CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215973Orig1s000
215974Orig1s000

OTHER ACTION LETTERS

NDA 215973

COMPLETE RESPONSE

Gilead Sciences, Inc.
Attention: Grace Gill, PharmD
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Gill:

Please refer to your new drug application (NDA) dated and received June 28, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lenacapavir injection.

We also acknowledge receipt of your amendments dated December 29, 2021, January 7, 2022, January 21, 2022, and February 11, 2022, which were not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this 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

1. Your data demonstrate that the drug product solution is incompatible with the proposed commercial borosilicate glass vials. The data provided in support of the compatibility of the alternative aluminosilicate glass vials are incomplete and ambiguous. As evidenced by your data and glass particles found in the clinical batches, glass containers are generally incompatible with highly alkaline solutions, (b) (4). In order to resolve this deficiency, we require a comprehensive study report with unambiguous data and fully validated methods to demonstrate the compatibility of the drug product solution with your proposed primary container closure system.

2. The information request response provided on December 29, 2021, regarding the Container Closure Integrity Testing (CCIT) performed with aluminosilicate vials with batches GB2007B, GB2008B, and GB2009B is acknowledged. However, this response is incomplete and additional information is needed to assess acceptability of aluminosilicate vials:

a. Provide the spectrophotometric data with all results from the CCIT dye ingress studies reported to be performed with 20 intact vials sourced from each of three batches GB2007B, GB2008B, and GB2009B respectively.

b. Provide details of the CCIT protocol used to include the date the study was performed. Additionally, confirm the dye ingress CCIT was conducted using units exposed to worst case (b) (4) conditions prior to CCIT and confirm that both pressure and vacuum conditions were applied during CCIT. These conditions may be necessary to ensure that debris, dried product, and/or particulate matter are completely removed from potential leak paths. In the absence of vials exposed to (b) (4) and both pressure and vacuum conditions being applied please provide a new CCIT.

PRESCRIBING INFORMATION

(1) 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 Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] 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

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

PROPRIETARY NAME

(3) Please refer to correspondence dated, August 10, 2021 which addresses the proposed proprietary name, Sunlenca. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

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[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

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 product 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 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 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 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 product. Include an updated estimate of use for product marketed in other countries.

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

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

Product Quality

1. The proposed acceptance criterion for the appearance test in drug product release and stability specifications is – '*a clear, yellow* (b) (4) *solution, essentially free of visible particles*.' Clarify whether any drug product batch(es) exhibited (b) (4) color at release or during stability and whether change in color from 'yellow (b) (4)' had any impact on other drug product CQAs. Also, report the exact color for the appearance test for future stability time points of drug product registration batches.

Virology

2. Please submit complete resistance data for optimized background drugs for all virologic failures in Study GS-US-200-4625 (including subjects (b) (6) [Week 26]; (b) (6) [Week 26], (b) (6) [Week 4]; (b) (6) [Week 4]; (b) (6) [Week 26 + LEN phenotype at Week 4 and Week 26]).

3. Please provide longer term (>24 weeks) efficacy and resistance (genotypic and phenotypic) data for Cohort 1 subjects.

4. Please provide all available efficacy and resistance data for Cohort 2 subjects.

5. Please provide information on whether lenacapavir binding to the hexamers is stoichiometric and what the stoichiometry is at maximum complex formation at low and high ionic strengths.

Clinical

6. Please submit a complete assessment of the extent to which glass particulate contamination, including sub-visible particles, may be associated with injection site nodules and indurations or other clinical effects. In addition, submit independent dermatologist evaluation assessments for subjects in Study GS-US-200-4625 or Study GS-US-200-4334 who met Grade 3 or higher adverse event injection site reaction criteria, or who had any injection site reactions (particularly indurations or nodules) that are not resolved within 24 weeks.

7. We acknowledge previous discussions regarding inclusion of both an alternative, simplified dosing regimen in labeling in addition to the oral lead-in regimen used in Study GS-US-200-4625. We continue to believe that inclusion in labeling of the oral lead-in regimen as studied in GS-US-200-4625 is appropriate. Therefore, we

recommend including both options in labeling and other associated aspects of your application as needed to accommodate these regimens (e.g., alternative packaging configurations).

8. If, at the time of your resubmission, data from Cohort 2 of Study GS-US-200-4625 are available, these data should be incorporated into your application and labeling.

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

If you have any questions, call Kevin Allen, Regulatory Project Manager, at 301-837-7467.

Sincerely,

{See appended electronic signature page}

Adam Sherwat, MD
Deputy Director
Office of Infectious 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/

ADAM I SHERWAT
02/28/2022 10:39:50 AM

NDA 215974

COMPLETE RESPONSE

Gilead Sciences, Inc.
Attention: Grace Gill, PharmD
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Gill:

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We also acknowledge receipt of your amendment dated January 21, 2022, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this 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

We have identified deficiencies in the product quality information for the lenacapavir injection NDA 215973. As the approval of lenacapavir tablet is contingent on the approval of lenacapavir injection, the lenacapavir injection deficiencies must be adequately addressed before this application can be approved.

To resolve the deficiency identified above, please submit a letter of authorization that identifies the date the Complete Response submission was submitted to NDA 215973.

PRESCRIBING INFORMATION

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Sincerely,

{See appended electronic signature page}

Adam Sherwat, MD
Deputy Director
Office of Infectious 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/

ADAM I SHERWAT
02/28/2022 10:41:17 AM