NDA 214787

NDA APPROVAL

Gilead Sciences, Inc.
Attention: Ashley Rhoades, MBS, RAC
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Rhoades:

Please refer to your new drug application (NDA) dated and received August 7, 2020, 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 new drug application provides for the use of VEKLURY (remdesivir) injection, and VEKLURY(remdesivir) for injection, for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. VEKLURY should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care.

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 (text for the

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Prescribing Information and Patient Package Insert) 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 for VEKLURY (remdesivir) injection, submitted on September 18, 2020, and VEKLURY (remdesivir) for injection, submitted on September 25, 2020, 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 *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 214787**" Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the data provided, the expiration dating period for VEKLURY (remdesivir) injection is 12 months when stored between 2°C to 8°C (36°F to 46°F). Based on the data provided, the expiration dating period for VEKLURY (remdesivir) for injection is 30 months when stored below 30°C (below 86°F).

MATERIAL THREAT MEDICAL COUNTERMEASURE (MCM) PRIORITY REVIEW VOUCHER (PRV)

We inform you that you have been granted a material threat medical countermeasure priority review voucher (PRV), as provided under section 565A of the FDCA. This PRV has been assigned a tracking number, PRV NDA 214787. All correspondences related to this PRV should refer to this tracking number.

This PRV entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologics license application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. This PRV may be transferred by you to another sponsor of a human drug or biologic application. If the PRV is transferred, the sponsor to whom the PRV has been transferred should include a copy of this letter (which will be posted on our website as

[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.

are all approval letters) and proof that the PRV was transferred. When redeeming this PRV, you should refer to this letter as an official record of the voucher. The sponsor who redeems the PRV must notify FDA of its intent to submit an application with a PRV at least 90 days before submission of the application and must include the date the sponsor intends to submit the application.

FDA has published a draft guidance, *Material Threat Medical Countermeasure Priority Review Vouchers,* at https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm592548.pdf. This guidance, when finalized, will represent the current thinking of the FDA on this topic.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Christine Kim
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6391
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

ADVISORY COMMITTEE

Your application for VEKLURY was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for the drug in the intended population and did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

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.

We are deferring submission of your pediatric study from birth to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under 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 the FDCA. This required study is listed below.

3919-1 Conduct a study to evaluate the safety, tolerability, pharmacokinetics, and treatment response to remdesivir in pediatric subjects from birth to less than 18 years of age including neonates, with coronavirus disease 2019 (COVID-19).

Final Protocol Submission:	Submitted
Study Completion:	03/2021
Final Report Submission:	10/2021

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 to your IND 147753, with a cross-reference letter to this NDA. Reports of this required pediatric postmarketing study must be submitted as a new drug application (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)

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 emergence and transmission of remdesivir-resistant SARS-CoV-2 variants.

[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.

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 studies:

3919-2 Conduct a study to select for remdesivir resistant SARS-CoV-2 variants in cell culture and characterize several independent isolates phenotypically and genotypically.

The timetable you submitted on September 22, 2020, states that you will conduct this study according to the following schedule:

Study Completion:	06/2021
Final Report Submission:	09/2021

3919-3 Submit all SARS-CoV-2 viral shedding and viral load data from ACTT-1, GS-540-5773, and GS-US-540-5774 assessing remdesivir including quantitation of viral shedding and viral load for any subject samples that have not been completed to date.

The timetable you submitted on September 22, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission:	09/2021

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 QTc interval prolongation
- Identify an unexpected serious risk of toxicity due to the potential increase in the exposures of remdesivir and/or metabolites in patients with hepatic impairment or renal impairment
- Identify an unexpected serious risk due to the potential effect of rifampin on the enzymes and transporters involved in the disposition of remdesivir

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

3919-4 Conduct a thorough QT trial to evaluate the effect of remdesivir on the QTc interval.

The timetable you submitted on September 22, 2020, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	06/2022
Trial Completion:	12/2022
Final Report Submission:	08/2023

3919-5 Conduct a clinical trial to evaluate the pharmacokinetics and safety of remdesivir in subjects with moderate and severe hepatic impairment to inform appropriate dosage recommendations in patients with COVID-19 with impaired hepatic function. If clinically significant increased exposures are observed in this trial, a subsequent evaluation in subjects with mild hepatic impairment may be required.

The timetable you submitted on September 22, 2020, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	Submitted
Trial Completion:	08/2021
Final Report Submission:	07/2022

3919-6 Conduct a clinical trial to evaluate the pharmacokinetics and safety of remdesivir in subjects with mild, moderate, and severe renal impairment to inform appropriate dosage recommendations in patients with COVID-19 with impaired renal function.

The timetable you submitted on September 22, 2020, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	Submitted
Trial Completion:	03/2022
Final Report Submission:	11/2022

3919-7 Conduct a drug interaction trial to evaluate the effect of rifampin on the pharmacokinetics of remdesivir.

The timetable you submitted on September 22, 2020, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	Submitted
Trial Completion:	02/2021
Final Report Submission:	10/2021

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.[4]

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.

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 SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3919-8 Submit all sequencing data from ACTT-1, GS-540-5773, and GS-US-540-5774 assessing remdesivir including sequencing of any subject samples that have not been completed to date.

[4] 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.

The timetable you submitted on September 22, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2021

3919-9 Submit comprehensive resistance study reports from ACTT-1, GS-US-540-5773, and GS-540-5774 describing all resistance assessments performed for remdesivir.

The timetable you submitted on September 22, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2021

3919-10 Submit a complete study report for the assessment of the antagonistic effect of chloroquine/hydroxychloroquine on the antiviral activity of remdesivir against SARS-CoV-2 in human lung cells.

The timetable you submitted on September 22, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/2021

3919-11 Conduct a trial to evaluate the pharmacokinetics and safety of remdesivir in pregnant individuals with coronavirus disease 2019 (COVID-19).

The timetable you submitted on September 22, 2020, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	Submitted
Trial Completion:	04/2022
Final Report Submission:	12/2022

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

We remind you of your postmarketing commitments:

3919-12 Release data for one registration batch of remdesivir drug substance manufactured at (b) (4) were submitted to the NDA. Two additional registration batches of remdesivir drug substance are to be manufactured at (b) (4) and the release data for each submitted under this PMC. The interim report should include release data for the second registration batch (displayed in a manner to facilitate comparison to previously submitted batch data). The final submission

report should include release data for the third registration batch. Both reports should be submitted as CBE-0 supplements.

The timetable you submitted on October 19, 2020, states that you will conduct this study according to the following schedule:

Interim Report Submission: 11/16/2020
Final Report Submission: 11/30/2020

3919-13 Release data for one registration batch of remdesivir drug substance manufactured at (b) (4) were submitted to the NDA. Two additional registration batches of remdesivir drug substance are to be manufactured at (b) (4) and the release data for both submitted under a separate PMC. Conduct stability studies on these three registration batches and submit three months of long-term and accelerated stability data for each batch in a CBE-0 supplement.

The timetable you submitted on October 19, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/31/2021

3919-14 Submit in a CBE-0 supplement release data for one batch of remdesivir for injection drug product manufactured at an approved manufacturing site to at least 1/10 production scale using drug substance from (b) (4)

The timetable you submitted on October 19, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/07/2021

3919-15 Release data for three batches of remdesivir drug substance manufactured at (b) (4) were submitted to the NDA. Conduct stability studies on these three registration batches and submit three months of long-term and accelerated stability data for each batch in a CBE-0 supplement.

The timetable you submitted on October 19, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/15/2021

3919-16 Submit in a CBE-0 supplement release data for one batch of remdesivir for injection manufactured at an approved manufacturing site to at least 1/10 production scale using drug substance from (b) (4)

The timetable you submitted on October 19, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 11/16/2020

3919-17 Submit in a CBE-0 supplement three months of long-term and accelerated stability data for three batches (#EW2019A1, # EW2020A1, # EW2021A1) of remdesivir for injection, 100 mg, manufactured on the (b) (4) line at the (b) (4) site.

The timetable you submitted on October 19, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/15/2021

3919-18 Submit in a CBE-0 supplement, three months of long term and accelerated stability data for two batches (# D20PV141 and D20PV142) of remdesivir for injection, manufactured on the (b) (4) line at the (b) (4) site.

The timetable you submitted on October 19, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/15/2021

3919-19 Submit in a CBE-0 supplement three months of long term and accelerated stability data for two batches (# AN7049B, # AN7050C) of remdesivir for injection, 100 mg, manufactured using the line (b) (4) at the (b) (4) site.

The timetable you submitted on October 19, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/15/2021

3919-20 Submit in a CBE-0 supplement six months of long term and accelerated stability data for three batches (EW2014A1, # EW2016A1, # EW2018A1) of remdesivir for injection, 100 mg, manufactured on the line (b) (4), at the (b) (4) site, to support the stoppers from (b) (4)

The timetable you submitted on October 19, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/15/2021

3919-21 Submit in a CBE-0 supplement three months of long-term and accelerated stability data for one batch of remdesivir for injection, 100 mg, manufactured on line (b) (4) at the (b) (4) site.

The timetable you submitted on October 19, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 04/15/2021

3919-22 The release data of two batches manufactured on lines (b) (4) (# 2041087.1, # 2041088.1), (b) (4) (# 2009106.1, # 2009107.1), and (b) (4) (201 131.1, 2010132.1) at (b) (4) was provided. Submit in a CBE-0 supplement three months of long-term and accelerated stability data of these batches of remdesivir for injection.

The timetable you submitted on October 19, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/15/2021

3919-23 Submit in a CBE-0 supplement three months of long-term and accelerated stability data for three batches (# 200553F, # 200613F and # 200653F) of remdesivir for injection manufactured at (b) (4).

The timetable you submitted on October 19, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/15/2021

3919-24 Submit in a CBE-0 supplement three months of long term and accelerated stability data for three process validation batches (# 00001, # 00003 and 00004) of remdesivir for injection manufactured on the (b) (4) line at the (b) (4) site.

The timetable you submitted on October 19, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/15/2021

3919-25 Submit in a CBE-0 supplement three months of long-term and accelerated stability data for one batch of remdesivir for injection, 100 mg, manufactured on the (b) (4) Line at the (b) (4) site.

The timetable you submitted on October 19, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 04/15/2021

3919-26 The stability batches of remdesivir injection, 150 mg were packaged with (b) (4) stopper. This rubber stopper is different than the rubber stopper proposed for commercial remdesivir injection, 100 mg (i.e. (b) (4) Submit as a CBE-0 supplement the six months of long-term and three months of accelerated stability data for three batches (#020953, #020954, #020955) to support the change in the stopper.

The timetable you submitted on October 19, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/15/2021

3919-27 Submit in a CBE-0 supplement the 6-month time point data for the pH stability studies of remdesivir injection, 5 mg/ml, at the 5°C condition to support the stability of remdesivir injection at the lower end (pH (b) (4)) of the proposed pH specification range.

The timetable you submitted on October 19, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/28/2021

3919-28 The 1-month leachable study data for three lots of each proposed commercial packaging configuration of remdesivir injection and remdesivir for injection was provided. The drug product representative batches should be tested for leachables through expiry. The data from these studies along with the final report should be submitted as a CBE-0 supplement. The interim reports should include the leachables study data for the 6-month, 12-month, and 24-month stability time points.

The timetable you submitted on October 19, 2020, states that you will conduct this study according to the following schedule:

Interim Report Submission: 03/31/2021, 09/30/2021
Final Report Submission: 09/30/2022

3919-29 Per the quality submission dated 09-22-2020, the leachable data for lot # EW1805A1 (at 23-month time point) of remdesivir for injection, can be available by end of December 2020. Submit as a CBE-0 supplement the leachables data.

The timetable you submitted on October 19, 2020, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/15/2021

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 147753 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 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.*[5]

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.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

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

REPORTING REQUIREMENTS

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

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biological products 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 Christine Kim, PharmD, RAC-US, Senior Regulatory Project Manager, at (301) 796-5964 or at the mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Director
Office of Infectious Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- 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/

JOHN J FARLEY
10/22/2020 01:37:51 PM