CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206927Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206927/Original 1
(b) (4)

COMPLETE RESPONSE

Dr. Reddy's Laboratories, Limited-
c/o Dr. Reddy's Laboratories, Inc.
Attention: Srinivasa Rao, PharmD
Senior Director and Head Regulatory Affairs
107 College Road East, 2nd Floor
Princeton, NJ 08540

Dear Dr. Rao:

Please refer to your New Drug Application (NDA) dated March 3, 2014, received March 4, 2014, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for bortezomib for injection 3.5 mg/vial.

We acknowledge receipt of your amendment dated November 23, 2015, which constituted a complete response to our December 17, 2014, action letter.

NDA 206927 provides for the use of bortezomib for injection 3.5 mg/vial for the following indications (b) (4)

- NDA 206927/Original 1 - Route of administration – Intravenous
  - Treatment of patients with multiple myeloma
  - Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

(b) (4)

The subject of this action letter is NDA 206927/Original 1 (b) (4)

All future submissions to NDA 206927/Original 1 (b) (4) should specify the NDA number and the Original number to which each submission pertains.

We have completed our review of NDA 206927/Original 1 (b) (4), as amended, and have determined that we cannot approve these applications in their present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

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 proces (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 flow 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.

LABELING

Please submit draft labeling and draft carton/container labeling revised as follows.

1. Change the respective labels that refer to the product as a "single-use vial" to a "single-dose vial".

2. Revise the labels to include the statement that indicates the product is sterile. Include this language in all applicable labels.

Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

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.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before NDA 206927/Original 1 (b) (4) may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

If you have any questions, call Alycia Anderson, Regulatory Project Manager, at (240) 402-4270.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EDVARDAS KAMINSKAS
05/04/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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COMPLETE RESPONSE

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Attention: Srinivasa Rao, PharmD
Senior Director and Head Regulatory Affairs
107 College Road East, 2nd Floor
Princeton, NJ 08540

Dear Dr. Rao:

Please refer to your New Drug Application (NDA) dated March 3, 2014, received March 4, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for bortezomib for injection 3.5 mg/vial.

We acknowledge receipt of your amendment(s) dated June 6; August 14 (2), 18, and 27; and October 14, 2014.

NDA 206927 provides for the use of bortezomib for injection 3.5 mg/vial for the following indications (b) (4)

- NDA 206927/Original 1 – Route of administration - Intravenous
  - Treatment of patients with multiple myeloma
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The subject of this action letter is NDA 206927/Original 1 (b) (4)

All future submissions to NDA 206927/Original 1 (b) (4) should specify the NDA number and the Original number to which each submission pertains.

We have completed our review of NDA 206927/Original 1 (b) (4) and have determined that we cannot approve these application(s) in their present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

Deficiencies - Original 1 (intravenous route of administration):

1. Your application referenced the Drug Master File (DMF) 23996. This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on December 4, 2014. These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.

2. The waiver request for the CFR requirement to provide data from an *in vivo* bioequivalence study for the intravenous route of administration cannot be granted at this time due to outstanding issues with the identity of the drug substance (refer to DMF) and the identity of the structures in the drug product and reconstituted solution. You may resubmit the biowaiver request or alternatively you may conduct a bioequivalence study between the proposed drug product and the listed drug product for the intravenous route of administration.

(b) (4)

LABELING

5. We reserve comment on the proposed labeling until NDA 206927/Original 1 (b) (4) are otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

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OTHER

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before NDA 206927/Original 1 (b) (4) may be approved. If you wish to have such a meeting, submit your meeting request as described

in the FDA's "Guidance for Industry - Formal Meetings between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed for these indication(s) until you have been notified in writing that NDA 206927/Original 1 (b) (4) are approved.

If you have any questions, call Alycia Anderson, Regulatory Project Manager, at (240) 402-4270.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Reference ID: 4504436

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
12/17/2014