CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

208464Orig1s000

Trade Name: VEMLIDY

Generic Name: tenofovir alafenamide

Sponsor: Gilead Sciences, Inc.

Approval Date: November 10, 2016

Indications: VEMLIDY is indicated for the treatment of chronic hepatitis B virus infection in adults with compensated liver disease

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208464

NDA APPROVAL

Gilead Sciences, Inc.
Attention: Sara Snow, PharmD, MBA
Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Snow:

Please refer to your New Drug Application (NDA) dated and received January 11, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VEMLIDY® (tenofovir alafenamide) tablet, 25 mg.

This new drug application provides for the use of VEMLIDY® for treatment of hepatitis B infection in adults with compensated liver disease.

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 text.

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and patient package insert). 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*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed immediate container label that are identical to the enclosed immediate container label, as soon as they are available, but no more than 30 days after they are printed. Please submit this label electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may

submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Container Label for approved NDA 208464**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for VEMLIDY® was not referred to an FDA advisory committee because this drug is not the first in its class; tenofovir alafenamide was previously approved.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement in patients from birth to less than 2 years of age because necessary studies are impossible or highly impracticable. This is because the number of patients in this age group is too small.

We are deferring submission of your pediatric studies for ages 2 years to less than 18 years 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 studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. These required studies are listed below.

3130-1 Conduct the deferred pediatric study to assess the pharmacokinetics, safety/tolerability, and antiviral activity of tenofovir alafenamide in HBV infected subjects 12 to less than 18 years of age, followed by a rollover to a long-term, open-label, extension to assess longer-term pediatric safety and antiviral activity.

Final Protocol Submission:	March 2016 (submitted)
Study Completion:	June 2019
Final Report Submission:	December 2019

3130-2 Conduct the deferred pediatric study to access the pharmacokinetics, safety/tolerability, and antiviral activity of tenofovir alafenamide in HBV infected subjects 2 to less than 12 years of age, followed by a rollover to a long-term, open-label, extension to assess longer-term pediatric safety and antiviral activity.

Final Protocol Submission:	January 2018
Study Completion:	September 2021
Final Report Submission:	March 2022

Submit the protocol to your IND 115561 with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies 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 virologic failure due to potential tenofovir alafenamide (TAF) resistance pathways and potential antagonistic interference of TAF anti-HBV activity when used in combination with sofosbuvir.

Furthermore, the new pharmacovigilance system that FDA is required to establish 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:

Clinical Virology

3130-3 Perform genotypic (also phenotypic if qualified) resistance analysis of baseline virus samples from all HBeAg-positive nucleos(t)ide reverse transcriptase inhibitor-experienced subjects and of Week-48 virus samples from all evaluable subjects in Study GS-US-320-0110, regardless of their Week 96 virologic outcome. Genotyping should be conducted using Next Generation Sequence analysis.

The timetable you submitted on October 11, 2016, states that you will submit the final report according to the following schedule:

Final Report Submission: June 2017

3130-4 Conduct a cell-culture 2-drug combination study to evaluate the anti-HBV activity of tenofovir alafenamide (TAF) in combination with sofosbuvir.

The timetable you submitted on October 11, 2016, states that you will submit the final report according to the following schedule:

Final Report Submission: June 2017

3130-5 To evaluate potential tenofovir alafenamide (TAF) resistance pathways, sequence the baseline and Week 48 time-points (by population sequencing or NGS) for all evaluable subjects who had HBV DNA >69 IU/mL and provide a study report that includes resistance data analysis.

The timetable you submitted on October 11, 2016, states that you will submit the final report according to the following schedule:

Final Report Submission: June 2017

3130-6 To evaluate potential tenofovir alafenamide (TAF) resistance pathways and provide a study report that includes resistance data analysis for evaluable samples at baseline, Week 48 and Week 96 and submit the fastq files and analyses for subjects 4296-4510, 5613-1163, and 9035-5187, that had HBV DNA titers at the last PCR assessment that were >159 IU/mL, qualifying them for deep sequencing analysis.

The timetable you submitted on October 11, 2016, states that you will submit the final report according to the following schedule:

Final Report Submission: June 2017

3130-7 Provide a study report that includes resistance data analysis and submit the fastq files and analyses for subjects 8006-5282 and 8600-4558 who had HBV DNA titers at the last PCR assessment that were >159 IU/mL.

The timetable you submitted on October 11, 2016, states that you will submit the final report according to the following schedule:

Final Report Submission: June 2017

Submit all final reports 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 REQUIREMENT UNDER SECTION 506B

We remind you of your postmarketing commitments:

3130-8 Phenotype Week-48 virus samples from Subjects 4296-5147 and 8758-5188 in the tenofovir alafenamide (TAF) group and Subjects 1507-4546 and 9035-4845 in the tenofovir disoproxil fumarate (TDF) group in Study GS-US-320-0110.

The timetable you submitted on October 17, 2016, states that you will submit the final report according to the following schedule:

Final Report Submission: June 2017

3130-9 Submit the long-term efficacy, safety and antiviral activity data for Studies GS-US-320-0108 and GS-US-320-0110. Include data and analyses for the entire study population through Week 144.

The timetable you submitted on October 25, 2016, states that you will submit the final report according to the following schedule:

Final Protocol Submission:	May 2013 (submitted)
Study Completion:	September 2017
Final Report Submission:	March 2018

Submit 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. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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, call Myung-Joo Patricia Hong, Senior Regulatory Project Manager, at (301) 796-0807.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEFFREY S MURRAY
11/10/2016