CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

205834Orig1s000

Trade Name: **Harvoni**

Generic Name: **ledipasvir and sofosbuvir**

Sponsor: **Gilead Sciences, Inc.**

Approval Date: **October 10, 2014**

Indication: **for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults**

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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 205834

NDA APPROVAL

Gilead Sciences, Inc.
Attention: Michele Anderson
Associate Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Anderson:

Please refer to your New Drug Application (NDA) dated February 7, 2014, received February 10, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Harvoni™ (ledipasvir and sofosbuvir) tablets, 90 mg/400mg.

We acknowledge receipt of your amendments dated:

February 27, 2014 (2)	May 21, 2014	July 16, 2014
February 28, 2014	May 27, 2014	July 29, 2014
March 4, 2014	June 5, 2014	August 4, 2014
March 11, 2014	June 18, 2014	August 7, 2014
March 13, 2014	June 19, 2014	August 11, 2014
March 25, 2014	June 26, 2014	August 14, 2014
March 28, 2014	June 30, 2014	July 19, 2014
April 25, 2014	July 1, 2014	September 3, 2014
May 1, 2014	July 3, 2014	September 17, 2014 (2)
May 2, 2014	July 7, 2014	September 18, 2014
May 5, 2014	July 8, 2014	September 24, 2014
May 20, 2014	July 14, 2014	

We also acknowledge receipt of the information related to the Harvoni™ (ledipasvir and sofosbuvir) tablets, 90 mg/400 mg, for the Gilead Access Program that was reviewed as a part of this application.

This new drug application provides for the use of Harvoni™ (ledipasvir and sofosbuvir) tablets for the treatment of chronic hepatitis C, genotype 1 infection.

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 text for the 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 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 205834**." 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: 6321
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 Harvoni™ (ledipasvir and sofosbuvir) tablets was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected and because outside expertise was not necessary as there were no significant issues identified that would benefit from an advisory committee discussion.

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

We are deferring submission of your pediatric studies for ages 3 to 17 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)(B) of the FDCA. These required studies are listed below.

2780-1 Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of ledipasvir/sofosbuvir in pediatric subjects 3 to 17 years of age with chronic hepatitis C.

Final Protocol Submission:	07/14/2014
Trial Completion:	06/30/2018
Final Report Submission:	02/28/2019

2780-2 Collect and analyze long-term safety data for subjects enrolled in the pediatric ledipasvir/sofosbuvir safety, pharmacokinetic and efficacy study. Data collected should include at least 3 years of follow-up in order to characterize the long-term safety of ledipasvir/sofosbuvir including growth assessment, sexual maturation and characterization of ledipasvir/sofosbuvir resistance associated substitutions in viral isolates from subjects failing therapy.

Final Protocol Submission:	05/15/2014
Trial Completion:	02/28/2023
Final Report Submission:	08/31/2023

Submit the protocol(s) to your IND 115268, 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 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 identify the unexpected serious risks of carcinogenicity and treatment-emergent viral substitutions with Harvoni™ (ledipasvir and sofosbuvir) treatment durations up to 24 weeks. Initially, the proposed duration of dosing for Harvoni™ (ledipasvir and sofosbuvir) for hepatitis C genotype 1 treatment ranged 8 to 12 weeks. During the review of the Harvoni™ (ledipasvir and sofosbuvir) application, FDA determined that longer durations of therapy resulted in higher efficacy for certain populations. These durations dictate the need for carcinogenicity studies in accordance with 21 CFR 314.50 (d)(2) and the ICH M3 (R2) and S1A guidances. In addition, we are aware of viral variants with treatment-emergent substitutions in subjects who relapsed during Harvoni™ (ledipasvir and sofosbuvir) clinical trials. The impact on the serious risk of resistance and persistence of some of these substitutions is not completely understood.

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:

2780-3 Submit the ledipasvir 2 year rat carcinogenicity study

The timetable you submitted on August 19, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/31/2015

2780-4 Submit the ledipasvir 26-week carcinogenicity study in rasH2 mice

The timetable you submitted on August 19, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/31/2015

2780-5 Submit an analysis of longitudinal data on persistence of NS5A resistance substitutions from subjects who did not achieve SVR12 in Phase 2 studies of LDV with other DAAs.

The timetable you submitted on August 19, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 06/21/2012
Final Report Submission: 03/31/2015

2780-6 Conduct a study to assess the impact of NS5B substitutions A112T, E127G, and S473T on the phenotypic susceptibility of sofosbuvir in the GT1a HCV replicon system.

The timetable you submitted on August 19, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/31/2015

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess signals for unexpected serious risks in and provide dosing recommendations for patients with advanced liver disease and/or in patients receiving concomitant immunosuppressive agents post-liver transplantation. Compared with subjects enrolled in the phase 3 Harvoni™ (ledipasvir and sofosbuvir) registrational trials, the decompensated liver disease/post-liver transplantation population is overall a sicker population with known associated comorbidities and thus there is a potential risk for serious toxicities in this population. In addition, only a clinical trial will be sufficient to assess the potential risk of elevated exposure to sofosbuvir in the setting of Harvoni™ (ledipasvir and sofosbuvir) and cyclosporine coadministration. Finally, only a clinical trial will be sufficient to assess a known serious risk of elevated exposure to tenofovir levels in chronic hepatitis C and HIV-1 co-infected patients receiving concomitant Harvoni™ (ledipasvir and sofosbuvir) and Atripla (efavirenz, emtricitabine, tenofovir disoproxil fumarate, or its components) and to provide dosing recommendations for this population.

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

2780-7 Submit the final report and datasets for the ongoing trial GS-US-337-0123, entitled “A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and

Efficacy of Sofosbuvir/Ledipasvir Fixed-Dose Combination + Ribavirin Administered in Subjects Infected with Chronic HCV who have Advanced Liver Disease or are Post-Liver Transplant", in order to provide safety data and dosing recommendations for subjects with decompensated cirrhosis and/or in subjects receiving concomitant immunosuppressive agents post-liver transplant (e.g. cyclosporine).

The timetable you submitted on August 19, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	08/07/2013
Trial Completion:	03/31/2015
Final Report Submission:	09/30/2015

2780-8 Submit the final report and datasets for the ongoing trial GS-US-337-0115, entitled "A Phase 3, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Ledipasvir Fixed-Dose Combination for 12 Weeks in Subjects with Chronic Genotype 1 or 4 Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV)-1 Co Infections" in order to obtain additional safety data in subjects receiving concomitant ledipasvir/sofosbuvir and Atripla (or its components) and to provide dosing recommendations for co-infected subjects.

The timetable you submitted on August 19, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	12/02/2013
Trial Completion:	03/15/2016
Final Report Submission:	09/16/2016

Submit the protocol(s) to your IND 115268, with a cross-reference letter to this NDA. Submit 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:

2780-9 Submit an interim report from the ongoing trial GS-US-248-0122, entitled, "A Long Term Follow-up Registry for Subjects Who Achieve a Sustained Virologic Response to Treatment in Gilead-Sponsored Trials in Subjects with Chronic Hepatitis C Infection", with the three year follow-up data from: GS-US-337-0102 (ION-1), GS-US-337-0109 (ION-2), GS-US-337-0108 (ION-3).

The timetable you submitted on September 24, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	06/21/2012
Trial Completion:	07/31/2017
Final Report Submission:	07/31/2018

Submit clinical protocols to your IND 115268 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 to:

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

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.

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

Sincerely,

{See appended electronic signature page}

Edward Cox, MD, M.P.H.
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and 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 on behalf of EDWARD M COX
10/10/2014
Acting on behalf of Edward Cox