

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212782Orig1s000

OTHER ACTION LETTERS



NDA 212782

COMPLETE RESPONSE

Shilpa Medicare Limited
c/o Shilpa Pharma Inc.
Attention: Krishna Chaithanya Konagalla
Director, Regulatory Affairs
1980 S. Easton Rd., Ste 220
Doylestown, PA 18901

Dear Krishna Konagalla:

Please refer to your new drug application dated and received May 21, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for bortezomib injection.

We acknowledge receipt of your amendment dated February 3, 2023, which constituted a complete response to our March 10, 2020, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

Drug Product

1. We acknowledge the justification provided that gross content test can be satisfied by the results of (b) (4) (submission dated 05-23-2023). However, to comply with MAPP 5019.1 (official as of January 28, 2022), we suggest you include a gross content test with upper and lower acceptance criteria in the drug product specification. Also, provide a description of the analytical procedure, an appropriate method validation study, and test results for the NDA exhibit batches.
2. Perform a risk assessment analysis for (b) (4) in the drug product. If risks of (b) (4) are identified, conduct confirmatory testing as needed, using sensitive and appropriately validated methods. Refer to the following Guidance for additional information: (b) (4)
(b) (4)
3. Perform a one-time leachable study on three drug product registration stability batches stored in an inverted position at the proposed long-term storage

conditions; and submit the leachable data for multiple time points (e.g., 18 months, 24 months, 36 months etc.) through expiry. Please note that your proposal to (b) (4)

(b) (4) is not acceptable, (b) (4)

(b) (4) Refer to USP <1664> for additional details regarding leachable assessment. Any leachables found must be adequately controlled, and those found above the applicable thresholds must be adequately qualified.

4. Provide updated long term stability data for three registration stability batches of Bortezomib Injection. Refer ICH Q1E – Evaluation of Stability Data for additional details regarding extrapolation of stability data.

Process

1. We acknowledge your submitted response in Sequence 0028 for Information Request #1-a. However, your response is not adequate. (b) (4)

(b) (4)

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources¹ and Pregnancy and Lactation Labeling Final Rule² websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.³

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

FACILITY INSPECTIONS

Following surveillance inspection of the (b) (4) manufacturing facility listed in this application, FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution of the observations is required before this NDA 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.

¹ <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

² <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

³ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

- (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 in the original submission.
 - Present tabulations of the new safety data combined with the original application data.
 - Include tables that compare frequencies of adverse events in the original application 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 subject 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 application 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

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call CAPT Bernetta Lane, Senior Regulatory Health Project Manager, DHSc, MBA, RN at (301) 796-0937.

Sincerely,

{See appended electronic signature page}

Nicholas Richardson, DO, MPH
Deputy Director (Acting)
Hematologic Malignancies II
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

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/

NICHOLAS C RICHARDSON
08/01/2023 06:53:22 PM



NDA 212782

COMPLETE RESPONSE

Shilpa Medicare Limited
c/o Shilpa Pharma Inc.
Attention: Krishna Chaithanya Konagalla
Director, Regulatory Affairs
1980 S. Easton Rd., Ste 220
Doylestown, PA 18901

Dear Mr. Konagalla:

Please refer to your new drug application (NDA) dated May 21, 2019, received May 28, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Bortezomib injection.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

- (1) The scientific bridge between the proposed Bortezomib injection and the Listed Drug (LD) is not adequately established because of the unresolved clinical safety concerns related to the hyperosmolality of the proposed drug product. The (b) (4) in the proposed formulation makes the osmolality (b) (4) times greater than the osmolality of the LD. This difference is clinically relevant because the drug's administration is once to twice weekly as a bolus intravenous injection over 3 to 5 seconds into a peripheral vein. The risks of potential vascular injury from the formulation-related changes outweigh the benefit of a formulation that does not require reconstitution. Shilpa Medicare Limited's approach of using the (b) (4) is insufficient to address the safety concerns of the high osmolality of the proposed drug product. Satisfactory resolution of these clinical safety concerns is required to establish the bridge between the proposed drug product and the LD for the intravenous route of administration.

In order to resolve the safety issues for your current proposed formulation, you must:

- (a) Conduct clinical studies to demonstrate the comparable bioavailability/bioequivalence and safety of your drug product. In addition, labeling specific to your product may be needed and your submission may need to include risk mitigation strategies to address the risks for medication error due to inappropriate product substitution.
- (b) Provide a thorough safety assessment based on a comprehensive literature search to support the safety of the proposed drug product.

Alternatively, consider reformulating the proposed product.

PRODUCT QUALITY

- (2) Explain the significant difference in Osmolality reported for developmental drug product batch BORP1068 (module 3.2.P.2, Table 50) with that reported at release for NDA exhibit batches 7Q10042A, 7Q10043A and 7Q10044A. Also, provide stability data which establishes that the values observed at release for the NDA exhibit batches does not change over time.
- (3) Revise the release and stability specification for Degradation Products to report all known and unknown impurities, and degradants observed at or above the method limit of quantitation, and to report total impurities as the sum of all observed known and unknown impurities, or degradants. This will permit trend analysis for degradants and establish mass balance.
- (4) Provide updated stability data from the on-going stability studies on the NDA exhibit batches to justify the proposed criteria in the release specification.
- (5) During a recent inspection of the [REDACTED] (b) (4) 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.

PRESCRIBING INFORMATION

- (6) We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information¹ and Pregnancy and Lactation Labeling Final Rule² websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

¹ <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

² <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.³

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:
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³ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

- (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.

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The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Jennifer Lee, Senior Regulatory Health Project Manager, at (240) 402-4622.

Sincerely,

{See appended electronic signature page}

Nicole J. Gormley, MD
Acting Director
Division of Hematologic Malignancies II
Office of Oncologic Diseases
Center for Drug Evaluation and Research

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/

NICOLE J GORMLEY
03/10/2020 01:07:19 PM