CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

208341Orig1s000

Trade Name:	Epclusa Tablet, 400 mg/100 mg
Generic or Proper Name:	sofosbuvir and velpatasvir
Sponsor:	Gilead Sciences, Inc.
Approval Date:	June 28, 2016
Indication:	For the treatment of adult patients with chronic hepatitis C virus (HCV) genotypes 1, 2, 3, 4, 5, or 6 infection: • Without cirrhosis or with compensated cirrhosis; and • With decompensated cirrhosis for use in combination with ribavirin.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208341Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208341

NDA APPROVAL

Gilead Sciences, Inc.
Attention: Prachi Shah, MBS, RAC
Manger, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Shah:

Please refer to your New Drug Application (NDA) dated and received October 28, 2015, and your amendments submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EPCLUSA® (sofosbuvir and velpatasvir) tablet, 400 mg/100 mg.

This new drug application provides for the use of EPCLUSA® (sofosbuvir and velpatasvir) tablet for the treatment of adult patients with chronic hepatitis C virus (HCV) genotypes 1, 2, 3, 4, 5, or 6 infection:

- without cirrhosis or with compensated cirrhosis; and
- with decompensated cirrhosis for use in combination with ribavirin.

We also acknowledge receipt of the information related to the EPCLUSA® (sofosbuvir and velpatasvir) tablet, 400 mg/100 mg, for the Gilead Access Program that was reviewed as a part of this application.

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, text for the patient package insert, Medication Guide). 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.

IMMEDIATE CONTAINER LABELS

Submit final printed immediate container labels that are identical to the enclosed immediate container labels submitted on May 18, 2016 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels 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 Labels for approved NDA 208341**." 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.

MARKET PACKAGE

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

Linda C. Onaga, MPH
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6360
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 EPCLUSA was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected and outside expertise was not necessary as there were not significant issues that would benefit from an advisory committee discussion.

REQUIRED PEDATRIC 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 from birth to less than 3 years because necessary studies are impossible or highly impracticable. This is because spontaneous HCV clearance is possible and very few patients in this age group require treatment.

We are deferring submission of your pediatric studies for ages 3 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.

3092-1 Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of sofosbuvir and velpatasvir in pediatric subjects 12 through less than 18 years of age with chronic hepatitis C virus infection.

Final Protocol Submission:	06/2016
Study Completion:	03/2019
Final Report Submission:	09/2019

3092-2 Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of sofosbuvir and velpatasvir in pediatric subjects 3 through less than 12 years of age with chronic hepatitis C virus infection.

Final Protocol Submission:	06/2016
Study Completion:	10/2020
Final Report Submission:	04/2021

Submit the protocols to your IND 118605, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies 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 these studies. 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:

- assess a signal of a serious risk of increased toxicity, including rhabdomyolysis, as a result of a potential pharmacokinetic-based interaction between atorvastatin and the components of EPCLUSA (sofosbuvir and velpatasvir);
- identify unexpected serious risks in HCV/HIV-1 coinfected patients receiving EPCLUSA (sofosbuvir and velpatasvir) concurrently with HIV antiretroviral therapy,
- assess a known serious risk of toxicity due to elevated exposure to tenofovir levels in HCV/HIV-1 coinfected patients receiving EPCLUSA (sofosbuvir and velpatasvir) with a tenofovir-containing regimen;
- assess a known serious risk of virologic failure and persistence of treatment-emergent drug resistant viral populations in hepatitis C virus genotype 3 patients with cirrhosis that may limit future re-treatment options;
- identify serious adverse events including progression of liver disease, liver-related mortality, or liver failure requiring liver transplantation in patients with decompensated Child-Pugh Turcotte (CPT) C cirrhosis treated with EPCLUSA (sofosbuvir and velpatasvir).

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.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to:

- assess a signal of a serious risk of increased toxicity, including rhabdomyolysis, as a result of a potential pharmacokinetic-based interaction between atorvastatin and the components of EPCLUSA (sofosbuvir and velpatasvir);
- identify unexpected serious risks in HCV/HIV-1 coinfected patients receiving EPCLUSA (sofosbuvir and velpatasvir) concurrently with HIV antiretroviral therapy,
- assess a known serious risk of toxicity due to elevated exposure to tenofovir levels in HCV/HIV-1 coinfected patients receiving EPCLUSA (sofosbuvir and velpatasvir) with a tenofovir-containing regimen;
- assess a known serious risk of virologic failure and persistence of treatment-emergent drug resistant viral populations in hepatitis C virus genotype 3 patients with cirrhosis that may limit future re-treatment options;
- identify serious adverse events including progression of liver disease, liver-related mortality, or liver failure requiring liver transplantation in patients with decompensated Child-Pugh Turcotte (CPT) C cirrhosis treated with EPCLUSA (sofosbuvir and velpatasvir).

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

3092-3 Conduct a drug interaction trial to evaluate the interaction between sofosbuvir and velpatasvir and atorvastatin.

The timetable you submitted on June 7, 2016, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	08/2016
Trial Completion:	12/2016
Final Report Submission:	05/2017

3092-4 Submit the final clinical report and datasets for the ongoing trial GS-US-342-1202 (ASTRAL-5), titled "A Phase 3, Open-label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5816 Fixed Dose Combination for 12 weeks in Subjects with Chronic Hepatitis C Virus (HCV) and Human immunodeficiency Virus (HIV)-1 Coinfection," to provide safety data in HIV-1/HCV co-infected subjects receiving sofosbuvir and velpatasvir concurrently with HIV antiretroviral therapy.

The timetable you submitted on May 13, 2016, states that you will conduct this trial according to the following schedule:

Trial Completion:	08/2016
Final Report Submission:	12/2016

3092-5 Conduct a trial in hepatitis C virus genotype 3 infected subjects with cirrhosis treated with sofosbuvir and velpatasvir to determine if the addition of ribavirin improves the efficacy (i.e., sustained virologic response rate) and reduces the rate of virologic failure.

The timetable you submitted on May 13, 2016, states that you will conduct this trial according to the following schedule:

Trial Completion:	06/2017
Final Report Submission:	06/2018

3092-6 Collect, analyze, and submit data from the HCV infected subjects with decompensated Child-Pugh Turcotte (CPT) C cirrhosis treated with sofosbuvir/velpatasvir regimen to obtain safety data in a broader decompensated cirrhosis population (genotype 1-6 HCV infection).

The timetable you submitted on May 13, 2016, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	08/2016
Trial Completion:	05/2018
Final Report Submission:	05/2019

Submit the protocols to your IND 118605, with a cross-reference letter to this NDA. 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 REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3092-7 Collect, analyze, and submit data on subjects with cirrhosis including decompensated cirrhosis who achieve sustained virologic response following treatment with a sofosbuvir/velpatasvir-based regimen to evaluate durability of virologic response and to characterize clinical outcomes such as progression or regression of liver disease, liver-related mortality, occurrence of hepatocellular carcinoma, or liver failure requiring liver transplantation. Data collected should include 5 years of follow-up.

The timetable you submitted on May 13, 2016, states that you will conduct this trial according to the following schedule:

Study Completion:	01/2022
Final Report Submission:	01/2023

3092-8 Conduct site-directed mutant phenotypic analyses of sofosbuvir against an HCV genotype 3 replicon with the following substitutions: NS5B_L314F, NS5B_L314I, and NS5B_L314P.

The timetable you submitted on May 13, 2016, states that you will conduct this trial according to the following schedule:

Final Report Submission: 02/2017

Submit clinical protocols to your IND 118605 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. 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).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details
at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics 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.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

FDA BENEFIT-RISK FRAMEWORK APPLICANT INTERVIEW

FDA has also contracted with Eastern Research Group, Inc. (ERG) to conduct an assessment of FDA's initial phase implementation of the Benefit-Risk Framework (BRF) in human drug review. A key element of this evaluation includes interviews with applicants following FDA approval of New Molecular Entity (NME) New Drug Applications (NDAs) and original Biologic License Applications (BLAs). The purpose of the interview is to assess the extent to which the BRF provides applicants with a clear understanding of the reasoning behind FDA's regulatory decisions for NME NDAs and original BLAs.

ERG will contact you to schedule a BRF applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final reports. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to this evaluation.

If you have any questions, call Linda C. Onaga, MPH, Regulatory Project Manager, at (301) 796-0759 or the Division mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Deputy Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure(s):
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/

JOHN J FARLEY
06/28/2016