CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206927Orig1s000

OTHER REVIEW(S)

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:	September 23, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 206927
Product Name and Strength:	Bortezomib for Injection, 3.5 mg per vial
Applicant/Sponsor Name:	Dr. Reddy's Laboratories, Inc.
OSE RCM #:	2019-974-2
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label, sticker label and carton labeling received on September 16, 2019 for Bortezomib. We reviewed the revised container label, (b) (4) and carton labeling 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.[ab] We note the Applicant has revised the packaging configuration to remove the (b) (4) label.

2 CONCLUSION

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

[a] Garrison N. Label and Labeling Review for Bortezomib (NDA 206927). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 19. RCM No.: 2019-974.
[b] Garrison N. Label and Labeling Review Memo for Bortezomib (NDA 206927). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 06. RCM No.: 2019-974-1.

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

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HINA S MEHTA
09/23/2019 03:04:51 PM

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

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

Memorandum

Date: September 16, 2019

To: Bindu N. Kanapuru, M.D., Clinical Reviewer
Division of Hematology Products (DHP)

Wanda Nguyen, PharmD, Regulatory Project Manager, (DHP)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling, (DHP)

From: Domenic D'Alessandro, PharmD, MBA, BCPS, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Lisa Hubbard, RPh, RAC, Deputy Division Director, DAPR1, OPDP

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

NDA: 206927

In response to DHP consult request dated June 6, 2019, OPDP has reviewed the proposed product labeling (PI), and carton and container labeling for the original NDA submission for BORTEZOMIB for injection, for intravenous use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DHP (Wanda Nguyen) on September 9, 2019, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 29, 2019, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Domenic D'Alessandro at (301) 796-3316 or domenic.dalessandro@fda.hhs.gov.

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

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DOMENIC G DALESSANDRO
09/16/2019 12:18:30 PM

LABELING

NDA 206927
Bortezomib for Injection, 3.5 mg/vial for injection
Dr. Reddy's Laboratories Ltd (Hyderabad, India)

NDA 206927 was submitted as a 505(b)(2) application based on Velcade, Bortezomib for Injection 3.5 mg/vial (Millennium Pharmaceuticals' NDA 21620). (b) (4) Complete Response letter #1 and Complete Response letter #2 have been issued (b) (4) CMC DP-Process Review #1 deferred labeling issues since the application was to receive a CR letter. (b) (4) Labeling discussion (b) (4) started with the submission of amendment SD-011. The most recent labels and labeling are provided in amendments SD-018 and SD-019.

Amendment	*Date Submitted*	*Content*
SD-001	03/04/14	New NDA
SD-005	08/18/14	Revised labeling per Velcade
	08/29/14	(b) (4)
	12/17/14	Complete Response Letter #1 [CR-1] referencing amendments SD-001, SD-002, SD-003, SD-004, SD-005, SD-006, SD-007 (DS, DP, biopharm, labeling/exclusivity)
	05/04/16	Complete Response Letter #2 [CR-2] referencing amendment SD-008 (DP, process, labeling. facility)
SD-014	08/01/19	Patent exclusivity
SD-015	08/07/19	IV sticker, vial, carton labels
SD-016	08/21/19	IV sticker, vial, carton labels, and package insert
SD-017	08/26/19	Package insert
SD-018	08/29/19	IV sticker, vial and carton labels
SD-019	08/30/19	IV sticker label, and package insert

R REGIONAL INFORMATION

1.14 LABELING

IV STICKER LABEL (amendment SD-019)

Reviewer's Assessment: ***Not Acceptable***

This labels is placed on the container of reconstituted solution. Diluent volume, solution strength, route of administration and drug name information are Accurate, but the diluent should be listed by its USP name.

* Revise the diluent to "0.9% sodium chloride, USP" on the IV sticker.

VIAL LABEL (amendment SD-018)

Reviewer's Assessment: ***Not Acceptable***

CMC information is complete and accurate except for the 3 items listed below.

* Revise the bolded statement to use "For Intravenous Use Only"; recommended by DMEPA.
* Revise ingredient list to use USP titles to "~~anhydrous~~ citric acid, USP" and tromethamine, USP" on the vial label. "Anhydrous" is not appropriate since this is a lyophilized and citric acid now an bortezomib ester and no longer an anhydrous powder.
* Revise the storage statement to delete reference to "~~USP Controlled Room Temperature~~"; see discussion and conclusion to the package insert.

SINGLE VIAL CARTON LABEL (amendment SD-018)

(b) (4)

Reviewer's Assessment*:* ***Not Acceptable***

Same comments as for the vial label.

* Revise the diluent to "0.9% sodium chloride, USP" on the top and back panel.
* Revise ingredient list to "~~anhydrous~~ citric acid, USP" and tromethamine, USP".
* Revise the storage statement to delete reference to "~~USP Controlled Room Temperature~~"

PACKAGE INSERT (amendment SD-019)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BORTEZOMIB safely and effectively. See full prescribing information for BORTEZOMIB.

BORTEZOMIB for injection, for intravenous use only
Initial U.S. Approval: 2003

----------DOSAGE FORMS AND STRENGTHS----------
For injection: Single-dose vial contains 3.5 mg of bortezomib as lyophilized powder for reconstitution and withdrawal of the appropriate individual patient dose. (3)

FULL PRESCRIBING INFORMATION

2 DOSAGE AND ADMINISTRATION
2.1 Important Dosing Guidelines
Bortezomib for injection is for intravenous use only. Do not administer Bortezomib for injection by any other route.

The recommended starting dose of Bortezomib for injection is 1.3 mg/m2. Bortezomib for injection is administered intravenously at a concentration of 1 mg/mL [see Dosage and Administration (2.8)].

2.8 Reconstitution/Preparation for Intravenous Administration
Use proper aseptic technique. Reconstitute only with 0.9% sodium chloride, USP. The reconstituted product should be a clear and colorless solution.
For each 3.5 mg single-dose vial of Bortezomib for injection reconstitute with the following volume of 0.9% sodium chloride, USP (Table: 5)

Table 5: Reconstitution Volumes and Final Concentration for Intravenous Administration

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

** Revise the text of the third box to "0.9% sodium chloride, USP".

Dose must be individualized to prevent overdosage. After determining patient body surface area (BSA) in square meters, use the following equations to calculate the total volume (mL) of reconstituted Bortezomib for injection to be administered:

• Intravenous Administration [1 mg/mL concentration]

$$\frac{\text{Bortezomib for injection dose (mg/m}^2\text{) x patient BSA(m}^2\text{)}}{\text{1 mg/mL}} = \text{Total Bortezomib for injection (mL) to be administered}$$

A sticker that indicates the route of administration is provided with each Bortezomib for injection vial. Place this sticker directly on the syringe of Bortezomib for injection once it is prepared to help alert practitioners of the correct route of administration for Bortezomib for injection.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If any discoloration or particulate matter is observed, the reconstituted product should not be used.

Bortezomib for injection contains no antimicrobial preservative. Administer reconstituted Bortezomib for injection within 8 hours of preparation. When reconstituted as directed, Bortezomib for injection ~~may~~ should be stored at 20°-25°C (68°-77°F). The reconstituted material may be stored in the original vial and/or the syringe prior to administration. The product may be stored for up to eight hours in a syringe; however, total storage time for the reconstituted material must not exceed eight hours when exposed to normal indoor lighting.

3 DOSAGE FORMS AND STRENGTHS

For Injection: Each single-dose vial of Bortezomib for injection contains 3.5 mg of bortezomib as a sterile lyophilized white to off-white powder for reconstitution and withdrawal of the appropriate individual patient dose [see Dosage and Administration (2.8)].

11 DESCRIPTION

Bortezomib for injection contains bortezomib which is an antineoplastic agent. Bortezomib is a modified dipeptidyl boronic acid. The chemical name is [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl] boronic acid. The molecular formula is C19H25BN4O4. The molecular weight is 384.24. Bortezomib has the following ~~chemical~~ molecular structure:

[molecular structure]

The solubility of bortezomib, as the monomeric boronic acid, in water is 0.8 to 0.9 mg/mL in a pH range of 2 to 6.5.

Bortezomib for injection is available for intravenous injection use only. Each single-dose vial contains 3.5 mg of bortezomib as a sterile lyophilized cake or powder. The inactive ingredients are ~~anhydrous~~ citric acid 10 mg and tromethamine 8.4 mg. The product is provided as a citric acid boronic ester which, when reconstituted, consists of the citric acid ester in equilibrium with its hydrolysis product, the monomeric boronic acid. The drug substance exists in its cyclic anhydride form as a trimeric boroxine.

15 REFERENCES

1. "OSHA Hazardous Drugs" (refer to antineoplastic weblinks including OSHA Technical Manual). OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html.

16 HOW SUPPLIED/STORAGE AND HANDLING

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.

3.5 mg single-dose vial NDC 43598-865-60
~~Unopened vials should may be stored~~ Store at 20°-25°C (68°-77°F). Retain in original package to protect from light.

Follow guidelines for handling and disposal for cytotoxic drugs, including the use of gloves and other protective clothing to prevent skin contact1.

Manufactured by:
Dr. Reddy's Laboratories Limited
Visakhapatnam 530 046- INDIA
[Dr. Reddy's logo]

Reviewer's Assessment: ***Not Acceptable***
Highlights
Header: Drug name is Acceptable and no trade name has been proposed. Per DMEPA comment, the phrase "IV use only" should be used.
* Revise the drug title to read "Bortezomib for injection, for intravenous use only".
Dosage Forms & Strengths: Acceptable
Full Prescribing Information
Section 2.1: Acceptable; "IV use only" phrase is used.
Section 2.8: Not Acceptable
Reconstitution instructions are accurate and complete, but USP title for the diluent should be used. Instructions for using the IV Sticker are included. In the last paragraph, the storage statement for reconstituted solution should be revised from "may be stored" to "should be stored" since other temperature conditions are not supported by the stability study.
* Revise section 2.8 to use"0.9% sodium chloride, USP" in paragraph 1 & 2, and table 5; and last paragraph to "~~may~~ should to be stored…"
Section 3: Acceptable
Section 11: Not Acceptable
Information in paragraph 1 is accurate and complete, however the term "chemical structure" should be revised to "molecular structure".
Information in paragraph 2 is acceptable.
Information in paragraph 3 essentially correct, but should be edited for clarity. The first sentence should use the phrase "IV use only". The inactive ingredient list should be revised to use the USP name and delete "anhydrous" since citric acid is present are a bortezomib ester not the salt; "~~anhydrous~~ citric acid, USP" and tromethamine, USP". For clarity, the fourth sentence should be revised as to "which, when ~~in~~ reconstituted ~~form,~~ consists".
* Revise Section 11 as follows:
(a) In paragraph 1, the term "molecular structure" should be used.
(b) In paragraph 3, the end of sentence 1 should use term "for intravenous injection use only"; the list of inactive ingredients should be revised to ~~anhydrous~~ citric acid, USP and tromethamine, USP; and, for clarity, the fourth sentence should be revised to "when reconstituted,".
Section 16: Not Acceptable

This section 16 addresses the required storage condition for the commercial product (unopened vials), thus the opening phrase should be deleted for clarity; "~~Unopened vials may be stored~~ Store at 20°-25°C (68°-77°F)." The revised statement is that provided on the vial and carton labels, and is the storage condition for reconstituted solution in section 2.8.
* Revise the storage statement in section 16 to "Store at 20°-25°C (68°-77°F):.

List of Deficiencies to be sent to the applicant:
[DMEPA comments sent 09/09/19 addressed the "IV use only" statement and the need for the term "0.9% sodium chloride, USP" on the labels and labeling, thus are not included in the CMC comments.]
1. The vial label, carton label and the package insert should be revised to use the USP names for listed formulation ingredients; "citric acid, USP", and "tromethamine, USP".
2. For the package insert:
(a) The second sentence of the last paragraph in section 2.8 should be revised to "… Bortezomib for injection ~~may~~ should be stored at 20°-25°C (68°-77°F)." This is the temperature range supported by the NDA stability studies.
(b) For clarity, in the last sentence of the first paragraph of section 11, the term "molecular structure" should be used.
(c) In section 16, revise the storage statement to read "Store at 20°-25°C (68°-77°F). Retain in original package to protect from light." Both unopened vial and reconstituted solution in vial and in syringe are all stored at this temperature condition.

Primary Labeling Reviewer: William Adams, CMC-DP/ONDP 09/12/19

Secondary Reviewer: Anamitro Banerjee, Ph.D., Branch Chief/ONDP 09/12/19

William Adams

Digitally signed by William Adams
Date: 9/12/2019 05:46:43PM
GUID: 508da7220002a12c3e992e212029c42b

Anamitro Banerjee

Digitally signed by Anamitro Banerjee
Date: 9/13/2019 09:22:25AM
GUID: 5075764700003844b7bc89632228509f

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:	September 6, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 206927
Product Name and Strength:	Bortezomib for Injection, 3.5 mg per vial
Applicant/Sponsor Name:	Dr. Reddy's Laboratories, Inc.
OSE RCM #:	2019-974-1
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label, sticker label and carton labeling received on August 29, 2019 for Bortezomib. We reviewed the revised container label, (b) (4) and carton labeling 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] We note the Applicant has revised the packaging configuration to remove the (b) (4)

2 CONCLUSION

The revised container label, sticker label, and carton labeling are unacceptable from a medication error perspective. We recommend revising the route of administration to ensure that this product is only administered by the intravenous route. Additionally, we recommend revising the presentation of the diluent (0.9% sodium chloride) on the sticker label and carton labeling using USP nomenclature.

3 RECOMMENDATIONS FOR DR. REDDY'S LABORATORIES, INC.

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

[a] Garrison N. Label and Labeling Review for Bortezomib (NDA 206927). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 19. RCM No.: 2019-974.

A. General Comments (Container labels & Carton Labeling)
    1. Revise the route of administration from “For Intravenous Use” to “For Intravenous Use Only” to mitigate the risk of administration errors.
B. Carton labeling
    1. Revise the presentation of the diluent, “0.9% Sodium Chloride” using USP nomenclature, to appear as “0.9% Sodium Chloride Injection, USP”.
C. Sticker label
    1. See B.1 and revise the sticker label accordingly.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON AUGUST 29, 2019

Container label

(b) (4)

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

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICOLE B GARRISON
09/06/2019 01:06:18 PM

HINA S MEHTA
09/06/2019 02:53:36 PM

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:	August 19, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 206927
Product Name and Strength:	Bortezomib for Injection, 3.5 mg per vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Dr. Reddy's Laboratories, Inc. (Dr. Reddy's)
FDA Received Date:	May 3, 2019 and August 7, 2019
OSE RCM #:	2019-974
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the approval process for NDA 206927 Bortezomib for Injection, 3.5 mg/vial, this review evaluates the proposed container label, sticker label, (b) (4), carton labeling, and Prescribing Information (PI) for areas that may lead to medication errors.

1.1 REGULATORY HISTORY

Dr. Reddy's submitted Bortezomib for Injection (NDA 206927) on March 3, 2014 and March 4, 2014, as a 505(b)(2) application which relies upon the listed drug, Velcade (bortezomib) for Injection under NDA 021602. The application received a Complete Response (CR) letter on December 17, 2014 due to product quality issues. Dr. Reddy's submitted a response to the CR letter for Bortezomib for Injection on November 23, 2015. Subsequently, the application for Bortezomib for Injection received another CR letter on May 4, 2016 due to product quality issues.

Dr. Reddy's submitted a response to the second CR letter for Bortezomib for Injection on May 3, 2019. Velcade is currently marketed as 3.5 mg per vial. The proposed product will be available in the same strength presentation as the reference product.

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
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

We note that the proposed Bortezomib for Injection has the strength (3.5 mg per vial), dosage form (for Injection), and the same concentration per mL of active ingredient upon reconstitution (intravenously at 1 mg/mL), dosage regimen (1.3 mg/m^2 dose) as the reference listed drug, Velcade. Velcade is currently approved for intravenous and subcutaneous use in patients with multiple myeloma and mantle cell lymphoma. However, we note that NDA 206927 is proposed for intravenous use only in patients with multiple myeloma and mantle cell lymphoma who have received at least 1 prior therapy.

DMEPA reviewed the proposed labels and labeling to determine whether there are significant concerns in terms of safety, related to preventable medication errors. We identified areas in the proposed labels that can be revised to improve clarity and readability of important information.

For the Division, we recommend removing negative statements and revising administration instructions for clarity.

For the Applicant, we recommend changes to the container label, (b) (4) and carton labeling to improve readability and prominence of important information. Specifically, we recommend bringing prominence to the route of administration, decreasing prominence of the Rx Only statement, defining the expiration date format, revising the usual dosage, reconstitution, and storage statements. Additionally, the product identifiers are absent from the drug package and refer the Applicant to the Guidance on Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers[a].

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed sticker label is acceptable from a medication error perspective. However, the container label, (b) (4) and carton 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 below in Section 4.1 for the Division and Section

---

[a] Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2018. Available from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf

4.2 for Dr. Reddy's to address our concerns. We advise these recommendations are implemented prior to approval of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Dosage and Administration Section

a. In section 2.1 *Important Dosing Guidelines*, delete the statement, "(b) (4) ." to prevent confusion as this product is indicated for intravenous use only.

b. In section 2.10 *Reconstitution/Preparation for Intravenous Administration* revise the statement, "(b) (4) ." to " A sticker that indicates the route of administration is provided with each bortezomib for injection vial."

4.2 RECOMMENDATIONS FOR DR. REDDY'S LABORATORIES, INC. (DR. REDDY'S)

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

A. General Comments (Container labels & Carton Labeling)

1. The Rx Only statement appears prominent on the principal display panel. Decrease the prominence by debolding the Rx Only statement.
2. Revise the statement, "(b) (4) " to "Recommended Dosage: See Prescribing Information".
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, identify the format you intend to use. We recommend 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 a space be used to separate the portions of the expiration date.

4. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. See draft guidance https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

5. On the side display panel, revise the statement, "(b) (4) " to "Protect from light (see Prescribing Information).

B. Carton Labeling

1. Include the net quantity statement (i.e. one vial) on the PDP in accordance with CFR 201.51.

2. Revise the statement, "(b) (4) to "Reconstitution: See back of this carton or Prescribing

C. (b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bortezomib received on May 3, 2019 from Dr. Reddy's Laboratories, Inc. (Dr. Reddy's).

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	
Indication	• For the treatment of adult patients with multiple myeloma • For the treatment of adult patients with mantle cell lymphoma who have received at least 1 prior therapy.	• For the treatment of adult patients with multiple myeloma • For the treatment of adult patients with mantle cell lymphoma
Route of Administration	Intravenous	Subcutaneous and intravenous
Dosage Form	for Injection	
Strength	3.5 mg per vial	
Dose and Frequency	The recommended starting dose of Bortezomib for Injection is 1.3 mg/m^2. <u>Untreated Multiple Myeloma</u>	The recommended starting dose of Velcade is 1.3 mg/m^2. <u>Untreated Multiple Myeloma</u> Velcade is administered in combination with oral melphalan and oral prednisone

[b] Velcade [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 AUG 12. Available from: https://www.accessdata.fda.gov/spl/data/0859677e-480a-4073-8900-6c69564143cb/0859677e-480a-4073-8900-6c69564143cb.xml

	Bortezomib for Injection is administered in combination with oral melphalan and oral prednisone for nine 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. <u>Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma</u> Bortezomib for 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 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 period (Days 23 to 35).	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. At least 72 hours should elapse between consecutive doses of Bortezomib for Injection. <u>Untreated Mantle Cell Lymphoma</u> Velcade is administered intravenously in combination with intravenous rituximab, cyclophosphamide, doxorubicin, and oral prednisone (VcR-CAP) for 6, 3-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. <u>Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma</u> 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, 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 period (Days 23 to 35).
How Supplied	Bortezomib for Injection is supplied as individually cartooned 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 cartooned 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 Injection concentration (mg/mL)
Intravenous	*3.5 mg*	*3.5 mL*	*1 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 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

On August 1, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, bortezomib. Our search identified one previous label and labeling review[c], and we considered our previous recommendations to see if they are applicable for this current review.

[c] Rutledge, M. Label and Labeling Review for Bortezomib (NDA 206927). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 MAR 04. RCM No.: 2014-879.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

On August 1, 2019, we searched FAERS using the criteria in the table below and identified 6 cases. We individually reviewed the cases, and limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[d] We excluded one cases because it involved dose omission of Revlimid (n =1).

Criteria Used to Search FAERS	
Initial FDA Receive Dates:	April 4, 2018 to August 1, 2019
Product Name:	Bortezomib
Product Active Ingredient (PAI):	Bortezomib
Event:	SMQ *Medication errors* (Narrow)
Country (Derived):	USA

E.2 Results

Our search identified 6 cases, of which 5 described errors relevant for this review.

Incorrect schedule of administration (n =1)

One case (FAERS Case No. 16169266) reported a patient started treatment with cyclophosphamide, bortezomib and dexamethasone (CyBorD) for kappa light chain multiple myeloma. He received bortezomib during hemodialysis. The patient developed staphylococcus epipdermidis endocarditis after starting treatment with bortezomib. The patient was treated with vancomycin followed by ampicillin-sulbactam for one month and Ursodiol (ursodeoxycholic acid). The patient presented with jaundice and a total bilirubin of 12 mg/dL, which peaked at 15.9 mg/dL one month later. Therapy with CyBorD was discontinued.

[d] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

Our review of Section 8.6 *Renal Impairment* of the proposed PI confirms the section clearly outlines that no dosage adjustments are needed and that bortezomib should be administered after the dialysis procedure. Therefore, we have no further recommendations at this time.

Incorrect route of administration (n=1)

One case (FAERS Case No. 15607716) reported a patient received intravenous bortezomib by the subcutaneous route. Outcomes or contributing factors were not reported.

Our review of Section 2 *Dosage and Administration* of the proposed PI indicates that bortezomib for Injection is for intravenous use only. In addition, our review of the proposed container label, sticker label, and carton labeling also indicates that bortezomib for Injection is for intravenous use. Therefore, we have no further recommendations at this time.

Dispensing error (n =3)

Three cases (FAERS Case No. 15680549, 15681660, and 1590314) reported patients were prescribed for bortezomib by subcutaneous administration and were inadvertently dispensed generic bortezomib which is approved for intravenous administration only. Dispensing error was discovered during review of drug use and the physicians were notified of the incorrect substitution. Outcomes or contributing factors were not reported.

Our review of Section 2 *Dosage and Administration* of the proposed PI indicates that bortezomib for Injection is for intravenous use only. In addition, our review of the proposed container label, sticker label, and carton labeling also indicates that bortezomib for Injection is for intravenous use. Therefore, we have no further recommendations at this time.

E.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

FAERS Case #
15607716
15680549
15681660
15690314

16169266

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

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,[e] along with postmarket medication error data, we reviewed the following Bortezomib labels and labeling submitted by Dr. Reddy's Laboratories, Inc. (Dr. Reddy's).

- Container label received on August 7, 2019
- Sticker label received on August 7, 2019
- (b) (4)
- Carton labeling received on August 7, 2019
- Prescribing Information (Image not shown) received on May 3, 2019

G.2 Label and Labeling Images

(b) (4)

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

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

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICOLE B GARRISON
08/19/2019 11:00:55 AM

HINA S MEHTA
08/19/2019 03:04:54 PM

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

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

Memorandum

Date: October 27, 2014

To: Alycia Anderson, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Davis, Team II Leader, OPDP

Subject: Comments on draft labeling (Package Insert) for Bortezomib for Injection
NDA 206927

In response to your consult dated May 29, 2014, we have reviewed the draft Package Insert (PI) for Bortezomib for Injection (Bortezomib) and offer the following comments. OPDP has made these comments using the version e-mailed to OPDP on October 22, 2014. Please note that we have also taken into consideration the labeling for Velcade® (bortezomib) for Injection (Reference listed drug, labeling dated 10/2012).

Section	Statement from draft	Comment
14 Clinical Studies	Figure 2: Overall Survival Bortezomib, Melphalan and Prednisone versus Melphalan and Prednisone	We note that the "Time (months)" and the "(b) (4)" depicted in Figure 2 in the Bortezomib labeling differs from Figure 2 in the Velcade labeling. Is Figure 2 in the Bortezomib labeling accurate?

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NISHA PATEL
10/27/2014

LABEL AND LABELING MEMO

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:	September 25, 2014
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 206927
Date of Submission:	March 4, 2014
Product Name and Strength:	Bortezomib for Injection, 3.5 mg per vial
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Dr. Reddy's Laboratories, Inc
OSE RCM #:	2014-879
DMEPA Primary Reviewer:	Michelle Rutledge, PharmD
DMEPA Team Leader:	Yelena Maslov, PharmD

1 INTRODUCTION

This memorandum responds to a request from the Division of Hematology Products (DHP) to evaluate the proposed container label, carton labeling, (b) (4) intravenous sticker carton labeling and prescribing information for Bortezomib for areas of vulnerability that could lead to medication errors. This product is a 505(b)(2) to RLD Velcade. Only the intravenous route will be reviewed in this application because there is patent exclusivity on the subcutaneous route of administration for Velcade. The reference listed drug (RLD), Velcade (Bortezomib) for injection, was approved on May 13, 2003 under NDA 021602 and is marketed as 3.5 mg per vial.

2 METHODS AND MATERIALS REVIEWED

We reviewed the proposed container label, carton labeling, (b) (4) intravenous sticker carton labeling and prescribing information for Bortezomib submitted on March 4, 2014.

A recent FAERS search from the last Velcade (Bortezomib) Label and Labeling memo NDA 21602 S-40, 2014-1549 and 2014-1550 dated September 18, 2014, identified no new cases related to medication errors.

3 CONCLUSIONS

DMEPA concludes that the proposed labeling is acceptable from a medication error perspective. We have no additional comments at this time.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHELLE K RUTLEDGE
09/25/2014

YELENA L MASLOV
09/25/2014