25. RCM No.: 2020-2295-2.

^x Garrison, N. Label and Labeling Review MEMO for Bortezomib for Injection (NDA 209191). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 June 11. RCM No.: 2018-1030.

^y Ogbonna, C. Label and Labeling Review MEMO for Bortezomib for Injection (NDA 209191). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Feb 13. RCM No.: 2017-2639.

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,^{cc} along with postmarket medication error data, we reviewed the following Bortezomib labels and labeling submitted by Hospira, Inc..

- Container labels received on June 30, 2021
- Carton labeling received on June 30, 2021
- Prescribing Information (Image not shown) received on June 30, 2021, available from <\\CDSESUB1\evsprod\nda209191\0054\m1\us\lab-0819-1-4-pkg-insert-track-change.doc>

G.2 Label and Labeling Images

Container label for 1 mg/vial



Container label for 2.5 mg/vial

^z Garrison N. Label and Labeling Review Memorandum for Bortezomib (NDA 209191). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 012 RCM No.: 2017-1845.

^{aa} Garrison N. Label and Labeling Review for Bortezomib (NDA 209191). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JAN 09. RCM No.: 2016-1533-1.

^{bb} Garrison N. Label and Labeling Review for Bortezomib (NDA 209191). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 NOV 09. RCM No.: 2016-1533.

^{cc} Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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HINA S MEHTA
10/15/2021 02:07:55 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
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:	June 11, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 209191
Product Name and Strength:	Bortezomib for Injection, 2.5 mg vial
Applicant/Sponsor Name:	Hospira, Inc.
FDA Received Date:	May 16, 2018
OSE RCM #:	2018-1030
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Hematology Products (DHP) requested that we review the proposed container label, carton labeling, sticker labels, and Prescribing Information (PI) for Bortezomib for injection (NDA 209191) for areas of vulnerability that may lead to medication errors (Appendix A). DHP requested this review as a part of their evaluation of the 505(b)(2) NDA class I resubmission for Bortezomib for injection. DMEPA had made recommendations during previous label and labeling reviews.^{a,b,c}

1.1 REGULATORY HISTORY

Hospira submitted Bortezomib for Injection (NDA 209191) on June 30, 2016. The application received a Tentative Approval letter on April 26, 2017 due to patent protection of the listed drug, Velcade (NDA 021602) upon which the application relies. Hospira submitted a request for

^a Garrison N. Label and Labeling Review for Bortezomib (NDA 209191). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 NOV 09. RCM No.: 2016-1533.

^b Garrison N. Label and Labeling Review for Bortezomib (NDA 209191). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JAN 09. RCM No.: 2016-1533-1.

^c Garrison N. Label and Labeling Review for Bortezomib (NDA 209191). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 12. RCM No.: 2017-1845.

final approval of Bortezomib for Injection (NDA 209191) on September 7, 2017. The application received a Complete Response on November 3, 2017 due to facility inspection issues. On December 22, 2017, Hospira submitted a Complete Response Amendment resubmission request for full approval. However, the application received a Complete Response on February 22, 2018 due to product quality issues.

2 CONCLUSION

We determined that the proposed container label, carton labeling, and sticker labels for Bortezomib for Injection are acceptable from a medication error perspective. However, we note the use of a trailing zero in Prescribing Information in Section 10 Overdosage. We provide a recommendation in Section 3 below and advise that it is implemented prior to approval of this NDA.

3 RECOMMENDATIONS FOR THE DIVISION

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

- A. Section 10 Overdosage
 - a. Remove the trailing zero (e.g. 3.0 mg/m²) to avoid a ten-fold misinterpretation.

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/s/

NICOLE B GARRISON
06/11/2018

HINA S MEHTA
06/11/2018



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Pediatric Labeling Review

From: Hari Cheryl Sachs, MD, Team Leader
Division of Pediatric and Maternal Health

Through: John J. Alexander, MD, MPH Deputy Director
Division of Pediatric and Maternal Health

NDA Number: 209191

Sponsor: Hospira

Drug: Bortezomib for injection

**Dosage Form and
Route of Administration:** Injection, subcutaneous or intravenous

**Reference Listed Drug
Approved Indication:** Treatment of patients with multiple myeloma
Treatment of patients with mantle cell lymphoma

**Sponsor Proposed
Indication:** Treatment of patients with multiple myeloma

Consult Request:

The Division of Hematology Products (DHP) is “reviewing a Class I resubmission of a 505(b)(2) application for bortezomib injection (the listed drug is Velcade). The Velcade labeling has pediatric information in Section 8.4 with pediatric exclusivity [expiring March 14, 2019]. The PDUFA goal date is Feb 22, 2018.”

DHP requests that DPMH “please review the proposed language from the applicant in section 8.4 of the PI and determine if this language needs revision under FDARA

NON-RESPONSIVE”

NON-RESPONSIVE

Background

The sponsor resubmitted a 505(b)(2) application on December 22, 2017 for Bortezomib for Injection, 2.5 mg/vial, NDA 209191, manufactured by Hospira.¹ The reference product for bortezomib is Velcade® (NDA 021602), manufactured by Millennium Pharmaceuticals, Inc. (Millennium). Velcade® was approved for the treatment of multiple myeloma on May 13, 2003 under Priority Review as a new molecular entity (NME) with orphan designation related to the indication for the treatment of multiple myeloma. Velcade was also approved for the treatment of patients with second line and then first line mantle cell lymphoma on December 8, 2006 and on October 8, 2014, respectively. Velcade received orphan designation for the treatment of mantle cell lymphoma on May 30, 2012. Currently, Velcade has orphan drug exclusivity for the treatment of patients with mantle cell lymphoma who have not received at least one prior therapy. This orphan drug exclusivity expires on October 8, 2021 and the pediatric exclusivity extension expires on April 8, 2022.

Millennium Pharmaceuticals, Inc., submitted an efficacy supplement (NDA 21602/Suppl-042) on March 25, 2015 for study (AALL07P1) entitled, “*A Phase II Pilot Trial of Bortezomib in Combination with Intensive Re-Induction Therapy for Children with Relapsed Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma*”, to fulfill a pediatric Written Request (WR) for Velcade issued on April 27, 2010.² A total of 140 pediatric and young adult patients (1 year to 26 years of age) with lymphoid malignancies (ALL or LL) failed to achieve an acceptable complete remission (CR) rate when compared to a historical control set of patients who received the identical chemotherapy backbone therapy without Velcade. No new safety concerns were observed when Velcade was added to a chemotherapy backbone regimen as compared with a historical control group without Velcade.³ A determination of pediatric exclusivity was made under the Best Pharmaceuticals for Children Act (BPCA) and exclusivity was granted on August 14, 2015. This pediatric efficacy supplement was approved on September 14, 2015 and received 3 years of Hatch-Waxman exclusivity (expires September 14, 2018) as well as an additional 6 months of pediatric exclusivity (expires March 14, 2019).

The Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) provided additional authority to permit the approval of drugs under 505(j) when pediatric information protected by exclusivity [three-year new clinical studies exclusivity (Hatch-Waxman)] had been added to the labeling and could not be safely “carved out”. It also expressly authorized FDA to include a disclaimer in ANDA labeling when such labeling was carved out. These provisions did not include retention of protected pediatric safety information from 505(b)(2) drug labeling or the inclusion of a disclaimer when protected pediatric information is carved out. The Food and Drug Administration (FDA) Reauthorization Act (FDARA) enacted on August 18, 2017 extended the provisions set forth under FDASIA of 2012 to NDA 505(b)(2) drug labeling.

¹ Pediatric assessments were not required under PREA for this product.

² DPMH Consult from DHP (dated June 2015), NDA 21602 Velcade (bortezomib) Injection labeling review based on pediatric WR study report, written by Ethan Hausman (dated August 4, 2015).

³ NDA 021602 Velcade (bortezomib) Injection, Section 8.4 extracted from labeling approved on September 14, 2015 based on a pediatric efficacy supplement.

DPMH previously reviewed the proposed labeling for this NDA (DPMH consult, 4/25/2017, Hari Cheryl Sachs, DARRTS Ref ID #408900)⁴ and concluded the protected pediatric study (AALL07P1) could be safely omitted without posing a concern for safe use for the purposes of this NDA (b) (4)

DPMH agreed with the sponsor's proposed language as follows:

8.4 Pediatric Use

In this DPMH review, proposed labeling for 505(b)(2), NDA 209191 Bortezomib Injection by Hospira, Section 8.4 Pediatric Use includes the statement, (b) (4)

and the pediatric study information is "carved out" as there is not a concern for safe use conditions without this information. Hospira NDA 209191, 505(b)(2) for Bortezomib received a tentative approval (TA) from FDA on 4/26/2017. On December 22, 2017, the sponsor submitted a complete, Class I response (request for approval) that includes proposed labeling and packaging that excludes the protected pediatric study results [performed to fulfill the pediatric Written Request (WR) under NDA 021602 Velcade (bortezomib) by Millennium issued on April 27, 2010] reported in Section 8.4 of Velcade® labeling.⁵

Discussion:

The proposed labeling in the resubmission is consistent with DPMH's April 2017 recommendations. Omission of the protected pediatric use information for the remaining conditions of use, namely multiple myeloma, which is a predominately adult indication, does not pose a concern for safe use.

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

The reference product, NDA 021602 Velcade (bortezomib) Injection by Millennium, most recent FDA-approved labeling is dated June 9, 2017 (Supplement 043) with updates to Section 6.2, Postmarketing Experience to add Steven Johnson Syndrome, and to Sections 5, 8, 13, and 17 per the Pregnancy and Lactation Labeling Rule (PLLR). Our recommendations for 505(b)(2) NDA 209191 Bortezomib Injection by Hospira reflect labeling provided to the DHP on December 22, 2017]. DPMH notes that the sponsor's proposed bortezomib labeling omits description of the protected pediatric study in Section

⁴ DPMH Consult from DHP (dated April 20, 2017) for NDA 209191 Bortezomib for Injection written by Hari Cheryl Sachs, MD Pediatric Team Leader (dated April 2017).

⁵ See footnote 3.

8.4 Pediatric Use, which is consistent with our previous recommendations (see DPMH review for NDA 209191, 505(b)(2) for Bortezomib Injection by Hospira).⁶ We believe that the Hospira 505(b)(2) application can be approved with the information about the protected pediatric study omitted. However, since the completion of the review for NDA 209191 in April, FDA has, as described above, been given new authority to add disclaimers and to retain pediatric information necessary for safe use for 505(b)(2) applications. Accordingly, we have determined that it is not appropriate (b) (4)

(b) (4) In light of FDA's new authority under FDARA, DPMH recommends revisions to add a disclaimer in Section 8.4.⁸

DPMH Labeling Recommendations:

DPMH recommended information to be added to labeling is underlined. Information to be deleted has a ~~striketrough~~.

USE IN SPECIFIC POPULATIONS

(b) (4)

⁶ See footnote 4.

⁷ The prior version of the pediatric use section (8.4) stated: (b) (4)

⁸ This approach is consistent with the approach taken for for Fresenius Kabi USA, LLC's product in November 2017 (NDA 205004, DPMH consult, 11/1/2017 Carolyn Yancey, DARRTS Ref ID 4175472).

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/s/

HARI C SACHS
02/21/2018

JOHN J ALEXANDER
02/21/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
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:	February 14, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 209191
Product Name and Strength:	Bortezomib for Injection, 2.5 mg vial
Applicant/Sponsor Name:	Hospira, Inc.
FDA Received Date:	December 22, 2017 and February 12, 2018
OSE RCM #:	2017-2639
DMEPA Safety Evaluator:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the proposed container label, carton labeling, sticker label, and Prescribing Information (PI) for Bortezomib for injection NDA 209191 (Appendix A) to determine if it is acceptable from a medication error perspective. DHP requested this review as part of their evaluation of the 505(b)(2) NDA class I resubmission for bortezomib for injection. DMEPA has made recommendations during previous label and labeling reviews.^{abc}

1.1 REGULATORY HISTORY

Hospira submitted Bortezomib for Injection (NDA 209191) on June 30, 2016. The application received a Tentative Approval letter on April 26, 2017 due to patent protection of the listed drug, Velcade (NDA 021602) upon which the application relies. Hospira submitted a request for final approval of Bortezomib for Injection (NDA 209191) on September 7, 2017. The application

^a Garrison N. Label and Labeling Review for Bortezomib (NDA 209191). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 NOV 09. RCM No.: 2016-1533.

^b Garrison N. Label and Labeling Review for Bortezomib (NDA 209191). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JAN 09. RCM No.: 2016-1533-1.

^c Garrison N. Label and Labeling Review Memorandum for Bortezomib (NDA 209191). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 012 RCM No.: 2017-1845.

received a complete response on November 3, 2017 for facility inspection issues. On December 22, 2017, Hospira submitted a Complete Response Amendment resubmission request for full approval.

2 CONCLUSION

The revised carton labeling, container label, and sticker labels are acceptable from a medication error perspective. We have no further recommendations at this time.

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CASMIR I OGBONNA
02/14/2018

HINA S MEHTA
02/14/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
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:	October 12, 2017
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 209191
Product Name and Strength:	Bortezomib for Injection, 2.5 mg vial
Applicant/Sponsor Name:	Hospira, Inc.
Submission Date:	September 7, 2017 and October 2, 2017
OSE RCM #:	2017-1845
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the proposed container label, carton labeling, sticker labels, and Prescribing Information (PI) for Bortezomib for injection (NDA 209191) for areas of vulnerability that may lead to medication errors (Appendix A). DHP requested this review as a part of their evaluation of the 505(b)(2) NDA class I resubmission for Bortezomib for injection. DMEPA had made recommendations during previous label and labeling reviews.^{a,b}

1.1 REGULATORY HISTORY

Hospira submitted Bortezomib for Injection (NDA 209191) on June 30, 2016. The application received a Tentative Approval letter on April 26, 2017 due to patent protection of the listed drug, Velcade (NDA 021602) upon which the application relies. Hospira submitted a request for final approval of Bortezomib for Injection (NDA 209191) on September 7, 2017.

^a Garrison N. Label and Labeling Review for Bortezomib (NDA 209191). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 NOV 09. RCM No.: 2016-1533.

^b Garrison N. Label and Labeling Review for Bortezomib (NDA 209191). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JAN 09. RCM No.: 2016-1533-1.

2 CONCLUSION

We conclude the proposed sticker labels are acceptable from a medication error perspective. However, the proposed container label, carton labeling, and Prescribing Information are unacceptable from a medication error perspective. We note that the labeling contains the term, (b) (4); we defer to the Office of Pharmaceutical Quality (OPQ) for the determination of the appropriate package type term on the labeling. Additionally, we note the use of a trailing zero in the Prescribing Information in Section 2 table 5 and absence of the degree symbol in Section 16. We provide recommendations in Section 3.1 below and advise that it is implemented prior to the approval of this NDA.

3 RECOMMENDATION

3.1 RECOMMENDATIONS FOR THE DIVISION

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

- A. Prescribing Information
 - 1. Section 2 Dosage and Administration
 - a. In Table 5, remove the trailing zero (e.g. 1.0 mL) in the third column, diluent (0.9% Sodium Chloride).
 - 2. Section 16 How Supplied/Storage and Handling
 - a. The degree symbol is omitted following the recommended temperatures for storage and handling for this product. We recommend including the degree symbol next to all temperatures to increase readability of this important information.

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/s/

NICOLE B GARRISON
10/12/2017

HINA S MEHTA
10/12/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Pediatric Labeling Review

From: Hari Cheryl Sachs, MD, Team Leader
Division of Pediatric and Maternal Health

Through: John J. Alexander, MD, MPH Deputy Director
Division of Pediatric and Maternal Health

NDA Number: 209191

Sponsor: Hospira

Drug: Bortezomib for injection

**Dosage Form and
Route of Administration:** Injection, subcutaneous or intravenous

**Reference Listed Drug
Approved Indication:** Treatment of patients with multiple myeloma
Treatment of patients with mantle cell lymphoma

**Sponsor Proposed
Indication:** Treatment of patients with multiple myeloma

Consult Request:

The Division of Hematology Products (DHP) is “reviewing a 505(b)(2) application for bortezomib injection (the listed drug is Velcade). The Velcade labeling has pediatric text in Section 8.4 with pediatric exclusivity out to 4/8/2022 listed in the Orange Book. The Division plans to grant Tentative Approval on the PDUFA date (TA is due to a patent lawsuit by the LD).”

DHP desires input on:

“Is the pediatric data in Section 8.4 appropriately carved out in the attached labeling so as to avoid compromising safe use of the product? (b) (4)

(b) (4)

Background

The sponsor submitted a 505(b)(2) application on June 30, 2016 which relies on the Reference Listed Drug (Velcade, NDA 021602). A Written Request was issued on 4/27/2010 and amended on 1/26, 2011 and 11/13/2012, describing pediatric studies of relapsed pre-B acute lymphoblastic leukemia (ALL). These pediatric studies did not show any activity of Velcade in this refractory ALL population, based on complete remission rate. Pediatric exclusivity was granted on 8/14/2015 and the results of the negative trial were described in approved labeling (9/14/2015), shown in Appendix 1.

Sponsor proposed labeling

8.4 Pediatric Use

(b) (4)

Reviewer comment: The sponsor's proposed labeling for subsection 8.4 Pediatric Use,

(b) (4)

Omission of the protected pediatric use information for the remaining conditions of use, namely multiple myeloma, which is a predominately adult indication, does not pose a concern for safe use,

(b) (4)

Recommendations

Pediatric information has been appropriately "carved out." DPMH has no recommended changes to subsection 8.4 Pediatric Use.

Labeling negotiations are ongoing. The final labeling may differ as a result of those negotiations (see action letter).

Appendix 1: Protected Pediatric Use Labeling

8.4 Pediatric Use

The effectiveness of VELCADE in pediatric patients with relapsed pre-B acute lymphoblastic leukemia (ALL) has not been established.

The activity and safety of VELCADE in combination with intensive reinduction chemotherapy was evaluated in pediatric and young adult patients with lymphoid malignancies (pre-B cell ALL 77%, 16% with T-cell ALL, and 7% T-cell lymphoblastic lymphoma (LL)), all of whom relapsed within 36 months of initial diagnosis in a single-arm multicenter, non-randomized cooperative group trial. An effective reinduction multiagent chemotherapy regimen was administered in 3 blocks. Block 1 included vincristine, prednisone, doxorubicin and pegaspargase; block 2 included cyclophosphamide, etoposide and methotrexate; block 3 included high dose cytosine arabinoside and asparaginase. VELCADE was administered at a dose of 1.3 mg/m^2 as a bolus intravenous injection on days 1, 4, 8, and 11 of block 1 and days 1, 4, and 8 of block 2. There were 140 patients with ALL or LL enrolled and evaluated for safety. The median age was 10 years (range 1 to 26), 57% were male, 70% were white, 14% were black, 4% were Asian, 2% were American Indian/ Alaska Native, 1% were Pacific Islander.

The activity was evaluated in a pre-specified subset of the first 60 evaluable patients enrolled on the study with pre-B ALL ≤ 21 years and relapsed < 36 months from diagnosis. The complete remission (CR) rate at day 36 was compared to that in a historical control set of patients who had received the identical backbone therapy without VELCADE. There was no evidence that the addition of VELCADE had any impact on the CR rate.

No new safety concerns were observed when VELCADE was added to a chemotherapy backbone regimen as compared with a historical control group in which the backbone regimen was given without VELCADE.

The BSA-normalized clearance of bortezomib in pediatric patients was similar to that observed in adults.

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/s/

HARI C SACHS
04/25/2017

JOHN J ALEXANDER
04/25/2017

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

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

Memorandum

Date: March 13, 2017

To: Kristopher Kolibab, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Davis, Team II Leader, OPDP

Subject: Comments on draft labeling (Package Insert and Carton and Container labeling) for Bortezomib for Injection, for subcutaneous or intravenous use
NDA 209191

In response to your consult dated August 22, 2016, we have reviewed the draft Package Insert (PI) and draft Carton and Container (CC) labeling for Bortezomib for Injection, for subcutaneous or intravenous use (Bortezomib for Injection), and our comments are provided below.

PI

OPDP has reviewed the version of the PI e-mailed to OPDP on March 09, 2017. OPDP has no comments on the draft PI at this time.

CC

OPDP has reviewed the version of the CC labeling via EDR:
[\\CDSESUB1\evsprod\NDA209191\209191.enx](#) e-mailed to OPDP on March 09, 2017. OPDP has no comments on the draft CC labeling at this time.

Thank you for your consult.

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/s/

DHARA SHAH
03/13/2017

Division of Hematology Products (DHP) Labeling Review

Application Number	NDA 209191
Application Type	505(b)(2)
Proprietary Name (nonproprietary name)	Bortezomib for Injection (bortezomib)
Receipt Date	06/30/2016
PDUFA Goal Date	04/30/2017
Review Classification	Standard
Proposed Indication (or current indication if unchanged)	Bortezomib for Injection is a proteasome inhibitor indicated for treatment of patients with multiple myeloma.
Dosing Regimen	The recommended starting dose of Bortezomib for Injection is 1.3 mg/m ² administered either as a 3 to 5 second bolus intravenous injection or subcutaneous injection.
From	Virginia Kwitkowski, MS, ACNP-BC Associate Director for Labeling, DHP

Background of Application:

In this review, I propose labeling recommendations and edits in the Bortezomib for Injection labeling to ensure that the prescribing information is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of Bortezomib for Injection.

The following pages contain the working version of the Bortezomib for Injection labeling with recommended edits and comments identified as 'VK1' through 'VK35'. This labeling version also includes comments from other members of the review team. Given that the scientific review of the labeling is ongoing, my labeling recommendations in this review should be considered preliminary and may not represent DHP's final recommendations for the Bortezomib for Injection labeling.

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

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
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:	January 5, 2017
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 209191
Product Name and Strength:	Bortezomib for Injection, 2.5 mg vial
Submission Date:	December 5, 2016
Applicant/Sponsor Name:	Hospira, Inc.
OSE RCM #:	2016-1533-1
DMEPA Primary Reviewer:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Hematology Products requested that we review the revised carton labeling and sticker label for Bortezomib (Appendix A) to determine if it is 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 revised carton labeling and sticker label for Bortezomib is acceptable from a medication error perspective. We have no further recommendations at this time.

^a Garrison N. Label and Labeling Review for Bortezomib (NDA 209191). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 NOV 09. 9 p. OSE RCM No.: 2016-1533-1.

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/s/

NICOLE B GARRISON
01/05/2017

HINA S MEHTA
01/05/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
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:	November 9, 2016
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 209191
Product Name and Strength:	Bortezomib for Injection, 2.5 mg vial
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Hospira, Inc.
Submission Date:	June 30, 2016 and September 2, 2016
OSE RCM #:	2016-1533
DMEPA Primary Reviewer:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader (Acting):	Hina Mehta, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container label, carton labeling, sticker labels and Prescribing Information (PI) for Bortezomib for Injection, 2.5 mg vial (NDA 209191) for areas of vulnerability that could lead to medication errors. The Division of Hematology Products requested this review as part of their evaluation to the 505(b) (2) submission Bortezomib For Injection.

1.1 REGULATORY HISTORY

Bortezomib for injection was approved in 2003 in 3.5 mg strength. In an effort to reduce wastage of drug Hospira is submitting a NDA for the 2.5 mg strength.

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

N/A=not applicable for this review

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Hospira, Inc. submitted a 505(b)(2) NDA to obtain marketing approval of Bortezomib for Injection. The Reference Drug (RD) for this product is Velcade (bortezomib injection). Velcade is currently approved for the treatment of patients with multiple myeloma and mantle cell lymphoma. The recommended starting dose of Velcade is 1.3 mg/m²dose. The RD, is currently approved in a 3.5 mg vial for injection and can be administered intravenously at a concentration of 1 mg/mL and subcutaneously at a concentration of 2.5 mg/mL. The proposed Bortezomib for Injection will be available in a 2.5 mg vial. We also note that the Applicant is only seeking approval for the treatment of patients with multiple myeloma. DMEPA reviewed the proposed labels and labeling to determine whether there are significant concerns in terms of safety, related to preventable medication errors.

Both the proposed Bortezomib for Injection and RD Velcade (when reconstituted) have the same final concentration when administered intravenously (1 mg/mL) and subcutaneously (2.5

mg/mL), but differ in terms of how much diluent is required to prepare the final concentration (see Appendix A). We acknowledge that approval of the 2.5 mg vial strength will increase the reconstitution scenarios from two to four and may increase the potential for incorrect reconstitution errors. However, since Bortezomib products are reconstituted differently based on the route of administration, practitioners would rely on the reconstitution directions on both the carton labeling and Prescribing Information. Taking into consideration the risk of medication errors, the Applicant intends to mitigate the risk by providing reconstitution instructions on the carton labeling, sticker labels and in the Prescribing Information. Of note, the RD also contains reconstitution directions on the carton labeling and Prescribing Information. The Applicant is also proposing additional risk mitigation strategies (b) (4)

Furthermore, since the Hospira product is proposing to be marketed in a different package size, it may reduce the risk of practitioners assuming that the reconstitution procedures are identical to the RD Velcade.

Additionally, we identified areas in the label and labeling that can be improved to increase the readability and prominence of important information and promote the safe use of the product. We note that the labels and labeling contains the term, (b) (4) which is inconsistent with the draft guidance^a ; we defer to CMC for the determination of the appropriate package type term on labels and labeling.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product. We provide recommendations in Sections 4.1 and 4.2 below and advise they are implemented prior to the approval of this NDA.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Section 2.8, Dosage in Patients with Hepatic Impairment
 - a. Delete all instances of trailing zeros. We recommend this revision to avoid use of a trailing zero, an error prone dose designation, which may be misinterpreted if the decimal point is not seen.^b

^a Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. 2015. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>

^b ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015[cited 2016 NOV 03]. Available from:

4.2 RECOMMENDATIONS FOR HOSPIRA

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

- A. Carton labeling
 - 1. Delete the trailing zeros. We recommend this revision to avoid use of a trailing zero, an error prone dose designation, which may be misinterpreted if the decimal point is not seen.^c
- B. Sticker label
 - 1. Bortezomib 2.5 mg/vial
 - a. See A.1 and revise the subcutaneous injection only sticker label accordingly.

<http://www.ismp.org/tools/errorproneabbreviations.pdf>.

^c ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015[cited 2016 NOV 03]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bortezomib for Injection that Hospira submitted on June 30, 2016, and the listed drug (LD) Velcade.

Table 2. Relevant Product Information for Bortezomib For Injection and the Listed Drug Velcade		
Product Name	Bortezomib for Injection	Velcade
Initial Approval Date	N/A	May 13, 2003
Active Ingredient	Bortezomib	Bortezomib
Indication	Treatment of patients with multiple myeloma	Treatment of patients with multiple myeloma and mantle cell lymphoma
Route of Administration	Intravenous and subcutaneous	Intravenous and subcutaneous
Dosage Form	For Injection	For Injection
Strength	2.5 mg vial	3.5 mg vial
Dose and Frequency	The recommended starting dose of Bortezomib for Injection is 1.3 mg/m ² . Bortezomib may be administered intravenously at a concentration of 1 mg/mL, or subcutaneously at a concentration of 2.5 mg/mL. When administered intravenously, Bortezomib is administered as a 3 to 5 second bolus injection.	The recommended starting dose of Velcade is 1.3 mg/m ² . Velcade may be administered intravenously at a concentration of 1 mg/mL, or subcutaneously at a concentration of 2.5 mg/mL. When administered intravenously, Velcade is administered as a 3 to 5 second bolus injection.
How Supplied	Bortezomib for Injection is supplied as individually cartoned 10 mL vials containing 2.5 mg of bortezomib as a white to off-white cake or powder.	Velcade 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	See Table A	See Table B
Storage	Unopened vials may be stored at controlled room temperature 20 to 25°C (68 to 77°F); excursions permitted from 15 to	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

	30°C (59 to 86°F) [see USP Controlled Room Temperature]. Retain in original package to protect from light.	Controlled Room Temperature]. Retain in original package to protect from light.
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Table A: Instruction for Reconstitution of Bortezomib for Injection

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

Table B: Instruction for Reconstitution of reference listed drug, Velcade

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

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On November 2, 2016, we searched the L:drive and AIMS using the terms, Bortezomib to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified seven previous reviews, and we confirmed that our previous recommendations were implemented.

(b) (4)

Rutledge, M. Label Labeling Memo for Bortezomib (NDA 206927). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 Mar 04.02 p. OSE RCM No.: 2014-879.

Rutledge, M. Label Labeling Review for Bortezomib (NDA 205004). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 Feb 03.11 p. OSE RCM No.: 2014-2237.

Rutledge, M. Label Labeling Review for Bortezomib (NDA 205004). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 Sep.22. 03 p. OSE RCM No.: 2014-2238.

(b) (4)

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,^d along with postmarket medication error data, we reviewed the following Bortezomib labels and labeling submitted by Hospira on June 30, 2016.

- Container label
- Carton labeling
- Sticker labels
- Prescribing Information (not listed)

G.2 Label and Labeling Images

Container label



Carton labeling

^d Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

(b) (4)



Sticker labels

(b) (4)



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NICOLE B GARRISON
11/09/2016

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