

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**209191Orig1s000**

**PRODUCT QUALITY REVIEW(S)**



MEMORANDUM

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

DATE: June 26, 2018

**FROM: Branch 2/DNDP1/ONDP/OPQ**

**SUBJECT: Evaluation of the Risk Assessment of Elemental Impurities for NDA 209552**

**APPLICATION/DRUG: NDA 209191 Bortezomib for Injection, 2.5 mg/vial**

**Background:**

In response to the Agency's February 22, 2018 Complete Response (CR) Letter, in which the following comment was included:

Establish a validated test method for elemental impurities as part of the drug product specification consistent with ICH Q3D and USP <232/233>. Update the drug product specifications accordingly with controls for elemental impurities, if necessary.

The applicant submitted Complete Response on May 16, 2018 providing a risk assessment for elemental impurities in the proposed drug product in accordance with ICH Q3D and USP<232/233>.

**Applicant's Evaluation of Risk Assessment for Elemental Impurities:**

[Redacted content]

(b) (4)

**CONCLUSION: The applicant's evaluation of the Risk Assessment of Elemental Impurities for NDA 209191 is acceptable per ICH Q3D.**

Sherita McLamore, Ph.D.  
Acting Quality Assessment Lead, Branch 2  
Division of New Drug Product I (DNDPI)  
Office of New Drugs Products (ONDP)  
Office of Pharmaceutical Quality/CDER/FDA



Sherita  
McLamore

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## Executive Summary

### I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 209191 for Bortezomib for Injection, 2.5 mg/vial. As part of this action, OPQ grants a <sup>(b) (4)</sup> month re-test period for the drug substance when stored at <sup>(b) (4)</sup>. A 24-month drug product expiration period may be granted when stored at USP controlled room temperature conditions 20°C to 25°C (68°F to 77°F). <sup>(b) (4)</sup>

<sup>(b) (4)</sup>

<sup>(b) (4)</sup>

**Study Completion: Six (6) months from Action Date**

### II. Summary of Quality Assessments

#### A. Product Overview

NDA 209191 was submitted for Bortezomib in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act. Bortezomib is therapeutic proteasome inhibitor that was originally approved under the brand name VELCADE<sup>®</sup> for the treatment of multiple myeloma under NDA 021602 in 2003. VELCADE<sup>®</sup> is the listed drug (LD) for this submission. VELCADE<sup>®</sup> is a sterile, lyophilized product contained in a single-use vial containing 3.5 mg of the active. The major difference between the Hospira drug product and the listed product is strength of vial (2.5mg/vial vs.3.5mg/vial). Hospira's proposed Bortezomib for Injection is presented as a 2.5 mg/vial sterile, lyophilized powder. The applicant is proposing the 2.5 mg/vial strength in an effort to reduce drug waste.

Bortezomib is administered for nine 6-week treatment cycles. Bortezomib he dosing regimen include dosing weekly (days 1, 4, 8, 11, 22, 25 29 and 32) in cycles 1-4 and once weekly (days 1, 8, 22 and 29) in cycles 5-9.

Based on the information provided in this application (original submission, responses to information requests and in the resubmission), OPQ considers all review issues adequately addressed and potential risks to patient safety and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 209191 and grants a <sup>(b) (4)</sup> month re-test period for the drug substance and a 24 month drug product expiration period when stored under controlled room temperature in the commercial packaging.

<b>Proposed Indication(s) including Intended Patient Population</b>	Multiple Myeloma
<b>Duration of Treatment</b>	54 weeks (nine 6-week cycles)
<b>Maximum Daily Dose</b>	1.3 mg/m <sup>2</sup>
<b>Alternative Methods of Administration</b>	SC or IV

**B. Quality Assessment Overview**

Following the review of the original submission of NDA 209191, all review disciplines including clinical, non-clinical and product quality recommended approval; however, the application was recommended for a Tentative Approval (TA) as the listed drug, Velcade<sup>®</sup>, was subject to a period of patent protection based on the outcome of the patent infringement suit against the applicant with respect to patent 6,713,446 in the United States District Court For The District of Delaware. NDA 209191 was resubmitted on June 30, 2016 and following the review of the June 30, 2016, resubmission the application was issued a Complete Response (CR) as a result of deficiencies associated with the drug substance manufacturing facility. The comment below was included in the Agency's October 2017 Complete Response letter:

During a recent inspection of the [REDACTED] (b) (4) [REDACTED] manufacturing facility for this NDA, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this NDA may be approved.

NDA 209191 was resubmitted on December 22, 2017. After review of the December 22, 2017 resubmission, it was determined that all deficiencies associated with the drug substance manufacturing facility had been resolved (see appended facility review) and that there were no outstanding issues to preclude the approval of this NDA. Accordingly, NDA 209191 is recommended for Approval from a product quality perspective.

**C. Special Product Quality Labeling Recommendations (NDA only)**

n/a

**D. Final Risk Assessment (see Attachment)**

n/a

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McLamore

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MEMORANDUM

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

DATE: 2/22/2018

**FROM: ONDP/OPQ**

**SUBJECT: Final OPQ Recommendation Memo for NDA 209191**

**APPLICATION/DRUG: NDA 209191 Bortezomib for Injection, 2.5 mg/vial**

**Decisional Memo:**

ONDP representatives attended a meeting on Wednesday (2/21/18) that included representation from OPQ, OGD, OCC, ORP, and OND [REDACTED] (b) (4) Hospira's 505(b)(2) NDA 209191 for bortezomib (PDUFA goal 2/22/18) [REDACTED] (b) (4)

[REDACTED]

[REDACTED] Therefore, since this issue is currently outstanding for the NDA, we recommend that a CR action be taken.

In working with OCC and partners across the center, **OPQ recommends a CR action** for NDA 209191.

**CR Comment:**

Establish a validated test method for elemental impurities as part of the drug product specification consistent with ICH Q3D and USP <232/233>. Update the drug product specifications accordingly with controls for elemental impurities, if necessary.

Giuseppe Randazzo, MS  
Director (acting), Office of New Drugs Products (ONDP)  
Director, Office of Program and Regulatory Operations (OPRO)  
Office of Pharmaceutical Quality/CDER/FDA

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Giuseppe  
Randazzo

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## Executive Summary

### I. Recommendations and Conclusion on Approvability

OPQ recommends **COMPLETE RESPONSE** of NDA 209191 for Bortezomib for Injection, 2.5 mg/vial as there are unresolved deficiencies associated with the drug substance manufacturing facility (b) (4). The outstanding deficiency is included below:

During a recent inspection of the (b) (4) manufacturing facility for this NDA, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this NDA may be approved.

### II. Summary of Quality Assessments

#### A. Product Overview

NDA 209191 was submitted for Bortezomib in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act. Bortezomib is therapeutic proteasome inhibitor that was originally approved under the brand name VELCADE® for the treatment of multiple myeloma under NDA 021602 in 2003. VELCADE® is the listed drug (LD) for this submission. VELCADE® is a sterile, lyophilized product contained in a single dose vial containing 3.5 mg of the active. The major difference between the Hospira drug product and the listed product is strength of vial (2.5mg/vial vs.3.5mg/vial). Hospira’s proposed Bortezomib for Injection is presented as a 2.5 mg/vial sterile, lyophilized powder. The applicant is proposing the 2.5 mg/vial strength to reduce drug waste.

Bortezomib is administered for nine 6-week treatment cycles. Bortezomib dosing regimen include dosing weekly (days 1, 4, 8, 11, 22, 25 29 and 32) in cycles 1-4 and once weekly (days 1, 8, 22 and 29) in cycles 5-9.

Based on the recommendation from OPF, OPQ recommends a COMPLETE RESPONSE for NDA 209191.

<b>Proposed Indication(s) including Intended Patient Population</b>	Multiple Myeloma
<b>Duration of Treatment</b>	54 weeks (nine 6-week cycles)
<b>Maximum Daily Dose</b>	1.3 mg/m <sup>2</sup>
<b>Alternative Methods of Administration</b>	SC or IV

#### B. Quality Assessment Overview

**Drug Substance**

No changes noted from the original submission.

**Drug Product**

No changes noted from the original submission.

**Process**

No changes noted from the original submission.

**Biopharmaceutics**

No changes noted from the original submission.

**Facilities**

Drug substance, Bortezomib USP, is manufactured by (b) (4)

(b) (4) has acceptable inspectional history, a PAI was deemed not necessary for the manufacturing of the key intermediates. No change was made to the status of this site since the review of the original submission. This facility remains acceptable based on its acceptable inspection history and years of experience of manufacturing non-sterile APIs by chemical synthesis. The drug substance manufacturing site (b) (4) was subjected to a surveillance inspection in (b) (4) which included Quality, Materials, Equipment & Facilities, Production, Laboratory, and Packaging/Labeling. This inspection resulted in the issuance of a 2-item 483 (see deficiencies below).

(b) (4)

Based on the potential OAI status, OPF recommends a WITHHOLD for NDA 209191. There are no other changes noted from original submission

**Environmental Assessment**

No changes noted from the original submission.

**C. Special Product Quality Labeling Recommendations (NDA only)**

n/a

**D. Final Risk Assessment (see Attachment)**  
see Attachment



Sherita  
McLamore

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Date: 10/31/2017 04:06:39PM

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**MICROBIOLOGY**

***Product Background:***

**NDA/ANDA:** 209191

**Drug Product Name / Strength:** Bortezomib for Injection, 2.5 mg/vial

**Route of Administration:** Subcutaneous or IV

**Applicant Name:** Hospira, Inc., 275 N Field Drive, (b) (4) Lake Forest, IL

**Manufacturing Site:**

Gland Pharma Limited,

(b) (4)

Visakhapatnam Special Economic Zone (VSEZ), Duvvada, Visakhapatnam – 530049. Andhra Pradesh, INDIA (IND).

**Method of Sterilization:** (b) (4)

***Review Summary:***

**List Submissions being reviewed (table):**

Submitted	Received	Assigned to Reviewer
6/30/2016	6/30/2016	7/13/2016
9/8/2016*	9/8/2016	N/A

\*IR response

**Highlight Key Outstanding Issues from Last Cycle:** N/A

**Concise Description Outstanding Issues Remaining:** N/A. The application is **recommended for approval** on the basis of sterility assurance.

**P.1 Description of the Composition of the Drug Product**

- **Description of drug product** – White to off-white lyophilized powder or cake.
- **Drug product composition** –

Component	Quantity per (mL)	Quantity per unit	Function
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Bortezomib	(b) (4)	2.5 mg	API
Mannitol		25.0 mg	(b) (4)
(b) (4)			

- **Description of container closure system –**

Component	Description	Manufacturer
Vial	(b) (4)	
Stopper		
Seal		

**Reviewer's Assessment:** Containers and closures are adequately described.

**ADEQUATE**

## 2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

### A. PACKAGE INSERT (P.1.14, P.2. Compatibility)

Storage temperature: 20 to 25°C, excursions permitted from 15 to 30°C; Route of administration: IV / SC; Container: (b) (4)

(b) (4)

Reconstitution: Bortezomib should be reconstituted with 0.9% sodium chloride. For IV injection, reconstitute with 2.5 mL 0.9% NaCl for a final concentration of

1 mg/mL. For Subcutaneous injection, reconstitute with 1.0 mL 0.9% NaCl for a final concentration of 2.5 mg/mL.

Reconstituted bortezomib for injection may be stored at 25°C and should be administered within 8 hours of preparation.

There is no further dilution of the reconstituted product prior to administration.

Adventitious microbial contamination study for Bortezomib for injection to support the label claim of the post-reconstitution storage condition was performed with the 1 mg/mL (worst case conditions) with 0.9% Sodium chloride injection.

The diluted drug product (1mg/mL) was inoculated with a range of microorganisms including *E. coli*, *S. aureus*, *P. aeruginosa*, *C. albicans*, *A. brasiliensis*, and *M. luterus* at the concentration of  $10^2$  cfu and incubated at  $25\pm 2^\circ\text{C}$ . Microbial counts were performed at 0, 4, 8 and 24 hours. Counts decreased at all time-points after initial inoculation for all microorganisms. RLD was included in the study and showed no increase in growth. Positive control without the presence of drug product showed no decrease of microorganism counts over the course of study.

**Reviewer's Assessment:** Microbiological study supports the label claim of the post-reconstitution storage condition of  $25\pm 2^\circ\text{C}$  for 8 hours.

**ADEQUATE**

***Primary Microbiology Reviewer Name and Date:***

Yuansha Chen, Ph.D.  
CDER/OPQ/OPF/DMA  
10/24/2016

***Secondary Reviewer Name and Date (and Secondary Summary, as needed):***

Neal J. Sweeney, Ph.D.  
CDER/OPQ/OPF/DMA  
10/22/16



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Sweeney

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Yuansha  
Chen

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## Executive Summary

### I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 209191 for Bortezomib for Injection, 2.5 mg/vial. As part of this action, OPQ grants a <sup>(b) (4)</sup> month re-test period for the drug substance when stored <sup>(b) (4)</sup>. A 24-month drug product expiration period may be granted when stored at USP controlled room temperature conditions 20°C to 25°C (68°F to 77°F). There are no outstanding issues and no post-approval quality agreement to be conveyed to the applicant.

### II. Summary of Quality Assessments

#### A. Product Overview

NDA 209191 was submitted for Bortezomib in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act. Bortezomib is therapeutic proteasome inhibitor that was originally approved under the brand name VELCADE<sup>®</sup> for the treatment of [multiple myeloma](#) under NDA 021602 in 2003. VELCADE<sup>®</sup> is the listed drug (LD) for this submission. VELCADE<sup>®</sup> is a sterile, lyophilized product contained in a single-use vial containing 3.5 mg of the active. The major difference between the Hospira drug product and the listed product is strength of vial (2.5mg/vial vs.3.5mg/vial). Hospira’s proposed Bortezomib for Injection is presented as a 2.5 mg/vial sterile, lyophilized powder. The applicant is proposing the 2.5 mg/vial strength in an effort to reduce drug waste.

Bortezomib is administered for nine 6-week treatment cycles. Bortezomib he dosing regimen include dosing weekly (days 1, 4, 8, 11, 22, 25 29 and 32) in cycles 1-4 and once weekly (days 1, 8, 22 and 29) in cycles 5-9.

Based on the information provided in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed and potential risks to patient safety and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 209191 and grants a <sup>(b) (4)</sup> month re-test period for the drug substance and a 24 month drug product expiration period when stored under controlled room temperature in the commercial packaging.

<b>Proposed Indication(s) including Intended Patient Population</b>	Multiple Myeloma
<b>Duration of Treatment</b>	54 weeks (nine 6-week cycles)
<b>Maximum Daily Dose</b>	1.3 mg/m <sup>2</sup>
<b>Alternative Methods of Administration</b>	SC or IV

## B. Quality Assessment Overview

### Drug Substance

Bortezomib drug substance is a white to off-white slightly hygroscopic powder.

Bortezomib has two chiral centers and four possible isomers. (b) (4)

Bortezomib drug substance is manufactured by (b) (4). The applicant referenced DMF (b) (4) for all aspects pertaining to the manufacture and control of Bortezomib. DMF (b) (4) was last reviewed in (b) (4) and is adequate to support the approval of this NDA.

### Drug Product

Bortezomib for Injection is available as a sterile lyophilized powder, intended for intravenous or subcutaneous route of administration and is manufactured by Gland Pharma. The drug product is comprised of a white to off white powder, packaged in clear (b) (4) glass vials and is reconstituted in 0.9% sodium chloride at a concentration of 1.0 mg/mL (IV) or 2.5 mg/mL (SC). The single dose vials are 2.5 mg fill in a 10 mL vial, closed with (b) (4) closures and aluminum seals with plastic flip-off tops. The formulation of Bortezomib for Injection was based on the Millennium Pharmaceutical's VELCADE and the amounts determined to closely match those in the innovator's samples. The grades of excipients used are Pharmacopoeial USP/NF grades. Mannitol USP is used as an excipient in the formulation of Bortezomib for Injection. (b) (4)

When reconstituted as directed, Bortezomib for Injection may be stored at 25°C (77°F). The drug product is not further diluted in an infusion bag and not admixed with other diluents or drug formulations prior to administration.

Based on the 18 months of stability data (via an update) generated on Bortezomib for Injection registration stability batches, Hospira proposed and FDA accepted that the expiration dating be set at **24 months** for drug product, when stored at controlled room temperature (20-25°C; 68- 77°F).

### Process

(b) (4)

**Biopharmaceutics**

The proposed drug product, Bortezomib for Injection, 2.5 mg/vial, is a lyophilized powder for solution, for intravenous (IV) and subcutaneous (SC) administration after reconstitution; and the proposed drug product has the same active ingredient (bortezomib) and inactive ingredient, and is the same dosage form, route of administration and indication as the Listed Drug, Velcade® (bortezomib) 3.5 mg/vial. The pH and osmolality of the proposed drug product and the LD, after reconstitution (with 0.9% sodium chloride injection, 1 mg/ml), are similar. Therefore, the disposition kinetics of Bortezomib should be similar from these two products [Bortezomib Injection, 2.5 mg/vial, and the LD product, Velcade® (bortezomib) 3.5 mg/vial]. The Applicant's request for a waiver of the in vivo study for the proposed drug product, Bortezomib Injection, 2.5 mg/vial, is granted.

**Facilities**

Drug substance, Bortezomib USP, is manufactured by (b) (4)

Both facilities have acceptable inspection history, and many years of experience of manufacturing non-sterile APIs by chemical synthesis (CSN).

Drug product, Bortezomib for Injection, 2.5mg/vial, is manufactured by GLAND PHARMA LIMITED (FEI 3009056604). (b) (4)

The company had a pOAI inspection in (b) (4) but was down-graded to VAI by CDER based on the information/response received.

The risk associated with manufacturing this drug product is Medium. No PAI is needed. All facilities are acceptable based on its manufacturing capability and inspectional history.

**Environmental Assessment**

A categorical exclusion was submitted under 21 CFR § 25.31(b). The applicant states that to the applicant's knowledge, no extraordinary circumstances exist. The drug substance and intermediates are not derived from plants or animals taken from the wild. There is no information indicating that additional environmental information is warranted.

The request for categorical exclusion is granted.

**C. Special Product Quality Labeling Recommendations (NDA only)**

n/a

**D. Final Risk Assessment (see Attachment)**  
**see Attachment**



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McLamore

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## LABELING

### R Regional Information

#### 1.14 Labeling

##### *Labeling & Package Insert*

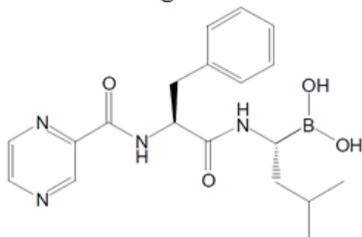
##### DESCRIPTION section:

#### 11 DESCRIPTION

Bortezomib for Injection is an antineoplastic agent. Bortezomib is a modified dipeptidyl boronic acid. The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1-[[[(2S)-1-oxo-3-phenyl-2[(pyrazinylcarbonyl) amino]propyl]amino]butyl] boronic acid.

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Bortezomib has the following chemical structure:



The molecular weight is 384.24 g/mol. The molecular formula is C<sub>19</sub>H<sub>25</sub>BN<sub>4</sub>O<sub>4</sub>. The solubility of bortezomib, as the monomeric boronic acid, in water is 3.3 to 3.8 mg/mL in a pH range of 2 to 6.5.

Bortezomib for Injection is available for intravenous injection or subcutaneous use. Each single dose vial contains 2.5 mg of bortezomib as a sterile lyophilized powder. It also contains the inactive ingredient: 25 mg mannitol, USP. The product is provided as a mannitol boronic ester which, in reconstituted form, consists of the mannitol ester in equilibrium with its hydrolysis product, the monomeric boronic acid. The drug substance exists in its monohydrate form.

Is the information accurate?  Yes  No

If "No," explain.

Is the drug product subject of a USP monograph?  Yes  No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

**HOW SUPPLIED section:**

**16 HOW SUPPLIED/STORAGE AND HANDLING**

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.

NDC 0409-1703-01

2.5 mg single dose vial

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.

Follow guidelines for handling and disposal for cytotoxic drugs, including the use of gloves and other protective clothing to prevent skin contact<sup>1</sup>.

i) Is the information accurate?  Yes  No

If "No," explain.

ii) Are the storage conditions acceptable?  Yes  No

If "No," explain.

**DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:**

**2 DOSAGE AND ADMINISTRATION**

**2.1 (b) (4) Dosing Guidelines**

The recommended starting dose of bortezomib for injection is 1.3 mg/m<sup>2</sup>. Bortezomib for injection may be administered intravenously at a concentration of 1 mg/mL, or subcutaneously at a concentration of 2.5 mg/mL [see *Dosage and Administration* (b) (4)]

When administered intravenously, bortezomib for injection is administered as a 3 to 5 second bolus intravenous injection. (b) (4)

(b) (4)

(b) (4)

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)?

Yes  No  N/A

If "No," explain.

## R Regional Information

### 1.14 Labeling

#### ***Immediate Container Label (2.5 mg/vial)***



**Reviewer's Assessment:** *The applicant responded to deficiencies and revised the label as recommended. Adequate.*

#### **Carton Labeling (2.5 mg/vial):**



**Sticker Sheet: (for subcutaneous injection):****Sticker Sheet: (for IV injection):****Reviewer's Assessment:**

*Hospira's proposed sticker sheet (subcutaneous and intravenous) labeling is provided herein. This labeling will be packed inside the carton to aid in preparation and administration of the drug product. This labeling is comparable to that provided in the US Velcade® product.*

*Side by side comparisons of Hospira's container label, carton label, and sticker sheet versus labeling for Velcade®, the listed drug, are provided. The proposed labeling is the same as the labeling of the listed drug except for those differences explained in the annotated comparison of labeling per 21 CFR 314.94(a)(8)(iii).*

*The deficiencies were identified and communicated to the applicant by DMEPA. The applicant responded satisfactorily to the deficiencies on 25-NOV-2016.*

*The container labeling is now adequate.*

***Conclusion:*** *Labels and Labeling are adequate from a CMC stand point.*

***Primary Labeling Reviewer Name and Date:***

Rajiv Agarwal, Ph.D, 22-FEB-2017

***Secondary Reviewer Name and Date (and Secondary Summary, as needed):***

*Anamitro Banerjee, PhD, March 15, 2017*



Rajiv  
Agarwal

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Banerjee

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## ATTACHMENT I: Final Risk Assessments

[IQA Review Guide Reference](#)

### A. Final Risk Assessment – NDA 209191 (Bortezomib for Injection), Hospira

#### a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
<b>Sterility</b>	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure</li> <li>Process parameters</li> <li>Scale/equipments</li> <li>Site</li> </ul>	H	Sterility testing, (b) (4) validation of (b) (4) manufacturing processes.	Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
<b>Endotoxin Pyrogen</b>	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure</li> <li>Process parameters</li> <li>Scale/equipments</li> <li>Site</li> </ul>	M	Endotoxin testing (b) (4) validation of (b) (4) manufacturing processes.	Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
<b>Assay (API), stability</b>	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure</li> <li>Raw materials</li> <li>Process parameters</li> <li>Scale/equipments</li> <li>Site</li> </ul>	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
<b>Physical Stability (solid state) Lyophilized small molecule products</b>	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure</li> <li>Raw materials</li> <li>Process parameters</li> <li>Scale/equipments</li> <li>Site</li> </ul>	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
<b>Uniformity of Dose (Fill Volume/delivera ble volume)</b>	<ul style="list-style-type: none"> <li>Formulation</li> <li>Container closure</li> <li>Process parameters</li> <li>Scale/equipments</li> <li>Site</li> </ul>	L	Assessed during Development and controlled via specs	Acceptable	Solid cake and not a solution therefore CU is monitored via USP <905>. Controls are in place, continue stability monitoring post approval
<b>Osmolality</b>	<ul style="list-style-type: none"> <li>Formulation</li> <li>Raw materials</li> <li>Process parameters</li> <li>Scale/equipments</li> </ul>	L	Assessed during Development	Acceptable	Similar to the reference drug.

	<ul style="list-style-type: none"> <li>• Site</li> </ul>				
<b>pH- (Low)</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	L	Controlled via specs during stability	Acceptable	Controls are in place during stability testing. Continue stability monitoring post approval
<b>Particulate matter (non aggregate for solution only)</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	M	Controlled via specs during stability	Acceptable	Controls are in place. Continue stability monitoring post approval
<b>Leachable extractables</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	L	USP testes are performed and conforms	Acceptable	Controlled via DMF
<b>Moisture Content (lyophilized)</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	L	Controlled via specs during stability	Acceptable	Controls are in place.
<b>Appearance (plug)</b>	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	L	Controlled via specs during stability	Acceptable	Controls are in place.



Rajiv  
Agarwal

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## CHAPTER VII: Biopharmaceutics

**NDA: 209191**

**Drug Product Name: Bortezomib for Injection**

**Strength(s): 2.5 mg/vial<sup>1</sup>**

**Route of Administration: IV and Subcutaneous**

**Applicant Name: Hospira**

### **EXECUTIVE SUMMARY:**

The proposed drug product, Bortezomib for Injection, 2.5 mg/vial, is a lyophilized powder for solution, for intravenous (IV) and subcutaneous (SC) administration after reconstitution; and the proposed drug product has the same active ingredient (bortezomib) and inactive ingredient, and is the same dosage form, route of administration and indication as the Listed Drug, Velcade<sup>®</sup> (bortezomib) 3.5 mg/vial. The pH and osmolality of the proposed drug product and the LD, after reconstitution (with 0.9 % sodium chloride injection, 1 mg/ml), are similar. Therefore, the disposition kinetics of Bortezomib should be similar from these two products [Bortezomib Injection, 2.5 mg/vial, and the LD product, Velcade<sup>®</sup> (bortezomib) 3.5 mg/vial]. The Applicant's request for a waiver of the in vivo study for the proposed drug product, Bortezomib Injection, 2.5 mg/vial, is granted.

From the Biopharmaceutics perspective, NDA 209191 for Bortezomib for Injection (2.5 mg/vial), is recommended for **APPROVAL**.

### **SUBMISSION:**

Hospira submitted the current NDA for Bortezomib for Injection, 2.5 mg/vial for IV and subcutaneous use under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. This 505 (b)(2) application relies for approval, on FDA's findings of safety and effectiveness for the listed drug (LD), Velcade<sup>®</sup> (bortezomib) for Injection lyophilized powder for subcutaneous or intravenous use (3.5 mg/vial) marketed by Millennium Pharmaceuticals under the approved NDA, 21602.

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<sup>1</sup> 2.5 mg/ mL (SC); 1 mg/mL (IV), after reconstitution

**BIOPHARMACEUTICS REVIEW:**

The LD, Velcade® (bortezomib) for Injection, is supplied in vials containing 3.5 mg of bortezomib as a white to off-white cake or powder. The LD, as specified in the Velcade® product label, must be reconstituted with 3.5 mL of sodium chloride, 9 mg/mL (0.9%) for injection prior to IV administration and 1.4 mL of sodium chloride 9 mg/mL (0.9%) for subcutaneous injection.

Hospira developed a new strength of Bortezomib for Injection, a 2.5 mg/vial, which is intended to be the same dosage form, route of administration, inactive ingredients (mannitol) and dosing regimen as the LD, Velcade® (bortezomib for injection, 3.5 mg/vial). The concentration per mL of active ingredient on reconstitution from the proposed 2.5 mg/vial product remains the same as the 3.5 mg/vial presentation of the LD product.

Hospira’s 2.5 mg strength is labeled to be reconstituted with the appropriate volume of 0.9% Sodium Chloride Injection to a concentration of either 1.0 mg/mL for IV administration or 2.5 mg/mL for subcutaneous administration. This is identical to the concentration for IV and SC administration as the LD, Velcade® (bortezomib for injection, 3.5 mg/vial). The Applicant stated that because the concentration per mL of active ingredient after reconstitution remains the same as the 3.5 mg/vial presentation of the reference drug product, the proposed 2.5 mg/vial presentation does not pose any safety or efficacy concerns.

In Table 1 below, a side-by-side comparison is provided to demonstrate that the conditions of use, active ingredient, route of administration, dosage form, strengths of the proposed drug product are similar to the LD.

**Table 1. Comparison of the proposed product, Bortezomib Injection, 2.5 mg/vial, and the LD product, Velcade® (bortezomib) 3.5 mg/vial**

	Listed Drug	Proposed Product
	Millennium Pharmaceuticals, Inc. Velcade®	Hospira, Inc. Bortezomib for Injection
Conditions of Use	Treatment of patients with multiple myeloma.  Treatment of patients with mantle cell lymphoma	Treatment of patients with multiple myeloma.
Active Ingredient(s)	Bortezomib	Bortezomib
Inactive Ingredient(s)	Mannitol, USP (35 mg)	Mannitol, USP (25 mg)
Route of Administration	Powder IV, SC	Powder IV, SC

Dosage Form	Injectable	Injectable
Strength	3.5 mg/vial	2.5 mg/vial

Table 2 below provides the proposed product formulation prior to lyophilization. (b) (4)



**Table 2. Comparison of the proposed product formulation prior to lyophilization and Velcade® (bortezomib) 3.5 mg/vial**

Component	Hospira Quantity per Milliliter (mL)	Function	Velcade [LD]
Bortezomib	(b) (4)	Active ingredient	(b) (4)
Mannitol	(b) (4)	(b) (4)	-
			-
			-
Total Volume	(b) (4)		

Table 3 below provides a summary of composition for Hospira’s Bortezomib for Injection 2.5 mg/vial compared to the LD. The table highlights the differences between Hospira drug product (2.5 mg/vial) and the LD (3.5 mg/vial) prior to reconstitution, including bortezomib and mannitol content per vial. It also compares the volumes of 0.9% Sodium Chloride (NaCl) injection required for reconstitution by IV and SC routes. While the content per vial for bortezomib and mannitol is different between Hospira and the LD products, the ratio of mannitol to drug substance is identical for both. Therefore upon reconstitution with the appropriate volume of 0.9% NaCl injection, the reconstituted drug concentration will be either 1.0 mg/mL for IV administration or 2.5 mg/mL for SC administration for both Hospira and the LD drug products. In addition, the administered volumes are identical for Hospira and the LD products, in accordance with LD where the total volume (mL) to be administered is calculated from the patient Body Surface Area (BSA) in m<sup>2</sup> and the recommended daily dose.

**Table 3: Comparison of the proposed Bortezomib Injection and the Listed Drug, after reconstitution** (b) (4)

Test	Hospira 2.5 mg/vial Bortezomib for Injection	LD 3.5mg/vial VELCADE®
<b>Prior to Reconstitution</b>		
Bortezomib content		
per vial	<b>2.5 mg/vial</b>	<b>3.5</b>
Mannitol content		
per vial	<b>25.0 mg/vial</b>	<b>35.0</b>
<b>After Reconstitution</b>		

<b>Reconstitution - Intravenous administration</b>		
Volume 0.9% NaCl (mL)	<b>2.5 mL</b>	<b>3.5 mL</b>
Bortezomib concentration (mg/mL)	<b>1 mg/mL</b>	<b>1 mg/mL</b>
<b>Reconstitution - Subcutaneous administration</b>		
Volume 0.9% NaCl (mL)	<b>1.0 mL</b>	<b>1.4 mL</b>
Bortezomib concentration (mg/mL)	<b>2.5 mg/mL</b>	<b>2.5 mg/mL</b>

Table 4 below provides comparison of the physicochemical properties of the proposed Bortezomib for Injection and the LD, after reconstitution (1 mg/mL). The data in table 4 demonstrate that the pH and the osmolality of the proposed product and the LD product, after reconstitution are similar.

**Table 4: Comparative physicochemical data of Bortezomib for Injection and the Listed Drug, Velcade®**

Test	Hospira Bortezomib for Injection 2.5 mg/vial				VELCADE® lot# 222505
	Acceptance Criteria/ Nominal Target	BORCB2015	BORCB2025	BORCB2035	
Expiry date		Mar 2017	Mar 2017	Apr 2017	May 2018
Date tested <sup>b</sup>		Aug 2016 <sup>b</sup>	Aug 2016 <sup>b</sup>	Aug 2016 <sup>b</sup>	Aug 2016
Description of plug	A white to off white cake or powder <sup>d</sup>	A white powder	A white powder	A white powder	A white powder
		A white powder	A white powder	A white powder	A white powder
		A white powder	A white powder	A white powder	A white powder
Osmolality <sup>c</sup> (Osmol/kg)	Internal only (b) (4)	<b>0.335</b>	<b>0.338</b>	<b>0.337</b>	<b>0.340</b>
	Osmol/kg)	<b>0.335</b>	<b>0.335</b>	<b>0.335</b>	<b>0.338</b>
		<b>0.340</b>	<b>0.343</b>	<b>0.340</b>	<b>0.334</b>
pH <sup>c</sup>	(b) (4)	5.1	5.2	5.2	5.0
		5.2	5.2	5.1	5.0
		<b>5.2</b>	<b>5.2</b>	<b>5.2</b>	<b>5.0</b>
Description of reconstituted solution <sup>c</sup>	A Clear, colourless solution	A clear colourless solution	A clear colourless solution	A clear colourless solution	A clear colourless solution

<sup>a</sup> Published information – The VELCADE® US Labeling Rev 18, reference ID: 3819536.

<sup>b</sup> Note test dates for Osmolality - samples 1&2 of BORCB2015, BORCB2025 and BORCB2035 is 02 Mar 2016 and sample 3 of BORCB2015, BORCB2025 and BORCB2035 is 22 Aug 2016.

<sup>c</sup> Reconstituted concentration 1 mg/mL

## BIOWAIVER REQUEST

In this NDA submission, the Applicant is requesting that the Agency waive the CFR's requirement to provide in vivo bioavailability/bioequivalence (BA/BE) data for their product. The Applicant's drug product is a parenteral solution intended solely for administration by injection and it contains the same active and inactive ingredients as the LD. The concentrations of the active and the inactive ingredients, for the proposed the LD product, are also the same as the LD after reconstitution with 0.9% Sodium Chloride.

The Applicant cited 21 CFR 320.22(b)(1)(i) [..the in vivo bioavailability/bioequivalence of the drug product may be self-evident] in support of the biowaiver request.

### **Reviewer's Final Assessment: Adequate**

This 505 (b)(2) Application relies, for its approval, on FDA's findings of safety and effectiveness for the listed drug. In addition, the NDA includes a biowaiver request for the conduct of bioavailability/bioequivalence study(ies).

The proposed drug product is a parenteral solution for administration by injection, and the proposed drug product has the same active (bortezomib) and inactive ingredients, is the same dosage form, has the same route of administration and indication as the LD. The pH [approximately pH 5.0] and osmolality of Bortezomib Injection and the Listed Drug, after reconstitution <sup>(b) (4)</sup> (with 0.9 % sodium chloride injection, 1 mg/ml), are similar.

The disposition kinetics of Bortezomib should be similar from these two drug products [Bortezomib Injection, 2.5 mg/vial, and the LD product, Velcade® (bortezomib) 3.5 mg/vial]. Therefore, the Applicant's request for a waiver of the in vivo study for their proposed product, Bortezomib Injection, 2.5 mg/vial, is granted.

## RECOMMENDATION

A waiver of the in vivo bioequivalence study requirement is granted. From the Biopharmaceutics perspective, NDA 209191 for Bortezomib for Injection (2.5 mg/vial), is recommended for **APPROVAL**.



Om Anand, Ph.D. [Date: 12/19/2016]

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