



NDA 214787/S-18

**SUPPLEMENT APPROVAL  
FULFILLMENT OF POSTMARKETING  
REQUIREMENTS/COMMITMENT**

Gilead Sciences, Inc.  
Attention: Madelyn Low, MBS  
Manager, Regulatory Affairs  
333 Lakeside Drive  
Foster City, CA 94404

Dear Ms. Low:

Please refer to your supplemental new drug application (sNDA) dated and received November 30, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Veklury (remdesivir) injection, 5 mg/ml; Veklury (remdesivir) for injection, 100 mg/vial.

This Prior Approval sNDA provides for the following:

- To update CLINICAL PHARMACOLOGY, Microbiology subsection of the Prescribing Information with clinical virology data regarding treatment-emergent resistance

**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**

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

**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.<sup>1</sup> Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, 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*.<sup>2</sup>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(I)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **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.

Because none of these criteria apply to your application, you are exempt from this requirement.

### **FULFILLMENT OF POSTMARKETING REQUIREMENTS/COMMITMENT**

We have received your submission dated September 30, 2022, containing the final reports for the following postmarketing requirements (4220-2 and 4220-3) and commitment (4220-4) listed in the January 21, 2022 approval letter.

- 4220-2 Evaluate the impact of the nsp12 A376V substitution on remdesivir susceptibility of virus or replicon in cell culture or in a biochemical assay of RdRp activity, if virus or replicon are unable to be recovered.

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<sup>1</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

<sup>2</sup> 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>.

- 4220-3 Evaluate by NGS sequence analysis the viral genes nsp8, nsp10, nsp12, nsp13, and nsp14, at baseline and Day 7 time points for subjects in Study GS-US-540-9012 who met the following criteria: Exhibited any post-baseline increase in viral RNA and had viral RNA levels at Day 7 that were greater than the Day 7 75<sup>th</sup> percentile value (5.0 log<sub>10</sub> copies/mL).

Submit phenotypic analysis for treatment-emergent amino acid substitutions in nsp8, nsp10, nsp12, nsp13, and nsp14.

- 4220-4 Submit viral sequencing data for baseline respiratory samples and post-baseline samples collected at Day 2, Day 3, Day 7, or Day 14, for remdesivir-treated subjects and evaluated placebo subjects in Study GS-US-540-9012 with viral RNA shedding above the limit of detection for the sequencing assay including submission of associated fastq files for successfully sequenced samples.

Submit phenotypic analysis for clinical isolates with treatment-emergent amino acid substitutions in accordance with the virology analysis plan for Study GS-US-540-9012.

We have reviewed your submission and conclude that the above requirements and commitment were fulfilled.

We remind you that there is a postmarketing requirement listed in the January 21, 2022 approval letter that is still open.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

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 assess a signal of serious risk of the development of resistance as a result of sequence variation in the SARS-CoV-2 replicase proteins that interact with remdesivir.

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 this serious risk.

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

- 4419-1 Evaluate the impact of the following substitutions on remdesivir susceptibility using the subgenomic replicon system: Nsp8: T123A; Nsp9:

T77A; Nsp12: W162R, P243L, A379T, A526V, S759F, and V792F; Nsp13: H245Y; Nsp14: N438I; Combination assessments: ACTT-1 subject (b) (6) (substitutions from D8 sample): nsp12\_W162R + nsp12\_P243L + nsp13\_H245Y. Assessments should include substitutions associated with resistance spanning the range of susceptibilities as references.

The timetable you submitted on March 14, 2023, states that you will conduct this study according to the following schedule:

Study Completion: 09/2023

Final Report Submission: 10/2023

4419-2 Evaluate the impact of the following substitutions identified in participants from Study GS-US-540-9012 on remdesivir susceptibility using the subgenomic replicon system: Nsp13: C26F, L83F, and P172L; and Nsp14: P24S, P106L, and A220V. Assessments should include substitutions associated with resistance spanning the range of susceptibilities as references.

The timetable you submitted on March 10, 2023, states that you will conduct this study according to the following schedule:

Study Completion: 09/2023

Final Report Submission: 10/2023

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.<sup>3</sup>

Submit clinical protocol(s) to your IND 147753 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.

<sup>3</sup> 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>.

**U.S. Food and Drug Administration**

Silver Spring, MD 20993

[www.fda.gov](http://www.fda.gov)

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.

### **PATENT LISTING REQUIREMENTS**

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

### **REPORTING REQUIREMENTS**

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

If you have any questions, contact Saebyeol Jang, PhD, RAC-US, Regulatory Project Manager, at (240) 402-9953 or at the mainline at (301) 796-1500.

Sincerely,

*{See appended electronic signature page}*

Debra Birnkrant, MD  
Director  
Division of Antivirals  
Office of Infectious Diseases  
Center for Drug Evaluation and Research

### **ENCLOSURE(S):**

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

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**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.**  
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/s/  
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POONAM MISHRA  
03/29/2023 12:55:50 PM  
on behalf of Division Director