NDA 215973

NDA APPROVAL

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 (FDCA) for Sunlenca (lenacapavir) injection.

We acknowledge receipt of your amendment dated June 27, 2022, which constituted a complete response to our February 28, 2022, action letter.

This NDA provides for the use of Sunlenca (lenacapavir) injection in combination with other antiretroviral(s) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at

FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (Prescribing Information, Patient Package Insert, and Instructions for Use) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 215973**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Sunlenca (lenacapavir) injection shall be 24 months from the date of manufacture when stored at 20°C - 25 °C (68°F - 77°F).

ADVISORY COMMITTEE

Your application for Sunlenca was not referred to an FDA advisory committee because the application did not raise significant efficacy issues that were unexpected. Outside expertise was not necessary, as there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

We are waiving the pediatric study(ies) for this application from birth to less than 12 years of age because the necessary studies are impossible or highly impracticable. This is because most children living with HIV-1 will not experience multiple courses of antiretroviral regimens and will therefore not be considered highly treatment experienced until adolescence.

We are deferring submission of your pediatric study for ages 12 to less than 18 years of age and weighing at least 35 kg for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of FDCA. This required study is listed below.

4351-1 Conduct a study to evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of lenacapavir in treatment-experienced children living with HIV-1 infection who are less than 18 years of age and weighing at least 35 kg. The safety and antiviral activity of lenacapavir in pediatric subjects must be evaluated for a minimum of 24 weeks.

Draft Protocol Submission:	08/2023
Final Protocol Submission:	11/2023
Study Completion:	03/2027
Final Report Submission:	09/2027

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 136260 with a cross-reference letter to this NDA. Reports of this required pediatric postmarketing study must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of carcinogenic potential.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

4351-2 Conduct a 2-year carcinogenicity study in rats to assess the carcinogenic potential of lenacapavir.

The timetable you submitted on November 15, 2022, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/2020 (Submitted)
Study Completion:	08/2023
Final Report Submission:	09/2023

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of persistent injection site nodules and indurations.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trial:

4351-3 Submit final study reports with datasets from Studies GS-US-200-4625 and GS-US-200-4334. Provide comprehensive assessments of injection site nodules and indurations associated with the first subcutaneous injections, which must be followed until resolution or until study completion, in the final study reports.

The timetable you submitted on November 15, 2022, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2019 (Submitted)
Trial Completion:	10/2023
Final Report Submission:	06/2024

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocol(s) to your IND 136260 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4351-4 Complete the [redacted] (b) (4) and submit the report as a CBE-0 supplement.

The timetable you submitted on December 14, 2022, states that you will conduct this study according to the following schedule:

Interim Report:	03/30/2023
Interim Report:	03/30/2024
Final Report Submission:	11/30/2024

4351-5 Evaluate the [redacted] (b) (4) Submit the interim and final study reports as CBE-0 supplements.

The timetable you submitted on December 9, 2022, states that you will conduct this study according to the following schedule:

Interim Report:	03/30/2023
Interim Report:	03/30/2024
Final Report Submission:	11/30/2024

4351-6 Evaluate an alternative device/s (i.e., vial access device, needle, etc.) and/or procedure for withdrawing the lenacapavir injection from the vial, which consistently reduces the presence of stopper particulates in the drug product solution to NMT 5 particles >50 µm per 12 vials as measured by optical microscopy, with these limits representing minimum requirements of USP <381>. USP <381> procedures do not employ drug product solution or a vial access device; however, USP <381> is currently official and does provide a 'baseline' for the 'selection of elastomeric injectable packaging/delivery system components' to demonstrate that it is 'proven suitable for its intended use'. Provide supporting data (e.g., optical microscopy, SEM-EDX, USP <788> sub-visible particulates data etc.) from multiple drug product batches (e.g., three batches) tested at release and multiple time points over stability studies (long-term and accelerated storage conditions) under both upright and inverted orientation to support the alternative device/procedure.

The timetable you submitted on December 9, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission:	08/30/2023

Submit clinical protocols to your IND 136260 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to

this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.[7]

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[7] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Kevin Allen, Regulatory Project Manager, at 301-837-7467 or 301-796-1500.

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

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Use
- Carton and Container Labeling

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/

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