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***APPLICATION NUMBER:***

# 206927Orig1s000

# SUMMARY REVIEW

# Summary Review for Regulatory Action

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| **NDA Number** | 206927 |
| **Applicant** | Dr. Reddy's Laboratories, Ltd |
| **Subject** | Division Director's Summary Review |
| **From** | Albert Deisseroth |
| **Date Report Completed** | October 3, 2019 |
| **Division/Office** | DHP/OHOP |
| **Submission Date** | May 06, 2019 |
| **Submission Type** | Resubmission of 505(b)(2) |
| **Brand (generic) Name** | Bortezomib Injection |
| **Trade Name** | Bortezomib Injection |
| **Dosage Form and Strength** | Injection/3.5 mg/vial |
| **Route of Administration** | Intravenous ONLY |
| **Proposed Indication** | Bortezomib for Injection 3.5 mg/vial is indicated 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 |
| **Recommended Regulatory Action** | Approval |

# Supervisory Associate Division Director's Review of NDA 206927

(This review was based in part on the reviews of Sherita D. McLamore, PhD and Bindu Kanapuru, MD).

**Background**: Dr. Reddy's Laboratories, Ltd initially submitted NDA 206927 (505(b)(2)) on March 4, 2014 requesting approval (b) (4) of bortezomib for injection. No clinical studies with the proposed drug product were included in NDA 206927. Instead, the Applicant was relying on the findings of safety and efficacy by the FDA for Velcade (bortezomib) contained in NDA 206927. (b) (4)

NDA 206927/original 1-Route of administration-Intravenous, (b) (4)

**Regulatory History:** A complete response (CR) was issued on December 12, 2014. (b) (4) On November 23, 2015, Dr. Reddy's Laboratory carried out a Class 2 resubmission which was given a Complete Response on May 4, 2016, due to product quality and facilities issues. The present submission (May 06, 2019) addresses the product quality issues outlined in the May 4, 2016 CR letter.

**Basis for Regulatory Action**: On the basis of the review conducted by the drug substance, drug product, drug process, microbiology, biopharmaceutics and facilities reviewers, the Office of Pharmaceutical Quality recommends approval of NDA 206927 for the indication cited on the previous page.

**Recommended Regulatory Action**: The Supervisory Associate Division Director also recommends Approval of NDA 206927 for the indication cited above.

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/s/

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ALBERT B DEISSEROTH
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# Cross-Discipline Team Leader Review

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| **Date** | 1-Oct-2019 |
| **From** | Sherita D. McLamore, Ph.D. |
| **Subject** | Cross-Discipline Team Leader (CDTL) Review |
| **NDA** | 206927 |
| **Type of Application** | 505(b)(2) |
| **Applicant** | Dr. Reddy's Laboratories, Ltd |
| **Date of Receipt** | 06-May-19 |
| **PDUFA Goal Date** | 06-Nov-19 |
| **Proposed Proprietary/Established Names** | Bortezomib Injection |
| **Dosage forms / Strength** | Injection/ 3.5 mg/vial |
| **Route of Administration** | Intravenous ONLY |
| **Proposed Indication(s)** | Bortezomib for Injection 3.5 mg/vial is indicated 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 |
| **Recommended:** | **APPROVAL** |

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Clinical (Bindu Kanapuru, M.D.)
- Pharmacology/Toxicology (Matthew Thompson, Ph.D.)
- DEMPA (Nicole Garrison, PharmD)
- Drug Product (William Adams, Ph.D.)
- DDMAC Labeling Consult (Domenic Dalessandro, Ph.D.)
- Microbiology (David Bateman, Ph.D.)
- Manufacturing Facilities (Derek Smith, Ph.D.)
- Biopharmaceutics (Qi Zhang, Ph.D.)

## 1. Introduction

NDA 206927/Original 1 was submitted for Bortezomib for Injection, 3.5 mg/vial in accordance with section 505(b)(2) of the Food, Drug and Cosmetic Act. Bortezomib is a modified dipeptidyl boronic acid and a potent antineoplastic agent. Bortezomib is therapeutic proteasome inhibitor that was originally approved under the brand name VELCADE® for the treatment of multiple myeloma. VELCADE® was approved under NDA 021602 in 2003 and is the listed drug (LD) for this NDA. VELCADE® is a sterile, lyophilized product supplied in a single-dose vial containing 3.5 mg of the active. The proposed drug product, Bortezomib for Injection 3.5 mg/vial is presented as 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 proposed drug product contains an identical amount of the active drug

ingredient and has the same dosage form (b) (4) as the LD. The differences in the Dr. Reddy's drug product and the LD are found in the excipients and in the route(s) of administration. The LD contains mannitol (b) (4) while Dr. Reddy's formulation contains tromethamine and citric acid (instead of mannitol). Additionally, the LD is approved to be administered via IV or SC while the Dr. Reddy product in this submission is limited to IV administration.

No clinical studies were performed with the proposed drug product as this submission relies on the agency's findings for VELCADE® (bortezomib) for Injection (NDA 021602) for safety and efficacy. Accordingly, approval of NDA 206927 from clinical, non-clinical and clinical pharmacology perspectives will be primarily based on publicly available information for VELCADE®.

## 2. Background

NDA 206927 presents a new formulation of Bortezomib. 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 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 Complete Response (May 4, 2016) due to outstanding product quality which included facilities issues. The current submission addresses the outstanding product quality concerns that were included in the Agency's May 4, 2016 Complete Response letter.

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.

## 3. Product Quality

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). The chemistry, manufacture and control of the drug substance was provided by way of DMF No. 23996 from Dr. Reddy's Laboratories, Ltd. The proposed drug product, Bortezomib for Injection 3.5 mg/vial is a white to off white sterile, lyophilized powder for reconstitution that 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 drug product formulation includes the active, tromethamine

and anhydrous citric acid. The manufacturing process for Bortezomib for injection includes (b) (4)

The product quality reviews for the May 2019 focused on the deficiencies and Lifecycle Management Considerations included in the agency's May 2016 CR letter which included deficiencies from drug product, drug process, microbiology, biopharm and facilities. Upon completion of the review, it was concluded that Applicant adequately addressed all deficiencies and Lifecycle Management Considerations.

In support of the proposed 24-month expiry, the applicant included 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. All data were acceptable. Accordingly, 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°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

NDA 206827 included 3 manufacturing, testing, and packaging facilities

- Dr. Reddy's Laboratories Limited (3002806851)
- Dr. Reddy's Laboratories Limited (FEI 3006549835
- Dr. Reddy's Laboratories Limited, Chemical Technical Operations-Unit II (FEI 3005448030)

At the time of submission, all sites were listed as ready for inspection. During this cycle, the previously the unacceptable facility was assessed, along with the newly proposed testing facility, both affiliated with Dr. Reddy's. No pre-approval inspections were conducted and the decision to approve is made based on the previous inspection history and current CGMP compliance status. All facilities proposed for commercial operations for NDA 206927 are acceptable.

**Overall Product Quality Recommendation**: The Office of Pharmaceutical Quality (drug substance, drug product, drug process, microbiology, biopharmaceutics and facilities reviewers) recommends **APPROVAL** for NDA 206927.

**6. Clinical Pharmacology**

No clinical/pharmacology information provide in the resubmission.

**7. Non-Clinical Pharmacology/Toxicology**

No non-clinical pharmacokinetic or toxicology information provided in the resubmission.

**8. Clinical/Statistical-Efficacy**

No clinical or statistical information provided in the resubmission.

**9. Safety**

Safety was based on the Prescribing Information for the Listed Drug, Velcade.

**10. Advisory Committee Meeting** N/A

**11. Pediatrics** N/A

**12. Other Relevant Regulatory Issues** N/A

**13. Labeling**

The labeling review was completed by Office of Prescription Drug Promotion (OPDP), Division of Medication Error Prevention and Analysis (DMEPA), Clinical, Non-Clinical, Clinical Pharmacology, and CMC. (b) (4) The Applicant included specific instructions for reconstitution and administration for the proposed 3.5 mg/ml intravenous route is included in the label.

**Overall Labeling Recommendation:**

The proposed labeling for Dr. Reddy's Bortezomib for Injection has been reviewed and comments from all disciplines were conveyed to the applicant. The applicant accepted the changes recommended by the agency and submitted revised labeling. The labeling for Dr. Reddy's Bortezomib Injection is acceptable with no additional recommendations.

**14. Recommendations/Risk Benefit Assessment**

- **Recommended Regulatory Action**

This product relies on the safety and efficacy of the Listed Drug, Velcade. Dr. Reddy's product has the same active ingredient, is the same dosage form and has the final concentration of bortezomib following dilution as the LD; however, the products differ in the excipients and in the route(s) of administration. The Applicant relied upon the FDA's previous findings of safety and effectiveness for Velcade, as described in the drug's approved labeling. Accordingly, there were no new clinical or nonclinical studies conducted for this 505(b)(2) application.

As there are no outstanding issues precluding the approval of this application and based on the recommendations from all review disciplines, the CDTL recommends granting **APPROVAL** of NDA 206927/Original 1**.**

- **Risk Benefit Assessment**

Please refer to NDA 021602.

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SHERITA D MCLAMORE
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