CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206927Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 206927
Review #1

Drug Name/Dosage Form	Bortezomib for Injection
Strength	3.5 mg/vial
Route of Administration	IV
Rx/OTC Dispensed	R_x
Applicant	Dr. Reddy's Laboratories
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	03-May-19	DP, Micro
Amendment (SD)	07-Aug-19	DP
Amendment (SD)	21-Aug-19	DP
Amendment (SD)	26-Aug-19	DP
Amendment (SD)	29-Aug-19	DP
Amendment (SD)	30-Aug-19	DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	n/a	n/a
Drug Product	William Adams	Anamitro Banerjee
Process and Facilities	Derek Smith	n/a
Microbiology	Erika Pfeiler	Valerie Huse
Biopharmaceutics	n/a	n/a
Regulatory Business Process Manager	Rabiya Laiq	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	n/a	n/a

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
23996	Type II	Dr. Reddy's Laboratory Limited	Bortezomib	n/a	No Review	Adequate
(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

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21602	Valcade (bortezomib)

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 206927 for Bortezomib for Injection, 3.5 mg/vial. As part of this action, OPQ grants a (b) (4) month re-test period for the drug substance when protected from light and stored between (b) (4) °C. Additionally, OPQ grants a 24-month expiration period for the drug product 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 206927 was submitted for Bortezomib for Injection, 3.5 mg/vial in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act for the treatment of patients with multiple myeloma and for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy. Bortezomib is therapeutic proteasome inhibitor that was originally approved under the brand name VELCADE® for the treatment of multiple myeloma and for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy. VELCADE® is a sterile, lyophilized product containing 3.5 mg of the active and packaged in a single-use vial. VELCADE®, which was approved under NDA 021602 in May of 2003, is the listed drug (LD) for this application.

NDA 206927 was originally submitted by Dr. Reddy's Laboratories Limited in March of 2014 (b) (4)

- NDA 206927/0riginal 1 - Route of administration - Intravenous (b) (4)

In December 2014, NDA 206927 was issued a complete response (CR) (b) (4) . In November 2015, a Class 2 resubmission was issued a CR (May 4, 2015) due to outstanding product quality which included facilities issues.

Bortezomib is a small, chiral, modified dipeptidyl boronic acid that is manufactured and release tested by Dr. Reddy's Laboratories Limited (b) (4) . The drug product, Bortezomib for Injection 3.5 mg/vial is supplied as a white to off white sterile, lyophilized powder for reconstitution in a single-dose, 10 mL vial. The drug product formulation includes the active, tromethamine, anhydrous citric acid, (b) (4) The proposed drug product contains an identical amount of the active and is intended to have the same dosage form, and dosing regimen as the Listed Drug. The major difference between the Dr. Reddy's drug product and the listed drug is the formulation and route(s) of administration. The listed drug contains mannitol while Dr. Reddy's formulation does not. The LD is designed to be administered by IV or SC while the Dr. Reddy product is limited to

IV admiration. There are no new clinical data submitted and no deviations from the current prescribing information for the LD. The clinical team notes that the benefit and risk of the proposed product is expected to be the same as the LD.

Bortezomib is administered for nine 6-week treatment cycles. The recommended dosing regimen for Bortezomib is 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 206927 and grants a (b) (4) **month re-test period** for the drug substance and **a 24-month expiry** for the drug product when stored under controlled room temperature in the commercial packaging.

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

B. Quality Assessment Overview

Drug Substance

Bortezomib is a modified dipeptidyl boronic acid. It is a small chiral molecule that is manufactured and release tested by Dr. Reddy's Laboratories Limited (b) (4) . Bortezomib is a white to off white powder that is freely soluble in DMF, soluble on MeOH and practically insoluble in n-Hexanes. Bortezomib has a very low solubility and degrades in aqueous media and exceptionally poor wetting characteristics. Bortezomib exhibits stereoisomerism due to the presence of the two chiral centers but does not exhibit polymorphism. The applicant references DMF 23996 for the manufacture and control of the drug substance. DMF 23996 was adequate to support the approval of NDA 206927 during the previous review cycle and remains adequate (last reviewed 3/1/19). Accordingly, there is no new information and NDA 206927 is recommended for approval from a drug substance perspective.

Drug Product

The drug product, Bortezomib for Injection 3.5 mg/vial is a white to off white sterile, lyophilized powder for reconstitution. The product is packaged in a single-dose, 10 mL USP (b) (4) tubular glass vial stoppered with 13 mm (b) (4) rubber stopper and sealed with 13 mm flip-off seal.

The formulation includes the active, tromethamine, anhydrous citric acid, (b) (4) All excipients are compendial and are within the IIG limits (b) (4) There are no overages nor antimicrobial preservatives in the formulation. (b) (4) this submission is only for the IV route of administration.

The review of the drug product focused on the following product quality deficiencies and Lifecycle Management Considerations which were included in the agency's CR letter.

1. Batch data for EH15031 shows slower reconstitution time relative to previous registration batches submitted to NDA 206-927. This slower reconstitution time appears to be related to the change in batch formula, manufacturing process (b) (4) Development batches such as EH15014 also demonstrate delayed reconstitution. Furthermore, only one stability data point is available for EH15031, and that 1 month stability data point under accelerated conditions shows and increase in reconstitution time, approaching the (b) (4) minute specification limit. Therefore, the changes to the batch formula and manufacturing process may have impacted the quality of the drug product and it may not be possible to bridge the stability data submitted for batches EH12023, EH12024, and EH13001. Provide the following to address concerns that changes to the batch formula and manufacturing process have not adversely impacted the drug product quality:
    a. Additional stability data for EH15031 to demonstrate stability trends mimic those of EH12023, EH12024, and EH13001.
    b. Additional batch data for drug product batches manufactured with the revised batch formula and manufacturing process as filed in the NDA resubmission (23-Nov-15).
    c. Justify the apparent changes in reconstitution time seen in recent batches such as EH15031 and the difference in reconstitution time relative to Velcade® with regards to product quality and potential medication errors due to long reconstitution times.

2. The manufacturing flow diagram does not include the lyophilization, capping and packaging steps. Submit a revised low diagram for all steps involved in the manufacturing process.
3. We are concerned that the physico-chemical characteristics (e.g., as shown in the reconstitution time) of the proposed commercial lyophilized drug product for injection at the end of its shelf-life will not be comparable to those of the reference drug product (Velcade®). To facilitate our review of the biowaiver request for the intravenous administration of the proposed Bortezomib for Injection (3.5 mg/vial), provide a table comparing side-by-side the physico-chemical properties of the exhibit batch(es) produced using the *final* proposed commercial manufacturing process at the time of batch release and during long-

term stability testing versus the Listed Drug. If applicable, provide justification for why you believe that any observed differences in the physico-chemical characteristics of the final test and the reference products would not impact usability, bioavailability, as well as efficacy of the drug product.

4. We note that Exhibit Batch EH15031 is being used as the test treatment in the ongoing BE study (14-VIN-648) in multiple myeloma patients (b) (4) When available, provide the clinical study report of this study so that FDA may consider the PK, PD and safety findings as supportive evidence in the review of the biowaiver request for the intravenous route.

After completion of the submission it was concluded that the Applicant adequately addressed all issues outlined in the CR letter by:

- Modifying the formulation to correct for drug substance form;
- Modifying the manufacturing process (b) (4)
- Submitting completed and acceptable stability studies on the original NDA exhibit batches and 1 new exhibit batch

The drug product team included the following Lifecycle Management Considerations:

- Optimization of drug substance manufacture
- Optimization of drug product manufacture
- Completed BA/BE studies (b) (4)
- Additional stability data from the on-going studies for new exhibit batches EH18062, EH18066 and EH15031

Based on the 36 months of stability data for the exhibit batches included in the original submission and the 24 months of data on a new exhibit batch generated on Bortezomib for Injection Dr. Reddy's Laboratories Ltd proposed and FDA accepts that the expiration dating be set at **24 months** for drug product, when stored at controlled room temperature (20-25°C; 68- 77°F).

NDA 206927 is recommended for approval from a drug product perspective.

Biopharmaceutics

The proposed drug product has the same active ingredient, drug concentration and dosing regimen as the LD. The biopharmaceutics review focused on the applicant's response to the biopharm comments included in the Agency's 5/2/2016 CR letter (comments 3 and 4) and assessed the acceptability of the in vitro data which was provided in support of the Applicant's biowaiver request for the IV route of administration of the proposed DP.

The biopharmaceutics reviewer concluded that the responses were acceptable and that the scientific bridge between the proposed drug product (Bortezomib Injection, 3.5 mg) and the Listed Drug, Velcade (bortezomib) 3.5 mg/vial, is adequately established based

on 21 CFR 320.24(b). Accordingly, NDA 206927 is recommended for approval from a Biopharmaceutics perspective.

Micro

The following changes were proposed in November 2015 submission:

(b) (4)

The micro reviewer determined that the finished product composition remains unchanged and per submission November 2015 submission "Analytical Procedures" in Module 3.2.P.5.2, (b) (4) testing are performed with the reconstituted lyophilized drug product. It was further determined that the adequate information was provided to support each of these changes from a microbiology perspective. Accordingly, it was concluded that no new verification studies were required with the new formulation and the application is recommended for approval from a microbiology perspective.

Facilities

The Complete Response letter included the following deficiency which resulted from the facility inspections:

> *During a recent inspection of the Dr. Reddy's Laboratories Limited (FEI 3006549835) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.*

This resubmission of NDA 206927 included 3 sites and all sites were listed as ready for inspection:

- **Dr. Reddy's Laboratories Limited (3002806851))**– Manufacturing, Analysis and Packaging of drug substance
- **Dr. Reddy's Laboratories Limited (FEI 3006549835)**- Drug product manufacturing, labeling and packaging, analytical testing of active ingredient, inactive ingredient, in-process control testing and drug product release testing, warehousing, shipping and administration
- **Dr. Reddy's Laboratories Limited, Chemical Technical Operations-Unit II (FEI 3005448030)**- Testing facility used by the DMF holder (b) (4)

All facilities listed in NDA 206927 were deemed acceptable for the responsibilities listed in the application. Accordingly, NDA 206927 is recommended for approval from a compliance perspective.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment (see Attachment)

n/a

Sherita McLamore

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DRUG PRODUCT/PROCESS

Product Background: 505(b)(2) application referencing Millennium Pharmaceuticals NDA 21602 for Velcade (bortezomib for injection), 3.5 mg/vial.

NDA 206927 DP/Process Review #2

Drug Product: Bortezomib for Injection, 3.5 mg/vial

Route of Administration: IV infusion

Applicant Name: Dr. Reddy's Laboratories Ltd (Hyderabad, India)

Review Recommendation: Approval

Review Summary:

Listed below is a summary of the Dr. Reddy's submissions and FDA documents.

* NDA 206927 was submitted, (b) (4)
* Complete Response letter #1 [CR-1] (b) (4) addressed issues related to the type II DMF 23996 for drug substance; biowaiver (IV route of administration cannot be granted, (b) (4) and labeling. A safety update was also requested.
* Complete Response letter #2 [CR-2] (b) (4) addressed issues related to product quality (DP/process), labeling, and facilities. It also requested a safety update. The quality issues were the identity of the drug form in the drug product; particles in a revised version of the drug product resulting in failed appearance and reconstitution time; reconstitution time for drug product increasing on stability; incomplete stability studies on the NDA exhibit batches; and biowaivers (b) (4)
* CMC DP/Process Review #1 addressed only amendments SD-001 and SD-006, but not amendments SD-007 and SD-008 which are addressed in CR-2.
* Amendments SD-009 and SD-010 address Dr. Reddy's plans to manufacture additional exhibit batches to address comments 1a and 1b in CR-2; that 24M (end of shelf life) stability will be available for new exhibit batch EH15031 to support comment 3; and that they will repeat the BE study. BE study protocol was revised per NCCN guidelines and submitted as IND 118389 amendments SN-010 (dated 11/16/17) and SN-011 (dated 11/21/17).
* Addressed in this review are CMC amendments SD-007, SD-008 and SD-011. It is noted that most of the discussion and information in amendment SD-008 is repeated in amendment SD-011.

* Labeling amendments are addressed in a separate CMC DP/Labeling Review.

The CMC/Process issues were addressed by modifying the formulation to correct for drug substance form; modifying the manufacturing process (b) (4) and submitting completed and acceptable stability studies on the original NDA exhibit batches and 1 new exhibit batch. Reconstitution time for the new NDA exhibit batch was found to be slightly longer at release and increase slightly over time, but remained within specification at release and on stability. The original NDA exhibit batches showed the same trend. The bioequivalence studies are to be performed using the new NDA exhibit batches.

List Submissions being addressed (table):

Submissions Reviewed	***Document Date***
Review Cycle #1	
SD-001: New NDA	03/04/14
CMC IR comments (DP, micro)	07/31/14
CMC IR comments (DP, micro)	08/14/14
SD-003: Response to 08/14/14 Tcon (DS molecular structure)	08/14/14
SD-006: Response to 07/31/14 CMC IR letter (DP, micro)	08/27/14
(b) (4)	08/29/14
CMC DP/Process Review #1 (SD-001, SD-006)	12/01/14
Complete Response Letter #1 [CR-1] referencing amendments SD-001, SD-002, SD-003, SD-004, SD-005, SD-006, SD-007 (DS, biowaiver, labeling and safety update)	12/17/14
Complete Response Letter #2 [CR-2] referencing amendment SD-008 (DP, process, labeling, facility, and safety update	05/04/16
Review Cycle #2	
CMC email comments (DS, DP)	10/09/14
SD-007: Response to 10/09/14 email	10/14/14
SD-008: Response to CR-1	11/23/15
SD-011: Response to CR-2	05/03/19

Highlight Key Outstanding Issues from Last Cycle:
CMC/quality issues addressed in the advice and IR letters during review cycle #1 were as follows:
* release/stability specifications
* method validation studies

* identity of the drug substance form in drug product
* drug substance manufacture
* microbiology in drug product manufacture
* labels and labeling

Concise Description Outstanding Issues Remaining: None

3.2.P.1 Description and Composition

Amendments SD-008 and SD-011

Composition Statement:

Ingredients	***per vial***	(b) (4) ***Batch***	***Function***
Bortezomib#	3.5 mg	g	active
Tromethamine, USP	8.4 mg	g	(b) (4)
Citric Acid, USP	10 mg	g	

(b) (4)

Reviewer Assessment: ***Adequate***

3.2.P.1

Revised composition statement is acceptable. (b) (4)

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

Found adequate in CMC Review #1

3.2.P.2.2 Drug Product

Amendment SD-007

IR Comment 1. Confirmation of the structure regarding DS.

Response 1

Refer to amendment SD-003; copy of drug substance structural characterization is attached.

Amendment SD-008

William Adams

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Anamitro Banerjee

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LABELING

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

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

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

R REGIONAL INFORMATION

1.14 LABELING

IV STICKER LABEL (amendment SD-019)

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

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

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

VIAL LABEL (amendment SD-018)

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

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

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

SINGLE VIAL CARTON LABEL (amendment SD-018)

(b) (4)

[redacted]

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

Same comments as for the vial label.

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

PACKAGE INSERT (amendment SD-019)

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

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

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

FULL PRESCRIBING INFORMATION

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

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

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

Table 5: Reconstitution Volumes and Final Concentration for Intravenous Administration

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

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

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

• Intravenous Administration [1 mg/mL concentration]

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

11 DESCRIPTION

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

[molecular structure]

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

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

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Bortezomib for injection is supplied as individually cartoned 10 mL vials containing 3.5 mg of bortezomib as a white to off-white cake or powder.

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

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

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

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

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

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

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

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

William Adams

Digitally signed by William Adams
Date: 9/12/2019 05:46:43PM
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Anamitro Banerjee

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

Inspection Management Form

NDA-206927-ORIG-1-RESUB-11

DR REDDY'S LABORATORIES LIMITED (UNIT II) | 3005448030 | (b) (4) LABORATORY, CHEMICAL/PHYSICAL TESTING | Approve Facility

DR REDDY'S LABORATORIES LIMITED | 3006549835 | SVS STERILE-FILLED SMALL VOLUME PARENTERAL DRUGS | Approve Facility

Overall Manufacturing Inspection Recommendation

- (•) Approve
- ( ) Withhold
- ( ) No Evaluation Necessary

BIOPHARMACEUTICS

NDA: 206927-ORIG-1-RESUB-10 Dated 05/03/2019
Submission Type: 505(b)(2) Type 5-New Formulation
Drug Product Name/Strength: Bortezomib Injection, 3.5 mg/vial
Dosage Form: Injection, solution
Route of Administration: Intravenous (IV)
Applicant Name: Dr. Reddy's Laboratories, Inc.
Intended Use: For the treatment of multiple myeloma and mantle cell lymphoma
Listed Drug (LD): VELCADE® (Bortezomib) for Injection (IV and subcutaneous (SC)), 3.5 mg/vial [NDA 021602, Millennium Pharms].
Primary Reviewer: Qi Zhang, Ph.D.
Secondary Reviewer: Banu Zolnik, Ph.D.

RECOMMENDATION: ADEQUATE

REVIEW SUMMARY

This 505(b)(2) NDA, for Bortezomib Injection, 3.5 mg single-dose vial, relies for approval on FDA's findings of safety and effectiveness of the Listed Drug (LD), VELCADE® (Bortezomib) for Injection, 3.5 mg/vial [NDA 021602, Millennium Pharms]. Because the formulation of the proposed to-be-marketed parenteral drug product (DP) is not qualitatively and quantitatively (Q1/Q2) the same as that of the LD, due to the absence of mannitol (35 mg) and the presence of (b) (4) (i.e. 8.4 mg tromethamine and 10 mg anhydrous citric acid), the biowaiver request per 21 CFR § 320.22(b)(1) is not feasible. However, a scientific bridge is established between the proposed DP and the the LD, based on 21 CFR 320.24(b)(6).

The Biopharmaceutics review focused on the Applicant's 05/03/2019 Responses to the Biopharmaceutics Complete Response Comments (FDA Comments #3 and #4 in the CR Letter dated 05/04/2016) and evaluated the adequacy of the provided in vitro comparative physiochemical properties information/data in supporting the Applicant's biowaiver request for the IV route of administration of the proposed DP.

Results of side-by-side comparison of drug product physicochemical properties show that the proposed drug product has comparable physiochemical properties as the LD product at batch release and on stability. Both, the proposed drug product and LD are sterile lyophilized white to off-white cake or powder for reconstitution, and colorless re-constituted solutions with comparable pH, osmolality, and reconstitution time (NMT (b) (4) minutes).

In conclusion, the scientific bridge between the proposed for Bortezomib Injection, 3.5 mg single-dose vial is adequately established to the LD, based on 21 CFR 320.24(b), based on the following criteria: (1) the proposed DP has the same active ingredient, same drug concentration, same dosing regimen, (2) is intended for administration by intravenous infusion with the same rate of

administration as the LD, (3) the proposed DP has comparable physiochemical properties as the LD, and (4) the Applicant conducted the comparative animal PK and toxicity studies to demonstrate the absence of mannitol and addition of tromethamine and anhydrous citric acid as (b) (4) to the formulation of the proposed DP, do not alter the PK of bortezomib in the animal model (refer to the Nonclinical Review in DARRTS dated 06/03/2014).

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 206927 for Bortezomib Injection, 3.5 mg/vial, for the IV route of administration, is recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

List of Submissions Being Reviewed:

eCTD # (SND #)	Received date	Document
0010 (11)	05/03/2019	Resubmission; Response to CR Comments

Highlight Key Outstanding Issues from Last Cycle:

The Biopharmaceutics Review dated 2/18/2016 found the original submission inadequate in the last review cycle due to the outstanding deficiencies with respect to the reconstitution time, i.e., the reconstitution time of the proposed DP (exhibit batch # EH15031) was longer than that of the LD and approached the upper threshold limit at the 1-month of accelerated stability testing, and there were no long-term stability data.

Note that the overall information provided in this NDA 206927/Original-1 in supportive of the biowaiver request for the IV route of administration were previously determined adequate, e.g., the identity of the active ingredient, comparable physiochemical properties (pH and osmolarity), and comparative animal PK and toxicity studies. Refer to the Biopharmaceutics Reviews by Dr. Elsbeth Chikhale dated 11/28/2014 in DARRTS, and by Dr. Gerlie Gieser dated 2/18/2016 in Panorama. Refer to the Nonclinical Review by Dr. Christopher M. Sheth dated 06/03/2014 in DARRTS.

Biopharmaceutics CR Comments (conveyed to the Applicant in CR letter dated 05/04/2016) and Applicant's Responses:

FDA Comment #3:

3. *We are concerned that the physico-chemical characteristics (e.g., as shown in the reconstitution time) of the proposed commercial lyophilized drug product for injection at the end of its shelf-life will not be comparable to those of the reference drug product (Velcade®). To facilitate our review of the biowaiver request for the intravenous administration of the proposed Bortezomib for Injection (3.5 mg/vial), provide a table comparing side-by-side the physico-chemical properties of the exhibit batch(es) produced using the final proposed commercial manufacturing process at the time of batch release and during long-term stability testing versus the Listed Drug. If applicable, provide justification for why you believe that any observed differences in the physico-chemical characteristics of the final test and the reference products would not impact usability, bioavailability, as well as efficacy of the drug product.*

Applicant's 05/03/09 Response to the FDA Comment #3:

The physico-chemical characteristics of the proposed DP (exhibit batch # EH15031) up to 6 months at accelerated (40±2°C/75±5%RH) and up to 24 months at long term (25±2°C/60±5%RH) stability conditions, and the LD, Velcade® (Lot #102683), are provided in section 3.2.P.2.2.3 (**Appendix**). The proposed DP was found to be stable and comparable to LD, since all the critical

parameters such as Completeness and Clarity of Solution, Reconstitution Time (0.5 – 1.9 minutes for the Test vs. 0.42 – 0.5 minutes for the LD), pH (3.9 – 4.2 for the Test vs. 3.92 – 3.96 for LD), Color of Solution, Assay, Related Substances, and Osmolality (308 – 358 for the Test vs. 342 – 428 for the LD) with different reconstitution volume (3.5 mL and 1.4 mL), are found to be complying with proposed specifications across all the stability intervals (24 months).

The Applicant also showed the comparative physio-chemical characteristics of two new additional exhibit batches (EH18062 and EH18066) relative to the current exhibit batch (#EH15031). The batch formula and manufacturing process are the same for all the three exhibit batches, and the reconstitution times (at batch release) for the two additional exhibit batches are 0.3 – 0.4 minutes, compared to 1.0 – 1.3 minutes for the current exhibit batch (#EH15031). Refer to the Applicant's responses to FDA Comment #1. Per the Applicant, the reconstitution time difference could be attributed to the variance between the product vials, differences in handling of the vial (shaking frequency, height of stroke, inclination of the shaking axis etc.) during the reconstitution procedure and time at which the product is visualized post reconstitution. The Applicant conducted the reconstitution time test of three current/new exhibit batches (EH15031, EH18062 and EH18066) as per the standardized reconstitution procedure, and the results of the testing and the statistical data analysis provides assurance that 100% of the product would meet the reconstitution specification of "not more than (b) (4) minutes" and thus the risk of reconstitution time longer than (b) (4) minutes is not anticipated. The detailed reconstitution time report is provided in section 3.2.P.2.2.3.

Based on the information/data provided, this Reviewer concludes that, the difference in reconstitution time of around 30 seconds to 1 minute between the proposed DP and the LD will not affect the product quality, since dissolution of the lyophilized powder is completed within the reconstitution limit, i.e., less than (b) (4) minutes. In addition, the provided physio-chemical characteristics data support the comparability between the proposed DP and the LD. Also refer to the Drug Product Review for the adequacy of the physiochemical stability (e.g. reconstitution and impurities) of the proposed DP.

FDA Comment #4:

4. ***We note that Exhibit Batch EH15031 is being used as the test treatment in the ongoing BE study (14-VIN-648) in multiple myeloma patients*** (b) (4) ***When available, provide the clinical study report of this study so that FDA may consider the PK, PO and safety findings as supportive evidence in the review of the biowaiver request for the intravenous route.***

Applicant's 05/03/09 Response to the FDA Comment #4:

(b) (4)

This Reviewer noted that the overall information provided in this NDA is supportive of the biowaiver request for the IV route of administration. (b) (4)

Reviewer's Overall Assessment: ADEQUATE

The Applicant's responses to the Biopharmaceutics CR comments (FDA Comments #3 and #4) are acceptable. In conclusion, a scientific bridge to the LD for the IV administration route is **adequately established** pursuant to 21 CFR 320.24(b)(6), based on the totality of the information/data provided in the previous and current submissions, i.e., the side-by-side comparison of the formulation, in vitro physicochemical properties (pH, osmolality, and reconstitution time), and in vivo animal PK between the proposed DP and the LD, as well as information available in the labeling of the LD.

Refer to the Drug Substance and Drug Product Reviews for additional CMC information. Refer to the FDA recommended labeling to ensure safe and effective use of the proposed drug product.

Appendix

Side by Side Comparison of Physico-chemical Parameters between Dr. Reddy's Bortezomib for Injection and RLD Velcade®

Specification	Limit	Test Results												Impact of Physico-chemical Properties		
		Dr. Reddy's Bortezomib for Injection 3.5 mg/vial - Batch # EH15031											RLD Velcade® Lot # 102683 (Expiry: 12/2015)	Usability (Yes/No)	Bioavailability (Yes/No)	Efficacy (Yes/No)
		40°C/75%RH					25°C/60%RH									
		Initial	1M	2M	3M	6M	3M	6M	9M	12M	18M	24M				
Description	White to off-white lyophilized powder	Complies					Complies						White to Off-white lyophilized powder	No	No	No
Description of Reconstituted Solution																
with 3.5 mL	Clear colorless solution free from visible extraneous matter	Complies					Complies						Clear colorless solution free from visible extraneous matter	No	No	No
with 1.4 mL	Clear colorless solution free from visible extraneous matter	Complies					Complies						Clear colorless solution free from visible extraneous matter	No	No	No
Completeness and Clarity of Solution																
with 3.5 mL	**	Complies					Complies						Complies as per the specification	No	No	No
with 1.4 mL		Complies					Complies						Complies as per the specification	No	No	No
Reconstitution Time																
with 3.5 mL	NMT (b) (4)	1.0	1.3	1.8	1.43	1.5	1.58	1.7	0.7	1.7	0.8	1.1	0.42 min (25 sec)	No*	No*	No*
with 1.4 mL	NMT	1.3	1.6	1.9	1.43	1.6	1.58	1.6	0.5	1.5	0.9	1.1	0.5 min (30 sec)	No*	No*	No*
pH of Reconstituted Solution																
with 3.5 mL	Between (b) (4)	4.2	3.9	4.1	4.09	4.0	4.11	4.0	4.1	4.0	4.1	4.1	3.92	No	No	No
with 1.4 mL		4.2	3.9	4.0	4.1	3.9	4.10	4.0	4.1	3.9	4.1	4.1	3.96	No	No	No
Color of Solution by UV																
with 3.5 mL	NMT (b) (4)	0.009	0.0010	0.007	0.01	0.015	0.009	0.012	0.023	0.009	0.018	0.015	0.004	No	No	No
with 1.4 mL	absorbance at 430nm	0.013	0.007	0.019	0.017	0.022	0.022	0.024	0.033	0.012	0.034	0.037	0.021	No	No	No
Assay by HPLC	NLT NMT (b) (4) labeled amount of Bortezomib	99.7	98.1	97.4	96.2	97.9	101.0	99.3	98.9	100.6	99.7	98.9	98.4	No	No	No
Related Substances by HPLC																
Impurity 1	NMT (b) (4) %	0.01	0.05	0.04	0.07	0.06	0.03	0.04	0.08	0.13	0.04	0.24	0.15	No	No	No
Impurity 2	NMT %	<LOQ	0.04	0.05	0.14	0.30	0.02	0.03	0.04	0.04	0.07	0.09	0.05	No	No	No
Impurity 3	NMT %	ND	ND	ND	ND	ND	ND	ND	ND	<LOQ	ND	0.02	0.07	No	No	No
Impurity 4	NMT %	<LOQ	ND	<LOQ	BLD	<LOQ	BLD	<LOQ	<LOQ	BLD	BLD	<LOQ	ND	No	No	No
Impurity 5	NMT %	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	No	No	No
Impurity 6	NMT %	0.10	ND	0.02	0.03	ND	0.05	<LOQ	0.12	0.10	0.02	0.13	0.04	No	No	No
Impurity 7	NMT %	ND	ND	ND	ND	ND	ND	ND	ND	0.04	<LOQ	0.04	0.02	No	No	No
Diastereomer (RR&SS)	NMT %	0.09	0.08	ND	0.07	0.07	0.08	0.07	0.05	0.10	0.07	0.06	0.03	No	No	No
BZM-9	NMT %	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	No	No	No
Maximum Individual Unknown Impurity	NMT %	0.03	0.03	0.12	0.02	<LOQ	0.03	ND	0.03	0.01	<LOQ	<LOQ	0.02	No	No	No
Total Impurities	NMT %	0.3	0.2	0.3	0.4	0.5	0.2	0.2	0.3	0.4	0.2	0.6	0.37	No	No	No
Osmolality																
with 3.5 mL	Between (b) (4)	308	316	312	311	306	315	311	321	313	324	309	342	No	No	No
with 1.4 mL	Between	354	357	355	345	340	357	352	352	350	358	352	428	No	No	No

ND: Not Detected; NMT: Not more than; NLT: Not less than; LOQ: Limit of Quantification; BLD: Below Limit of Detection;
** There is a minor difference in the reconstitution time between Dr. Reddy's Bortezomib for Injection and RLD Velcade® but this minor difference will not impact the drug product quality and will not lead to any potential medication errors*
*** The solid dissolves completely, leaving no visible residue as undissolved matter and the reconstituted solution is not significantly less clear than an equal volume of the water contained in a similar vessel and examined similarly and should be free from visible particles of foreign matter.*

Qi Zhang

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Banu Zolnik

Digitally signed by Banu Zolnik
Date: 9/13/2019 11:52:29AM
GUID: 508da7270002a568e175a2c0dd90f334

Sherita McLamore

Digitally signed by Sherita McLamore
Date: 10/01/2019 03:24:40PM
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/s/

SHERITA D MCLAMORE
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NDA 206927

Bortezomib for Injection

Review of Drug Product Sections

Z. Jean Tang

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II

Chemistry, Manufacturing, and Controls (CMC)
Team Review of Original NDA
For the Division of Drug Oncology Products 2

Table of Contents

CMC Review Data Sheet

1. NDA 206927

2. REVIEW #: 1

3. REVIEW DATE: 25-Apr-2014

4. REVIEWER: Z. Jean Tang

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA Submission	04-Mar-2014

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	1	03-Mar-2014	04-Mar-2014
Amendment (Revised drug product specification and updated stability data))	6	27-Augt-2012	27-Augt-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Bortezomib for Injection
Address:	Dr. Reddy's Laboratories Limited Bachupally Village, Qutubullapur Mandal Hyderabad, Andhra Pradesh, India 500090
Representative:	Srinivasa Rao
Authorized U.S. agent	Dr. Reddy's Laboratories, Inc., 107 College Road East, 2nd Floor, Princeton, NJ 08540
Telephone / email:	908-450-1476 / srao@drreddys.com

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name: Bortezomib for Injection
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: Type 5
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Treatment of patients with multiple myeloma and patients with mantle cell lymphoma.

11. DOSAGE FORM: Lyophilized powder for injection

12. STRENGTH/POTENCY: 3.5 mg/vial

13. ROUTE OF ADMINISTRATION: Intravenous (Original 1) and Subcutaneous (Original 2)

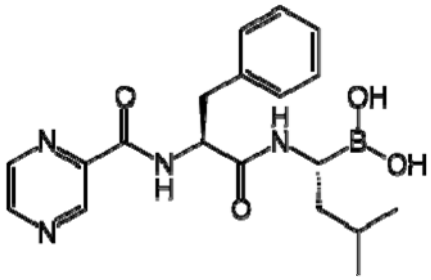
14. Rx/OTC DISPENSED: __√__ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____ SPOTS product – Form Completed
__√___ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical structure



Molecular formula	$C_{19}H_{25}BN_4O_4$
Molecular weight	384.24 g/mol
United States Adopted Name (USAN)	Bortezomib for Injection
International Nonproprietary Name (INN)	Bortezomib
CAS Chemical (IUPAC) name	[(1R)-3-met hyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl) mino]propyl]amino]butyl] boronic acid
(CAS) registry number	[179324-69-7] (trihydrate)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[a]	STATUS[b]	DATE REVIEW COMPLETED	COMMENTS
023996	II	Dr. Reddy's Laboratories Limited, Andhra Pradesh, India	**Drug Substance, Bortezomib**	4	Inadequate	N/A	OGD reviewed the DMF, and found it is inadequate.
(b) (4)	III	(b) (4)		4	N/A	N/A	
	III			4	N/A	N/A	

Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[b] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A	N/A	N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable		Zhong Li
Pharm/Tox	Acceptable	3-Jun-2014	Christopher Sheth
Biopharm	Pending	Date of this review	Elsbeth Chikhale, Ph.D.
LNC*	N/A		
Methods Validation	N/A		
DMEPA**	Acceptable	25-Sep-2014	Michelle Rutledge
EA	Categorical exclusion (see review)	Date of this review	Jean Tang
Microbiology	Acceptable	10-Sep-2014	ERIKA A PFEILER

*LNC: Labeling and Nomenclature Committee
**DMEPA: Division of Medication Error Prevention and Analysis

The CMC Review for NDA 206927

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the perspective of chemistry, manufacturing, and controls, this NDA is not recommended for APPROVAL due to Inadequate drug substance DMF 23996.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

Bortezomib is a proteasome inhibitor used to treat cancer. It is a modified dipeptidyl boronic acid that exists as a trimeric boroxine in anhydrous environments. Overall, the holder has not adequately supported the structure of the drug substance as the provided physical data supports both boroxine and boronic acid forms of bortezomib. Refer to DMF review conducted by Erin M Skoda for details.

(2) Drug Product

Bortezomib for injection is an antineoplastic agent available for intravenous injection. Each single use vial contains 3.5 mg of bortezomib, 10 mg anhydrous citric acid, and 8.4 mg tromethamine and is available as a sterile lyophilized powder.

Bortezomib is a modified dipeptidyl boronic acid. The product is provided as a citric acid boronic ester which, in reconstituted form, consists of the citric acid ester in equilibrium with its hydrolysis product, the monomeric boronic acid. The drug substance exists in monomeric boronic acid form.

The applicant submitted stability data up to 18 months for three batches of commercial scale Bortezomib for injection 3.5mg/vial. All the stability data up to 18 months under the long term storage condition and 6 months under the accelerated storage condition are well within the specification. According to ICH guideline Q1E, the applicant proposed a shelf life of 24 months stored at 20°-25°C (68°-77°F); [see USP Controlled Room Temperature]. Retain in original package to protect from light. The Office of

Compliance has issued an overall recommendation for the inspection of the drug product manufacturing site (Attachment I).

B. Description of How the Drug Product is Intended to be Used

Bortezomib for injection is an antineoplastic agent available for intravenous injection. Bortezomib is indicated for the treatment of patients with multiple myeloma and with mantle cell lymphoma who have received at least 1 prior therapy

The recommended starting dose of bortezomib is 1.3 mg/m^2. Bortezomib may be administered intravenously at a concentration of 1 mg/mL. When administered intravenously, bortezomib is administered as a 3 to 5 second bolus intravenous injection. Bortezomib is for intravenous use only. Bortezomib should not be administered by any other route.

C. Basis for Approvability or Not-Approval Recommendation

In order for this NDA to be recommended for Approval from a Chemistry, Manufacturing, and Controls standpoint, adequate drug substance DMF 23996 is required; currently the DMF is inadequate Pertinent CMC information is recommended in a Complete Response letter.

III. Administrative

A. Reviewer's Signature:
(See appended electronic signature page)

Zhe Jean Tang, Ph.D, Reviewer, ONDQA

B. Endorsement Block:
(See appended electronic signature page)

Ali Al Hakim, Ph.D., Branch Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

C. CC Block: entered electronically in DARRTS

IV. Chemistry Assessment

Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

S DRUG SUBSTANCE

Refer to the CMC review of the drug substance in DMF 23996 by Dr. Erin Skoda.

P DRUG PRODUCT

Bortezomib for Injection 3.5 mg/vial is a white to off white lyophilized powder for reconstitution. The product is packed in 10 mL USP (b) (4) tubular glass vial stoppered with 13 mm (b) (4) rubber stoppers and sealed with 13 mm flip-off seal.

P.1 Description and Composition of the Drug Product

The composition Bortezomib for Injection 3.5 mg/vial is shown in Table 1. Table 2 lists the comparison of qualitative and quantitative composition with reference listed drug VELCADE® for Injection (NDA # 021602) marketed by Millennium Pharmaceuticals, Inc.

Table 1 Composition of 3.5 mg/vial Bortezomib for Injection

Components	Reference	Quantity (mg / vial)	
Bortezomib	In-house	3.5 mg	
			(b) (4)
		(b) (4)	

(b) (4)

Table 2 Comparison of Qualitative and Quantitative Compo
Drug

Components	Function	VELCADE® (Bortezomib) for Injection Millennium Pharmaceuticals, Inc. (Quantity/vial)	Bortezomib for Injection Dr. Reddy's Laboratories (Quantity/vial)
Bortezomib	1	3.5 mg	
Mannitol	(b) (4)	5 mg	
Tromethamine		-	(b) (4)
Anhydrous Citric Acid		-	
(b) (4)		-	
		-	
		-	

(b) (4)

Quantitative composition of Inactive Ingredients of Bortezomib for Injection 3.5 mg/vial was compared to the Inactive Ingredients Database (Centre for Drug Evaluation and Research) (Table 3).

Table 3 Quantitative composition of Inactive Ingredients of Bortezomib with the Inactive Ingredients Database

Inactive ingredients	Route of administration	Allowable	Allowable Quantity	Quantity Per Vial in Proposed Formulation
Tromethamine USP	IV (Reconstitute with 3.5 mL)	1.0%	35 mg	8.4 mg
				(b) (4)
Anhydrous Citric Acid USP	IV (Reconstitute with 3.5 mL)	0.8%	28 mg	10 mg
				(b) (4)

Evaluation: **Satisfactory**

The section is acceptable. As compared to the listed drug Velcade®, the different excipients are used in the formulation. However, as indicated in the Table 3, all the inactive ingredients were

(b) (4)

80 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Tang -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Zhe Tang -A, 0.9.2342.19200300.100.1.1=2000329044
Date: 2014.12.01 14:49:42 -05'00'

Ali H. Al-Hakim -S

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Product Quality Microbiology Review

10 September 2014

NDA: 206927

Drug Product Name
Proprietary: N/A
Non-proprietary: Bortezomib for Injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
03 MAR 2014	04 MAR 2014	07 MAR 2014	18 MAR 2014
06 JUN 2014	06 JUN 2014	N/A	N/A
27 AUG 2014	27 AUG 2014	N/A	N/A

Applicant/Sponsor
Name: Dr. Reddy's Laboratories, Ltd.
Address: Bachupally Village, Qutubullapur Mandal, Hyderabad, Andhra Pradesh, India
Representative: Srinivasa Rao
Telephone: 609-375-9911

Name of Reviewer: Erika Pfeiler, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: 505(b)(2)

2. SUBMISSION PROVIDES FOR: Initial marketing of a sterile drug product

3. MANUFACTURING SITE:
Dr. Reddy's Laboratories Ltd.
Formulations Unit VII, Plot No. P 1 to P 9, Phase – III, VSEZ, Duvvada, Visakhapatnam, Andhra Pradesh - 530 046, India.

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Sterile lyophilized powder
- Intravenous (b) (4)
- 3.5 mg/vial, 10 mL vial

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Treatment of multiple myeloma

B. SUPPORTING/RELATED DOCUMENTS:
Microbiology Review 25a1 of DMF (b) (4) (DARRTS Date 10 April 2014)/
Microbiology Review 28 of DMF (b) (4) (DARRTS Date 13 May 2014)

C. REMARKS: N/A

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Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended for Approval

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4)

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

D. Contains Potential Precedent Decision(s)- ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____
Erika Pfeiler, Ph.D.
Microbiologist

B. Endorsement Block_____
Stephen Langille, Ph.D.
Senior Review Microbiologist

C. CC Block
N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE

The drug substance is rendered sterile by the drug product manufacturer. Drug substance specifications state that (b) (4)

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product –

The drug product is a sterile lyophilized powder, intended for reconstitution prior to injection. This is a single-use product.

- Drug product composition – See Table 1.

Table 1. Drug Product Composition. From 3.2.P.1.

Components	Reference	Quantity (mg / vial)	Pharmaceutical Function
Bortezomib	In-house	3.5 mg	Active Pharmaceutical Ingredient
Tromethamine	USP	8.4 mg	(b) (4)
Anhydrous Citric Acid	USP	10.0 mg	
			(b) (4)

- Description of container closure system –

The primary container closure system consists of a 10 mL (b) (4) tubular glass vial and 13 mm (b) (4) rubber stopper.

P.2 Pharmaceutical Development

(b) (4)

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/s/

ERIKA A PFEILER
09/10/2014

STEPHEN E LANGILLE
09/10/2014

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/s/

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