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 (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.

Reference ID: 4275960

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/m^2) to avoid a ten-fold misinterpretation.

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

Reference ID: 4275960

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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 (b) (4)

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 (b) (4) 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.

Reference ID: 4224011

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**
>
> (b) (4)

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.

Reference ID: 4224011

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. (b) (4) , 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) 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 <u>underlined</u>. Information to be deleted has a ~~strikethrough~~.

USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

(b) (4)

<u>Additional information describing a clinical study in which efficacy was not demonstrated in pediatric patients is approved for Millennium Pharmaceuticals, Inc. VELCADE (bortezomib) Injection. However, due to Millennium Pharmaceuticals, Inc.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.</u>

Reviewer comment: DPMH recommends that the statement, (b) (4) *be deleted* (b) (4)

DPMH recommends adding a disclaimer to Section 8.4 to acknowledge omission of the protected pediatric information without inclusion of the diagnoses of the pediatric patients in the study report to not potentially describe or support an indication.

Recommendations

Protected pediatric information can be safely "carved out" with a disclaimer added to section 8.4. Labeling negotiations are ongoing. The final labeling may differ as a result of those negotiations (see approval letter).

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[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).

Reference ID: 4224011

Once pediatric exclusivity expires, the protected pediatric information should be added back to the approved labeling.

APPEARS THIS WAY ON ORIGINAL

Reference ID: 4224011

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 $\leq$ 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.

Reference ID: 4224011

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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.

Reference ID: 4221681

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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/s/

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.

Reference ID: 4166611

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
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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).

Reference ID: 4089000

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.

Reference ID: 4089000

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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

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

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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/m^{2}dose. 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

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mg/mL), but differ in terms of how much diluent is required to prepare the final concentration (see Appendix A). (b) (4) 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]

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[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:

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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.

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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.

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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 cartooned 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

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	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.

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

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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)

[redacted]

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)

[redacted]

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APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[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

(b) (4)

Carton labeling

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

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(b) (4)

Sticker labels

(b) (4)

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/s/

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11/09/2016

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