CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209191Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 209191
Review #5

Drug Name/Dosage Form	Bortezomib for Powder for Injection
Strength	2.5 mg/vial and 1 mg/vial
Route of Administration	IV or SC
Rx/OTC Dispensed	Rx
Applicant	Hospira, Inc
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Resubmission	02-Mar-2022	All
Amendment (SD 58)	11-Mar-2022	DP
Amendment (SD 59)	17-Mar-2022	Process

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	n/a	n/a
Drug Product	Olen Stephens	Sherita McLamore
Process	n/a	n/a
Microbiology	n/a	n/a
Facility	n/a	n/a
Biopharmaceutics	n/a	n/a
Regulatory Business Process Manager	Dahlia Walters	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
ORA Lead	n/a	n/a
Environmental	n/a	na/

Reference ID: 4970303

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	N/A	No Review	Adequate information provided in the NDA
	Type III			N/A	No Review	Adequate information provided in the NDA
	Type V			N/A	No Review	Adequate information provided in the NDA
	Type IV			N/A	No Review	Adequate information provided in the NDA
	Type II			N/A	No Review	MF reviewed by OGD 10/17/16

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	021602	VELCADE (3.5 mg) RLD

2. CONSULTS

N/A

Reference ID: 4970303

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 209191 which was submitted for Bortezomib for Injection, 2.5 mg/vial and 1 mg/vial. There are no outstanding issues and no post-approval quality agreements to be communicated to the applicant.

II. Summary of Quality Assessments

A. Product Overview

NDA 209191 was submitted for Bortezomib for Injection, 2.5 mg/vial and 1 mg/vial 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-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. Hospira's proposed Bortezomib for Injection is presented as a 2.5 mg/vial and a 1 mg/vial sterile, lyophilized powder. The applicant is proposing the new strengths in an effort to reduce drug waste.

Bortezomib is administered for nine 6-week treatment cycles. Bortezomib dosing regimen includes 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, 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. As part of this action, OPQ grants a 36-month expiration for the 2.5 mg/vial drug product and a 24-month expiration for the 1 mg/vial drug product when stored at USP controlled room temperature conditions 20°C to 25°C (68°F to 77°F). OPQ also grants a (b) (4) month re-test period for the drug substance when stored at (b) (4).

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

Reference ID: 4970303

B. Quality Assessment Overview

NDA 209191 was originally submitted on June 30, 2016, and subsequently issued an APPROVAL (AP) on July 12, 2018; however, on April 14, 2021, the AP was converted to a Tentative Approval (TA) based on the Final Judgment regarding patent exclusivity of the LD that was issued on October 10, 2019. During this arbitration period and while the NDA was still considered AP, the Applicant submitted one quality post-approval change supplement (SDN 33) for this NDA. SDN 033 provided for the addition of a 1 mg/vial dosage strength and was approved on December 28, 2018. As a result of the conversion from AP to TA, the Agency's action on SDN 33 was reversed and the changes were therefore considered invalid. Accordingly, because the application was considered Tentatively Approved and not Approved, the Applicant was forced to incorporate the changes that were previously approved in SDN 33 to the NDA in the form of a Class 1 Resubmission (SDN 52) to the NDA. While all discipline recommended full approval of the resubmission (SDN 52), the expiration dates for the two patents were still outstanding (January 25, 2022 and July 25, 2022 with pediatric extension). Accordingly, the changes were accepted and the SDN 52 was granted a TA on December 17, 2021.

The current Class 1 Resubmission (SDN 57) was submitted in response to the Agency's December 17, 2021 Tentative Approval Letter. SDN 57 provides for a request for final approval of NDA 20919. No other changes are included in this resubmission.

Accordingly, as no deficiencies or changes related product quality have been included or identified, this application 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)

see review #1

Reference ID: 4970303

CHAPTER IV: LABELING

NDA 209191 has a complicated regulatory history:

- July 12, 2018 granted approval
- December 28, 2018 quality post approval change supplement for an additional 1 mg/vial strength that was also approved
- April 14, 2021 approval was converted to a tentative approval based on a Final Judgement (October 10, 2019) regarding patent exclusivity of the reference product.
- June 30, 2021 the applicant requested full approval; the review team requested confirmation that no changes had been made since the supplement for the new strength.
- November 10, 2021 CMC team recommended approval
- December 17, 2021 granted tentative approval again because of patent exclusivities.
- March 2, 2022 resubmission of NDA under SDN 57 for full approval.

The CMC review team sent the following information request on March 7, 2022, "Provide a summary of changes to Module 3, manufacturing/testing/packaging/labeling sites, and the product labeling that were made since the tentative approval letter. If there were no changes, provide a statement that there were no changes since the date of the most recent amendment to the NDA for any of these sections." The applicant responded March 11, 2022 in SDN 58 that other than the formal submission of the package insert on December 22, 2021, there were no changes since the receipt of tentative approval on December 17, 2021.

This labeling review captures the current state of the labeling and confirms there were no significant changes since the labeling review by Rajiv Agarwal on March 20, 2017 (secondary review by Anamitro Banerjee March 20, 2017). At the time of the review by Dr. Agarwal, the 1 mg strength had not been introduced, so differences in the label largely regard the inclusion of the new strength. Other changes were proposed by the wider clinical review team and are consistent with previous labeling negotiations.

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

Reference ID: 4970303

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	BORTEZOMIB for injection
Route(s) of administration	Adequate	For Injection, for subcutaneous or intravenous use
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	1 mg or 2.5 mg
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	Single-Dose
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	Bolded caution to alert HC provider that different route of administration requires different dilution. 0.9% Sodium Chloride Injection, USP specified as the diluent. Reconstitution volumes described in tabular format Stickers provided for vial and syringe to confirm route of administration
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	Storage statements for unopened vials and protection from light stipulated. In-use period of 8 h at 25ºC stipulated.
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	Adequate	Statement provided
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable*	Adequate	Statement provided in this section with appropriate reference in Section 15

special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs".		

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Powder for reconstitution for Injection
Strength(s) in metric system	Adequate	1 mg or 2.5 mg
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	Lyophilized white to off-white powder
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Adequate	Single-dose vial

Section 11 (DESCRIPTION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	Bortezomib for Injection
Dosage form(s) and route(s) of administration	Adequate	Lyophilized powder for intravenous injection or subcutaneous use
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	Adequate	Provided.
Pharmacological/Therapeutic class	Adequate	Proteasome inhibitor
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	Mirrors information in the reference product and accepted in Review 01 by Dr. Rajiv Agarwal

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	Adequate	No promotional material present.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	No monograph available.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Powder for injection
Strength(s) in metric system	Adequate	1 mg and 2.5 mg
Available units (e.g., bottles of 100 tablets)	Adequate	1 mg or 2.5 mg per vial
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	White to off-white cake or powder
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	Single-dose vial
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	Retain in original package to protect from light. Hazardous drug statement and reference included.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	USP Controlled Room Temperature stipulated
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling - None.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Manufactured by: Gland Pharma Limited; Visakhapatnam Andhra Pradesh 530049 India Manufactured for: Hospira, Inc., Lake Forest, IL 60045 USA

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information): No Patient Labeling

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	N/A	
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	N/A	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	N/A	
Alphabetical listing of inactive ingredients (if applicable)	N/A	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	N/A	

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING

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

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

Reference ID: 4970303

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	Bortezomib for Injection
Strength(s) in metric system	Adequate	1 mg or 2.5 mg
Route(s) of administration	Adequate	For Injection, for subcutaneous use or intravenous injection
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	1 mg/vial and 2.5 mg/vial
"Rx only" displayed on the principal display	Adequate	Provided
NDC	Adequate	Provided
Lot number and expiration date	Adequate	Serialized details printed on bottom of carton
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	USP Controlled Room Temperature conditions stipulated
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	Adequate	Single-dose vial
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	Mannitol is the sole excipient
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	Provided

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	Manufacturer and distributor provided
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	No Monograph
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: Adequate; no significant differences since the previous review cycles. All previous comments from the CMC reviewer and clinical review team have been incorporated. Inclusion of the 1 mg strength is consistent with comments provided for the 2.5 mg strength.

ITEMS FOR ADDITIONAL ASSESSMENT

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See Carton/Container Labeling Specific Resources for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these as deficiencies in this section.

Overall Assessment and Recommendation:

The applicant has incorporated all prior comments communicated in previous review cycles. The current labeling addresses the new 1 mg strength. No significant changes are observed in the package insert and the applicant confirmed no changes were made since the last round of negotiations.

Primary Labeling Assessor Name and Date: Olen Stephens, April 18, 2022

Secondary Assessor Name and Date: Sherita McLamore, April 18, 2022

Olen Stephens

Digitally signed by Olen Stephens
Date: 4/18/2022 02:00:22PM
GUID: 508da71e00029e680c3cf42984dfa0ee
Comments: Revised with typographical edits.

Sherita McLamore

Digitally signed by Sherita McLamore
Date: 4/18/2022 02:06:30PM
GUID: 503257950000415755492db5bb8b1a5c

Sherita McLamore

Digitally signed by Sherita McLamore
Date: 4/18/2022 03:07:04PM
GUID: 50325795000041575549 2db5bb8b1a5c

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/

SHERITA D MCLAMORE
04/18/2022 03:29:02 PM

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 209191
Assessment #4

Drug Product Name	Bortezomib for Injection
Dosage Form	Injection
Strength	2.5 mg/vial; 1 mg/vial
Route of Administration	Intravenous; subcutaneous
Rx/OTC Dispensed	Rx
Applicant	Hospira Inc.
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
Resubmission	06/30/2021	All CMC
Amendment	08/10/2021	All CMC

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Sibaprasad Bhattacharyya	Ramesh Raghavachari
Drug Product	Sibaprasad Bhattacharyya	Ramesh Raghavachari
Manufacturing	Kshitij Patkar Ephrem Hunde	Ephrem Hunde Kshitij Patkar
Microbiology	Julie Nemecek	Bryan Riley
Biopharmaceutics	Om Anand	Om Anand
Regulatory Business Process Manager	Dahlia Walters	
Application Technical Lead	Anamitro Banerjee	
Laboratory (OTR)	NA	NA
Environmental	NA	NA

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	06/29/2021	NA
	III					
	IV					
	Other					

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
NA		

2. CONSULTS

None

Reference ID: 4886723

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The OPQ recommends APPROVAL of this NDA from Quality perspective for both the strengths. The OPQ review team did not identify any deficiencies or concerns at this time.

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-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 (1 mg/vial and 2.5 mg/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 recommendation from OPF, OPQ recommends APPROVAL action for NDA 209191. The OPQ recommends a 36 months drug product expiration period for the 2.5 mg/vial and 24 months for the 1 mg/vial strength, when stored under controlled room temperature in the commercial packaging.

Proposed Indication(s) including Intended Patient Population	• Treatment of adult patients with multiple myeloma. • Treatment of adult patients with mantle cell lymphoma who have received at least 1 prior therapy.
Duration of Treatment	54 weeks (nine 6-week cycles)
Maximum Daily Dose	1.3 mg/m^2
Alternative Methods of Administration	Intravenous or Subcutaneous

B. Quality Assessment Overview

This NDA was APPROVED on July 12, 2018, however, on April 14, 2021, this approval was converted to a tentative approval based on Final Judgement on October 10, 2019. During this intervening period, the Applicant submitted one efficacy and one quality post approval change supplements for this NDA, with the CMC supplement being approved on December 28, 2018. The CMC supplement provided for additional strength of 1 mg/vial. Due to conversion of the status to tentative approval, the Agency's action on the CMC supplement was reversed, and the changes approved are now considered invalid. In the current resubmission, the applicant requests a full approval of their NDA and included the changes provided in the now invalid CMC supplement.

On July 30, 2021, the OPQ review team asked the Applicant to indicate if the information provided in current resubmission is the same as the one provided in the previously submitted supplement and list the differences, if any. In response, on August 10, 2021, the Applicant provided a detailed list of changes/differences in the information provided in the original NDA and the previously approved CMC supplement, and the current resubmission.

Drug Substance: Adequate

The Applicant referred to the DMF (b) (4) for drug substance information. The DMF is currently adequate for this NDA based on review by Dr. Yanhong Li dated June 29, 2021. No deficiencies related to the drug substance were identified in this resubmission.

Drug Product: Adequate

All supporting data for the 1 mg/vial strength were evaluated in the CMC supplement that was approved in December 28, 2018. The stability data provided in this resubmission to extend the shelf life of the 2.5 mg/vial strength was acceptable. The risk assessment for (b) (4) related impurities provided in this submission is acceptable. No deficiencies related to the drug product were identified in this resubmission.

Labeling: Adequate

Updated to include the new strength as approved in the supplement previously. The labeling negotiations are currently ongoing.

Manufacturing: Adequate

The change to commercial batch size was previously assessed in the now invalid CMC supplement and was found to be acceptable. The proposed change remains acceptable.

The sponsor proposed that BET and microbial enumeration tests will be carried out at the drug substance manufacturing site and indicate a name change for this facility. This was deemed acceptable by the OPQ manufacturing review team.
No deficiencies related to the manufacturing process and facilities were identified in this resubmission.

Biopharmaceutics: Adequate

The proposed new strength (1 mg/vial) was previously reviewed by the biopharmaceutics review team and found to be acceptable. The email

(b) (4)

The drug product microbiology aspects for the new 1 mg/vial was assessed for the CMC supplement and was found to be adequate from the microbiology perspective.
No deficiencies related to microbiology were identified in this resubmission.

C. Risk Assessment

As the information provided in this submission were evaluated previously and found to be acceptable, no new risk assessment for this product is performed at this time.

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

NA

2. Drug Substance Deficiencies

NA

3. Drug Product Deficiencies

NA

4. Labeling Deficiencies

NA

5. Manufacturing Deficiencies

NA

6. Biopharmaceutics Deficiencies

NA

7. Microbiology Deficiencies

NA

8. Other Deficiencies *(Specify discipline, such as Environmental)*

NA

Application Technical Lead Name and Date:
Anamitro Banerjee, November 10, 2021

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

None

2. Drug Substance Deficiencies

None

3. Drug Product Deficiencies

None

4. Labeling Deficiencies

None

5. Manufacturing Deficiencies

None

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

None

8. Other Deficiencies *(Specify discipline, such as Environmental)*

None

Application Technical Lead Name and Date:

Anamitro Banerjee, November 10, 2021

Anamitro Banerjee

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Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Resubmission Number: NDA-209191-RESUB-52 Class-2 (OND managed)**

2. **Submission(s) Being Reviewed**:

Submission	**Type**	**Submission Date**	**CDER Stamp Date**	**Assigned Date**	**PDUFA Goal Date**	**Review Date**
Original Submission	Resub. Class 2 (OND managed)	6/30/2021	6/30/2021	07/23/2021	12/30/2021	09/28/2021
	Agency's IR Date			Applicant's Response Date		
Amendment	07/30/2021			08/10/2021		09/03/2021

3. **(a) Provides for from Cover Letter:**

   Resubmission of the post-approval changes that have been withdrawn for the conversion of the approved NDA to tentatively approved NDA.

4. **Review #**: 1

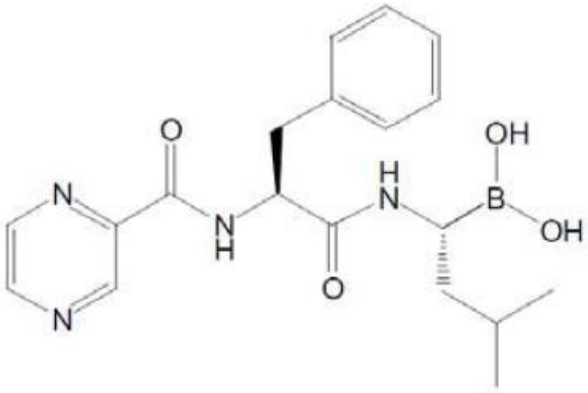
5. **Clinical Review Division**:
   Division of Hematology Products (DHP), Office of Hematology and Oncology Products, OHOP, HFD-150

6. **Name and Address of Applicant**:
   Pfizer Essential Health Global Regulatory Affairs
   Hospira Inc, a Pfizer company
   275 North Field Drive, Bldg. H1
   Lake Forest, IL 60045
   Attn: Pamela Cabrera Mitchell
   Senior Associate Regulatory Affairs
   Pfizer Essential Health Global Regulatory Affairs
   Tel: (224)212-5347
   Fax: (224)212-5401
   Email: pamela.cabrera@pfizer.com

7. Drug Product:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Bortezomib for Injection	Injectable	2.5 mg/vial and 1 mg/vial	Intravenous (1.0 mg/mL) or subcutaneous (2.5 mg/mL)	Rx	No

8. Chemical Name and Structure of Drug Substance:

	USAN: Bortezomib Chemical name: [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2[(pyrazinylcarbonyl) amino]propyl]amino]butyl]boronic acid Molecular formula: $C_{19}H_{25}BN_4O_4$ MW: 384.24

9. Indication:
Treatment of patients with multiple myeloma.

10. Supporting/Relating Documents: Supplement 01 and original NDA

11. Consults:

Consults	Recommendation	Date	Reviewer
Microbiology	Approve	10/06/2021	Julie Nemecek
OPF/Facility	Approve	09/21/2021	Ephrem Hunde
DMF (DS)	Adequate	06/29/2021	Yanhong Li

(b) (4)

12. Executive Summary:

This amendment is the resubmission of the post-approval changes that have been withdrawn for the conversion to tentative approval. An IR was sent on July 30, 2021 for the list of changes made to the original NDA since its approval. In response to IR, applicant has provided the list of proposed changes with justification and supporting data. Proposed changes have been evaluated and found acceptable.

Reference has been to the DMF (b) (4) for all DS related changes proposed since the approval of this NDA. DMF has been evaluated and found to be adequate (Yanhong Li, 06/29/2021).

All the drug product related changes listed in the IR responses that include product quality, microbiological changes, facility, etc. have been evaluated and found acceptable (see the table in section 11).

Overall, the applicant has provided adequate information and data to support the proposed changes in this resubmission.

13. Conclusions & Recommendations:

This NDA 209191 resubmission is recommended for approval.

14. Comments/Deficiencies to be Conveyed to Applicant: None.

15. Primary Reviewer:
Sibaprasad Bhattacharyya, Ph.D., CMC reviewer, Branch 1, DPMAI, OLDP, OPQ

16. Secondary Reviewer:
Ramesh Raghavachari, Ph.D., Branch Chief, Branch 1, DPMA I, OLDP, OPQ

CMC Assessment

I. Background Information

NDA 209191 (Bortezomib for Injection) was approved on July 12,2018 as a 505(b)(2) NDA. It is sterile, lyophilized powder in single-dose vial, which is reconstituted with 0.9% sodium chloride prior to administration. 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. The major difference between NDA 209191 and the reference listed drug (RLD) NDA 021602 is strength – 2.5 mg/vial for NDA 209191 versus 3.5 mg/vial for RLD. Additional 1 mg/vial strength was approved under supplement 01 on 12/28/2018. However, on April 14, 2021 this NDA was converted to tentatively approved NDA.

II. Proposed Changes

This NDA resubmission is for the changes that have been withdrawn for the conversion of the approved NDA to tentatively approved NDA

III. Data Submitted to Support the Proposed Changes and Reviewers' Comments/ Evaluation

(b) (4)

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Comments: Acceptable. All the supporting data related to the additional strength (1 mg/vial) have been evaluated and approved under Supplement #001 on Dec. 2018. Reference has been made to the DMF (b) (4) for the changes related to the drug substance manufacturing process and facilities. DMF amendments related to these changes have been evaluated by DMF reviewer and found to be adequate (Yanhong Li, 06/29/2021). Facility related information have been evaluated and recommended for approval by OPF (Ephrem Hunde, 09/21/2021). Stability data to support the extension of shelf-life of DP (2.5 mg/vial strength only) to 36 months have been submitted as annual report and found acceptable. Applicant has stated that (b) (4) risk assessment has been performed for DS and DP. Based on the detailed assessment of all elements of the product manufacturing materials and processes, the risk of formation of (b) (4) related impurities in injected DP is very low.

IV. Risk Associated with the Proposed Changes and Impact to Product Quality and Patient Safety

Low. Supporting information for all the changes proposed in this resubmission have been evaluated and found acceptable. No changes have been proposed to DP manufacturing, composition, and release specifications.

V. Recommendation: This NDA resubmission is recommended for approval.

Ramesh Raghavachari

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Sibaprasad Bhattacharyya

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	209191
Assessment Cycle Number	02
Drug Product Name/ Strength	Bortezomib for Injection, 2.5 mg/vial and 1 mg/vial
Route of Administration	Subcutaneous or intravenous injection
Applicant Name	Hospira, Inc.
Therapeutic Classification/ OND Division	CDER/OND/OOD/DHM
Manufacturing Site	Gland Pharma Limited, Unit-II, Block C, Phase-I, Visakhapatnam Special Economic Zone (VSEZ), Duvvada, Visakhapatnam – 530049 Andhra Pradesh, INDIA
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0054 (52) ORIG-1	6/30/2021
0055 (53) ORIG-1	8/10/2021

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: During the previous review cycle, this NDA was recommended for approval on the basis of sterility assurance. The application was converted to tentatively approved on April 14, 2021 due to patent related issues. This amendment is a resubmission of post-approval changes that had previously been withdrawn during the conversion to tentative approval. Major changes include: the addition of another manufacturing facility, addition of another strength of the drug product, changes to sterilization and depyrogenation processes, and shelf life extensions.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): N/A

Supporting Documents:

- N209191MR01.docx, 10/24/2016, recommended for approval. Original

Reference ID: 4886723

submission.

- [redacted] MR01.docx, 5/6/2021, recommended for approval. Referenced for information related to the depyrogenation process.

During the previous review cycle, this NDA was recommended for approval on the basis of sterility assurance. This amendment is a resubmission of post-approval changes that had been previously withdrawn. This review will focus on the impact of the proposed change since the original review. Tables of proposed changes with different levels of detail are provided in the 6/30/2021 submission (1.11.1 Summary of Changes.pdf) and the 8/10/2021 submission(1.11.1 Response to Information Request 30-Jul-2021).

S DRUG SUBSTANCE

The drug substance is not provided sterile. Therefore, a product quality review of the drug substance was not performed.

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:

The summary of changes indicates that a 1 mg/vial presentation will be added. The batch formulas for both presentations are provided for reference:

Table 3.2.P.1-2. Quantitative Composition

Component	Quantity per Milliliter (mL)	Presentation	
		1.0 mg/vial	2.5 mg/vial
		Quantity per unit	Quantity per unit
Bortezomib	[redacted]	1.00 mg[1]	2.50 mg[1]
Mannitol USP		10.00 mg	25.00 mg
[redacted]			
Water for Injection USP[2]			
[redacted]			

Description of the container closure system:

An additional vial size (5 mL) and an alternate aluminum seal have been proposed. This vial size will be used for the new 1 mg/vial presentation. The following is a summary of the proposed container closure system for both presentations:

Component	Description	Manufacturer
10 mL Vial for the 2.5 mg/vial presentation	[redacted]	
5 mL Vial for the 1.0 mg/vial presentation		

Stopper	(b) (4)
Seal	

Assessment: *Adequate*
The applicant provided an adequate description of the drug product's composition and container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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Bryan Riley

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/s/

ANAMITRO BANERJEE
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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:
The applicant provided a risk assessment of the potential sources for the elemental impurities in this submission including the drug substance (including drug substance manufacture equipment and contact surfaces), excipients, container and closure system and drug product manufacture (including all equipment and contact surfaces). (b) (4)

(b) (4)

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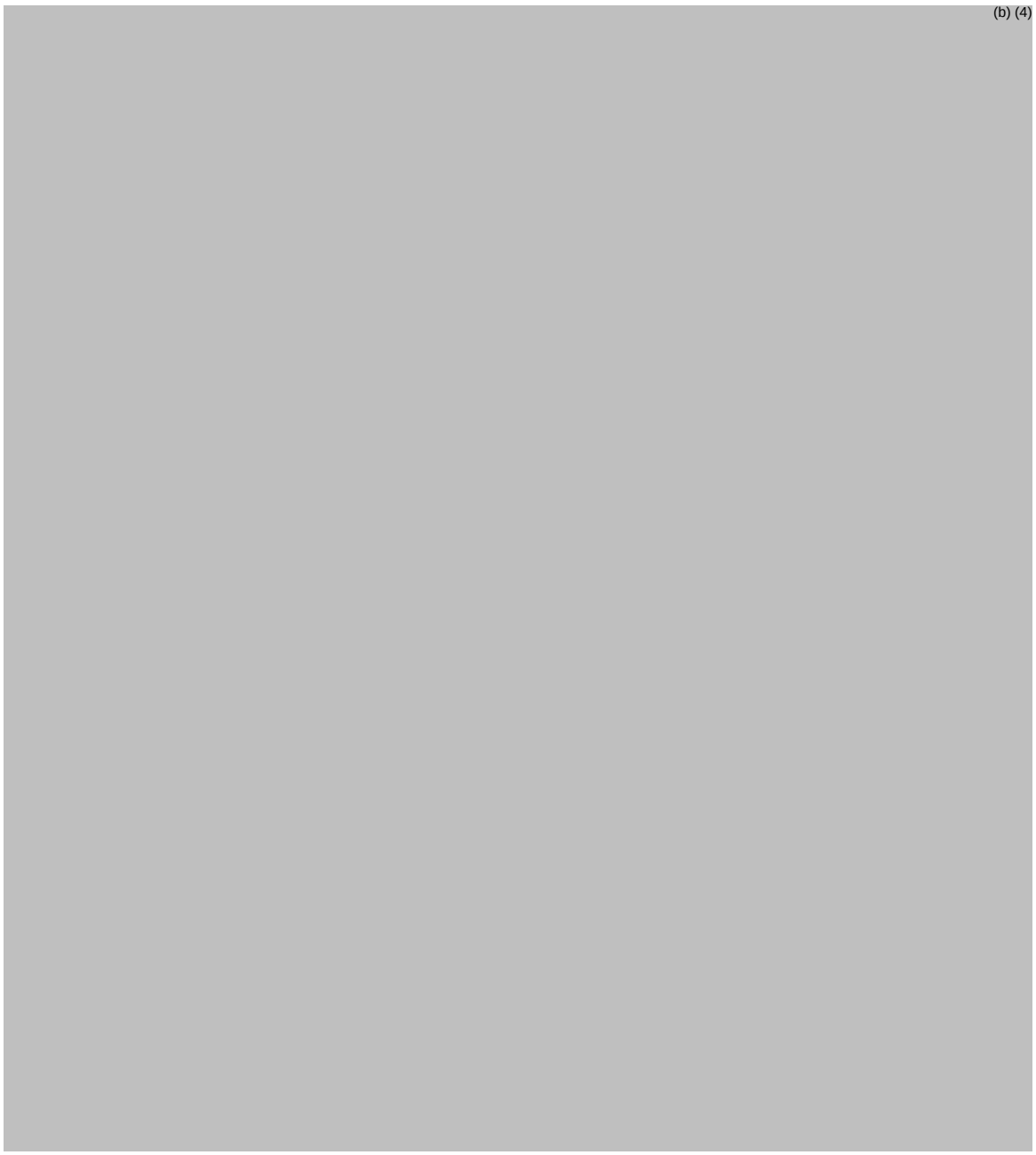

Comment: Acceptable

The elemental impurities in the final drug product including all potential sources introducing elemental impurities are at a level well below 30% of the PDE. The data provided by the applicant is consistent with the applicant's conclusion that the product has a low risk of contamination from the elemental impurities in the drug product as per ICH Q3D Option 2b.

The risk of the critical 10 elemental impurities exceeding the PDE in the drug product of was assessed as low; accordingly, no additional corrective actions or control measures are required.

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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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 which focused on two currently pending products: Hospira's 505(b)(2) NDA 209191 for bortezomib (PDUFA goal 2/22/18) NON-RESPONSIVE NON-RESPONSIVE The agency's upcoming actions for these marketing applications were discussed as an elemental impurity issue was identified as the only outstanding issue and potential deficiency for both applications. It was recommended that the Agency's actions ensure this issue is addressed for both applications in a consistent manner. An information request has been previously issued NON-RESPONSIVE and, if not resolved NON-RESPONSIVE a CR action would likely be recommended. 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

APPEARS THIS WAY ON ORIGINAL

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 (b) (4) month re-test period for the drug substance when stored at (b) (4) 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). The Office of Pharmaceutical Quality has the following has the following Post-Marketing Commitments (PMCs) to be conveyed to the applicant:

> Establish a validated test method for elemental impurities as part of the drug product specification to comply with USP <232>. The updated drug product specification and release data from 3 batches with data for elemental impurities should be submitted as Changes Being Effected-30 Supplement. We recommend that you refer to Refer to ICH Q3D: Guideline for Elemental Impurities for further guidance.
>
> **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® 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-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 (b) (4) 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.

Proposed Indication(s) including Intended Patient Population	Multiple Myeloma
Duration of Treatment	54 weeks (nine 6-week cycles)
Maximum Daily Dose	1.3 mg/m^2
Alternative Methods of Administration	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®, 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 (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.

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

APPEARS THIS WAY ON ORIGINAL

Sherita McLamore

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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.

Proposed Indication(s) including Intended Patient Population	Multiple Myeloma
Duration of Treatment	54 weeks (nine 6-week cycles)
Maximum Daily Dose	1.3 mg/m^2
Alternative Methods of Administration	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) 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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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 (b) (4) month re-test period for the drug substance when stored (b) (4) 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® 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-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 (b) (4) 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.

Proposed Indication(s) including Intended Patient Population	Multiple Myeloma
Duration of Treatment	54 weeks (nine 6-week cycles)
Maximum Daily Dose	1.3 mg/m^2
Alternative Methods of Administration	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 October 2016 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. Water for Injection USP, (b) (4) are used during formulation and subsequently removed during lyophilization. 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

Sherita McLamore

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LABELING

R Regional Information

1.14 Labeling

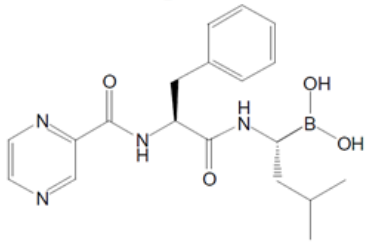
Labeling & Package Insert

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.

Bortezomib has the following chemical structure:



The molecular weight is 384.24 g/mol. The molecular formula is $C_{19}H_{25}BN_4O_4$. 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 (b) (4) drugs, including the use of gloves and other protective clothing to prevent skin contact[1].

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:

(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)

(b) (4)

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

Carton Labeling (2.5 mg/vial):

(b) (4)

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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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** (b) (4)	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipments • Site	H		Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M		Acceptable to microbiologist	Controls are in place and continue stability monitoring post approval
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place, continue stability monitoring post approval
Physical Stability (solid state) Lyophilized small molecule products	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place, continue stability monitoring post approval
Uniformity of Dose (Fill Volume/deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L		Acceptable	Solid cake and not a solution therefore CU is monitored via USP <905>. Controls are in place, continue stability monitoring post approval
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipments	L		Acceptable	Similar to the reference drug.

			(b) (4)		
	• Site				
pH- (Low)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place during stability testing. Continue stability monitoring post approval
Particulate matter (non aggregate for solution only)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M		Acceptable	Controls are in place. Continue stability monitoring post approval
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controlled via DMF
Moisture Content (lyophilized)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place.
Appearance (plug)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	Controls are in place.

Rajiv Agarwal

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Anamitro Banerjee

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CHAPTER VII: Biopharmaceutics

NDA: 209191

Drug Product Name: Bortezomib for Injection

Strength(s): 2.5 mg/vial [1]

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® (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.

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® (bortezomib) for Injection lyophilized powder for subcutaneous or intravenous use (3.5 mg/vial) marketed by Millennium Pharmaceuticals under the approved NDA, 21602.

[1] 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)			-
Water for Injection		Vehicle/co-solvent	-
(b) (4)		(b) (4)	-
Total Volume			

a: Removed by lyophilization

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^2 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®**
Prior to Reconstitution		
Bortezomib content		
per vial	**2.5 mg/vial**	**3.5**
Mannitol content		
per vial	**25.0 mg/vial**	**35.0**
After Reconstitution		

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

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®

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

[a] Published information – The VELCADE® US Labeling Rev 18, reference ID: 3819536.

[b] 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.

[c] 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 (b) (4) (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]

Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products/OPQ

Okpo Eradiri, Ph.D. [Date: 12/20/2016]

Acting Biopharmaceutics Lead
Division of Biopharmaceutics
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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, Dept. 0389 / Bldg. H2-2, Lake Forest, IL

Manufacturing Site:
Gland Pharma Limited,
Unit-II, Block C, Phase-I,
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

Bortezomib	(b) (4)	2.5 mg	API
Mannitol		25.0 mg	(b) (4)
			(b) (4)
WFI		(b) (4)	Co-solvent (removed by lyophilization)
			(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

(b) (4)

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