CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209195Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 209195

Product Name: VOSEVI; sofosbuvir (SOF), velpatasvir (VEL) and voxilaprevir (VOX) fixed dose combination (FDC) tablet

PMR Description: Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of VOSEVI in pediatric subjects 12 through less than 18 years of age with chronic hepatitis C virus (HCV) infection GT 1- 6 infection and who are DAA-experienced.

PMR Schedule Milestones:		
	Final Protocol Submission:	March 2018
	Study/Trial Completion:	January 2021
	Final Report Submission:	July 2021

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☒ Unmet need
   ☐ Life-threatening condition
   ☐ Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☒ Other

   Adult trials are completed and ready for approval. The Applicant has requested a deferral of pediatric studies of children 12-17 years of age until data from Phase 3 studies and the preliminary pharmacokinetic (PK) data from the lead-in portion of the SOF/VEL adolescent Study GS-US-342-1143 are available and have been reviewed by the Agency. The Division is in agreement with this proposal.
   The review team met with the Pediatric Review Committee (PeRC) on April 19, 2017. The deferral request was presented to the PeRC, and the PeRC agreed with the Applicant's proposal and the Division's recommendations.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Reference ID: 4118831

(b) (4)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   Which regulation?

   ☐ Accelerated Approval (subpart H/E)
   ☐ Animal Efficacy Rule
   ☒ Pediatric Research Equity Act
   ☐ FDAAA required safety study/clinical trial

   If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

   ☐ Assess a known serious risk related to the use of the drug?
   ☐ Assess signals of serious risk related to the use of the drug?
   ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

   ☐ Analysis of spontaneous postmarketing adverse events?
   Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

   ☐ Analysis using pharmacovigilance system?
   Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

   ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
   Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

   ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Reference ID: 4118831

A clinical trial is required to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of VOSEVI in pediatric subjects 12 through less than 18 years of age with chronic HCV infection and who are DAA-experienced. (b) (4)

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☒ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☒ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

_____

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

_____

- ☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Reference ID: 4118831

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

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PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference ID: 4118831

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 209195

Product Name: VOSEVI; sofosbuvir, velpatasvir and voxilaprevir fixed dose combination tablet

PMR/PMC Description: Determine the phenotype of NS5A H54R against velpatasvir in the GT4d replicon and report fold shifts in the EC_{50} value.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	N/A
	Study/Trial Completion:	N/A
	Final Report Submission:	01/15/2018

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☒ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

   Additional treatment-emergent substitutions were identified from virologic failures in the sponsor's clinical studies. The sponsor will need to phenotypically characterize these.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Reference ID: 4118831

The impact of these substitutions on the antiviral activity of velpatasvir needs to be evaluated to understand the possible impact on efficacy.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

Which regulation?

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct site-directed mutant phenotypic analyses of NS5A H54R against velpatasvir in the GT4d replicon and report fold shifts in the EC_{50} value.

Reference ID: 4118831

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☒ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
The impact of these substitutions on the antiviral activity of velpatasvir needs to be evaluated to understand the possible impact on efficacy.

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

Reference ID: 4118831

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

Reference ID: 4118831

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/s/

ANDREW A GENTLES
06/30/2017

POONAM MISHRA
07/03/2017

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 31, 2017
To:	Debra Birnkrant, MD Director **Division of Antiviral Products (DAVP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Wendy Lubarsky, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	VOSEVI (sofosbuvir, velpatasvir, voxilaprevir)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 209195
Applicant:	Gilead Sciences, Inc.

1 INTRODUCTION

On December 8, 2016, Gilead Sciences, Inc. submitted for the Agency's review an original New Drug Application (NDA) 209195 for VOSEVI (sofosbuvir, velpatasvir, voxilaprevir) tablets, a New Molecular Entity (NME). This submission proposes an indication for the treatment of adult patients with chronic hepatitis C virus (HCV).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antiviral Products (DAVP) on December 29, 2016, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for VOSEVI (sofosbuvir, velpatasvir, voxilaprevir) tablets.

2 MATERIAL REVIEWED

- Draft VOSEVI (sofosbuvir, velpatasvir, voxilaprevir) tablets PPI received on December 8, 2016, and received by DMPP and OPDP on May 16, 2017.
- Draft VOSEVI (sofosbuvir, velpatasvir, voxilaprevir) tablets Prescribing Information (PI) received on December 8, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 16, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
05/31/2017

WENDY R LUBARSKY
06/01/2017

SHARON R MILLS
06/01/2017

LASHAWN M GRIFFITHS
06/01/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: **May 31, 2017**

To: **Andrew Gentles**
Regulatory Project Manager
Division of Antiviral Products

From: **Wendy Lubarsky, PharmD**
Regulatory Review Officer
Office of Prescription Drug Promotion

Subject: **NDA 209195 – VOSEVI (sofosbuvir, velpatasvir, and voxilaprevir) tablets, for oral use**

As requested in the Division of Antiviral Products' (DAVP) consult dated December 29, 2016, the Office of Prescription Drug Promotion (OPDP) has reviewed the VOSEVI (sofosbuvir, velpatasvir, and voxilaprevir) tablets, for oral use prescribing information, patient labeling, and carton/container labeling.

OPDP reviewed the proposed substantially complete version of the prescribing information and patient labeling sent via email by Andrew Gentles and downloaded from link on May 16, 2017. OPDP reviewed the substantially complete version of the carton/container labeling sent via email by Andrew Gentles on May 18, 2017.

OPDP has reviewed the substantially complete prescribing information and carton/container labeling in the attached documents below. We have included one comment in the CLINICAL STUDIES section of the prescribing information.

The Division of Medical Policy Programs and OPDP provided a single, consolidated review of the patient labeling under a separate cover on May 31, 2017.

Thank you for your consult. OPDP appreciates the opportunity to provide comments. If you have any questions, please contact Wendy Lubarsky at (240) 402-7721 or wendy.lubarsky@fda.hhs.gov.

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/s/

WENDY R LUBARSKY
05/31/2017

Clinical Inspection Summary

Date	May 15, 2017
From	Antoine El Hage, Ph.D. Susan Thompson, M.D./ Team Leader Kassa Ayalew, M.D., MPH. /Branch Chief Division of Clinical Compliance Evaluation
To	Andrew Gentles, Pharm.D, Regulatory Health Project Manager Kirk Chan-Tack, M.D., Medical Reviewer Kimberly Struble, PharmD., Team Leader Division of Antiviral Products (DAVP)
NDA #	NDA 209195
Applicant	Gilead Sciences, Inc.
Drug	Sofosbuvir, Velpatasvir, and Voxilapravir (SOF/VEL/VOX) Fixed dose tablets
NME (Yes/No)	No
Therapeutic Classification	Priority
Proposed Indication(s)	Treatment of adult subjects with chronic hepatitis C virus infection
Consultation Request Date	January 1, 2017
Summary Goal Date	July 10 , 2017
Action Goal Date	August 8, 2017
PDUFA Date	August 10 , 2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspections for this NDA were conducted at three domestic clinical sites and one foreign site. The inspection of the four clinical investigators listed below revealed no regulatory violations. Based on the inspections of the four clinical sites, the inspectional findings support validity and acceptability of the data as reported by the sponsor under this pending NDA.

The preliminary classification for Drs. Lawitz, Myron, Ramji, and Ruane is No Action Indicated (NAI). No regulatory violations were noted. Data from these sites are acceptable for use in support of the pending application.

The final classification for the above four sites will be made at a later date after receiving and reviewing the EIRs provided by the field investigators. An inspection summary addendum will be generated if conclusions change upon receipt and review of the pending EIRs.

II. BACKGROUND

Velpatasvir (VEL-GS-5816) is a novel HCV NS5A inhibitor that has demonstrated a potent anti-HCV activity against all genotypes. More than 1000 HCV infected subjects have been dosed with GS-5816 in ongoing Phase 2 clinical studies which demonstrated that co-administration of Sofosbuvir (SOF) 400 mg with GS-5816 100 mg for 12 weeks is well tolerated and results in high SVR across a broad range of HCV genotypes.
Voxilapravir (VOX; GS-9857 is a novel macrocyclic HCV NS3/4A protease inhibitor (PI) with potent *in vitro* antiviral activity against genotype 1or 6 HCV, broad coverage of NS3/4A protease polymorphs, and an improved resistance profile compared with previously developed PIs. The applicant has co-formulated SOF 400 mg, VEL 100 mg, and VOX GS-9857 100 mg into a single agent administered together as an oral tablet. The use of a fixed-dose combination may have a major impact on the global prevalence and burden of HCV, as it may represent a simple, well-tolerated, highly efficacious pan-genotype treatment for ALL HCV infected subjects.

The Applicant-sponsored two studies submitted in support of the application:
Study Protocols GS-US-367-1170 for HCV treatment with or without cirrhosis of all genotypes and GS-US-367-1171 for treatment of HCV-infected subjects compared to placebo in NS5A inhibitor-experienced subjects with chronic HCV infection.

Inspections were requested for the above studies for HCV treatment of treatment experienced subjects with or without cirrhosis. Each study protocol is outlined below:

Protocol GS-US-367-1170:

A Phase 3, Global, Multicenter, Randomized, Open-Label, Placebo-Controlled Study to Investigate the Safety and Efficacy of Sofosbuvir/Velpatasvir-9857 Fixed-Dose Combination for 12 Weeks and Sofosbuvir/Velpatasvir for 12 Weeks in Direct Acting Antiviral-Experienced Subjects With Chronic Hepatitis C (HCV) Who Have Not Received an NS5A Inhibitor" (POLARIS-4).

Subjects: 380 subjects enrolled
Sites: 120 centers in the U.S., Canada and Europe

The primary objectives of this study were to: 1) determine the efficacy of treatment with SOF/VEL/GS-9857 VOX fixed dose combination (FDC) for 12 weeks and of SOF/VEL/ FDC for 12 weeks as measured by the proportion of subjects with sustained viral response (SVR) 12 weeks after cessation of treatment, and 2) to evaluate the safety and tolerability of each treatment regimen.

This protocol was an international, randomized, multicenter, open label study that evaluated the safety and efficacy of sofosbuvir/VEL/GS-9857 (VOX) for 12 weeks and SOV/VEL for 12 weeks in direct acting antiviral-experienced subjects with chronic HCV infection with or without cirrhosis who have not received prior treatment with a regimen containing an inhibitor of the HCV NS5A protein. 380 non-NS5A inhibitor DAA-experienced subjects with chronic HCV infection with or without cirrhosis were enrolled. Subjects whose sole DAA exposure was a NS53/4 protease inhibitor were excluded. A target of at least 30% of subjects with genotype 1, 2, or 3 who had cirrhosis were randomized; subjects with documented chronic genotype 1, 2, 4, 5, or 6 HCV infections were randomized to either treatment group:

- Group 1 (N=205): SOF/VEL/GS9857 FDC tablet (SOF 400 mg/ 100 mg/100mg) once daily with food for 12 weeks
- Group 2: (N=175) SOF/VEL FDC tablet (400 mg/100mg) once daily without regard to food for 12 weeks

Subjects were randomized by genotypes and the presence or absence of cirrhosis at screening. Subjects with any liver disease of non-HCV etiology or with human immunodeficiency virus (HIV) or hepatitis B co-infection, malignancy, or transplantation were excluded.

According to the sponsor, no significant drug related safety concerns were identified.

Protocol GS-US-367-1171:

A Phase 3, Global Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Safety and Efficacy of Sofosbuvir/Velpatasvir-9857 Fixed-Dose Combination for 12 Weeks and Sofosbuvir/Velpatasvir for 12 Weeks in Direct Acting Antiviral-Experienced Subjects with Chronic Hepatitis C (HCV) Infection" (POLARIS-1).

Subjects: 550 subjects enrolled
Sites: 100 Centers in the U.S., Canada, Australia, and Europe

The primary objectives of this study were to: 1) evaluate the efficacy of treatment with sofosbuvir (SOF)/velpatasvir (VEL, GS-5816) fixed dose combination (FDC) for 12 weeks in direct-acting antiviral (DAA)-experienced subjects with chronic hepatitis C virus infection as measured by the proportion of subjects with SVR 12 weeks after cessation of treatment (SVR12), and 2) evaluate the safety and tolerability of treatment with SOF/VEL/GS-9857.

This protocol was an international, randomized, multicenter, double-blind, placebo-controlled phase 3 study to evaluate the safety and efficacy of SOF/VEL/GS-9857 FDC for 12 weeks in direct acting antiviral-experienced subjects with chronic HCV infection with or without cirrhosis. A total of 550 DAA-experienced subjects with chronic HCV infection with cirrhosis or without cirrhosis were enrolled.

Subjects with genotype 1, and prior treatments were included either an NS5A inhibitor or > than 2 DAAs of different classes. Subjects were randomized to either treatment group:

- Group 1: (N=450): SOF/VEL/GS9857 (400 mg/100 mg/100mg) once daily with food for 12 weeks
- Group 2: (N=100): SOF/VEL/GS-9857 placebo once daily with food for 12 weeks

Randomization was stratified by the presence or absence of cirrhosis at screening and prior treatment experience. Approximately 20% of the subjects were treatment experienced and approximately 20% of subjects had cirrhosis. Subjects with any liver disease of non-HCV etiology or with human immunodeficiency virus (HIV) or hepatitis B co-infection were excluded.

The CDER review division and OSI performed the site selections for inspection. The sites were selected principally due to relatively high patient accrual in the study and a prior history of inspection and protocol violations. The clinical site inspections were intended to help verify the data integrity.

Site Selection for Study Protocols GS-US 367-1170 and 1171

Site #2760 in Texas (Dr. Lawitz) and Site #1171 in California (Dr. Ruane) had relatively large numbers of subjects, and each had a prior history of a single inspection with VAI results. Also Site #381 in California (Dr. Tong) had a relatively large number of subjects and one prior history of inspection classified VAI. The foreign site enrolled a relatively large number of subjects and had no history of previous inspection in our FDA database.

III. RESULTS (by site):

Name of CI, Site #, Address, Country if non-U.S. or City, State if U.S.	Protocol # and # of Subjects	Inspection Date	Final Classification
Eric Lawitz, M.D. 607 Camden Street San Antonio, TX 78215 Site #2760	Polaris-4-GS-US367-1170 Enrolled =9 subjects	2/28-3/3/2017	Pending (preliminary classification NAI)
Myron Tong, M.D. 660 South Fair Oaks Avenue Pasadena, CA 91105 Site #381	Polaris-4-GS-US367-1170 Enrolled =9 subjects	3/1-6/2017	Pending (preliminary classification (NAI)

Alnoor Ramji, M.D. 1190 Homby Street, Suite 770 Vancouver, British Columbia V6z2k5, Canada Site #4001	Polaris-1-GS-US367-1171 Enrolled =15 subjects	4/3-7/2017	Pending (preliminary classification NAI)
Peter Ruane, M.D. 5901 W. Olympic Blvd., Suite 401 Los Angeles, CA 90036 Site# 407	Polaris-1-GS-US367-1171 Enrolled =14 subjects	2/21-28/2017	Pending (preliminary classification NAI)

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data are unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

NOTE: Site inspections focused on 100% review of informed consent documents, IRB, ethics committee correspondence, financial disclosures, training records, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, vital signs, subject source documents, including medical history records, drug accountability, and the use of concomitant medications. Source documents were compared to data listing for primary efficacy endpoints and adverse events reporting.

1. **Eric Lawitz, M.D./Site #2760 / Study Protocol GS-US-372-1170**
   San Antonio, TX 78215

   There were 10 subjects screened, one subject was reported as a screen failure, nine subjects were enrolled in the study, and nine subjects completed the study.

   The medical records for all subjects were reviewed for informed consent and primary efficacy endpoints. Records were organized and legible. Medical records/source documents were compared to case report forms and data listings for primary efficacy endpoints and adverse event reporting.

   The audit revealed adequate adherence to the regulations and investigational plan. There were no objectionable conditions noted, and no Form FDA 483 was issued to Dr. Lawitz.

   The data generated by this site appear acceptable.

2. **Myron Tong, M.D./ Site #381/Study Protocol GS-US-367-1170**
   Pasadena, CA 91105

   There were 9 subjects screened, nine subjects enrolled in the study, and all nine subjects completed the study. The medical records for all subjects were reviewed. Record*s* were organized and legible. Medical records/source documents were compared to data listings for primary efficacy endpoint and adverse events reporting.

   The audit revealed adequate adherence to the regulations and investigational plan. No discrepancies were found. There were no objectionable conditions noted, and no Form FDA 483 was issued to Dr.Tong.

   Overall, the data generated at Dr. Tong's site appear acceptable in support of clinical efficacy and safety is considered reliable and may be used in support of the pending application.

3. **Alnoor Ramji, M.D./ Site #4001/Study protocol GS-US-367-1171**
   Vancouver, BC, Canada

   There were 16 subjects screened, one subject was reported as a screen failure, and 15 subjects were enrolled. There was one subject reported as lost to-follow-up. All 15 subjects completed the study. The medical records for all subjects were reviewed.

   The medical records/source documents were compared to case report form and data listings for primary efficacy endpoint and adverse event reporting. No deficiencies were noted. The inspection revealed adequate adherence to the regulations and investigational plan. There were no objectionable conditions noted, and no Form FDA-483 Inspectional Observations was issued. The field investigator reported that the medical records were organized and legible.

   The data generated by this site appear acceptable. The inspection did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

4. **Peter Ruane, M.D./ Site #407/Study Protocol GS-US-367-1171**
   Los Angeles, CA 90036

   There were 16 subjects screened, two subjects were reported as screen failures, and 14 subjects were enrolled. The ORA investigator reported that four subjects deferred treatment, one subject discontinued due to lack of efficacy, and one subject transferred to another state. The remaining eight subjects completed the study. The medical records for all subjects were reviewed.

The medical records/source documents were compared to case report form and data listings for primary efficacy endpoint and adverse event reporting. No deficiencies were noted. The inspection revealed adequate adherence to the regulations and investigational plan. There were no objectionable conditions noted, and no Form FDA-483 Inspectional Observations was issued. The field investigator reported that the medical records were organized and legible.

The data generated by this site appear acceptable.

{See appended electronic signature page}

Antoine El Hage, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Enforcement
Office of Scientific Investigations

{See appended electronic signature page}

Kassa Ayalew, M.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Enforcement
Office of Scientific Investigations

cc:
Central Doc. Rm. NDA 209195
DAVP /Division Director/Debra Birnkrant
DAVP /Medical Team Leader/Kimberly Struble
DAVP /Project Manager/Andrew Gentles
DAVP/Medical Officer/Kirk Chun-Tack
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/ Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Susan Thompson
OSI/DCCE/GCPAB/ Reviewer/ Antoine El Hage
OSI/ GCP Program Analysts/ Yolanda Patague/ Joseph Peacock
OSI/Database PM/Dana Walters

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

/s/

ANTOINE N EL HAGE
05/16/2017

SUSAN D THOMPSON
05/16/2017

KASSA AYALEW
05/16/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 13, 2017
Requesting Office or Division:	Division of Antiviral Products
Application Type and Number:	NDA 209195
Product Name and Strength:	Vosevi (sofosbuvir, velpatasvir, and voxilaprevir) Tablet, 400 mg/100 mg/100 mg
Product Type:	Multi-ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Gilead Sciences, Inc.
Submission Date:	December 8, 2016
OSE RCM #:	2016-2984
DMEPA Primary Reviewer:	Valerie Wilson, PharmD
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

Reference ID: 4069021

1 REASON FOR REVIEW

Gilead submitted NDA 209195 for a fixed-dose combination tablet of sofosbuvir, velpatasvir, and voxilaprevir. We reviewed the proposed label and labeling for areas of concern that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Vosevi (sofosbuvir, velpatasvir, and voxilaprevir) tablet is proposed for use in adult patients for the treatment of chronic hepatitis C virus (HCV) infection. The tablets will be supplied in bottles of 28 tablets to support a once-daily dosing regimen for 12 weeks.

Our assessment of the proposed Dosage and Administration, Dosage Forms and Strengths, How Supplied/Storage and Handling, Patient Counseling, and Patient Information sections of the full prescribing information (FPI) and the container label identified deficiencies that may lead to medication errors and other areas for improvement.

Prescribing Information

The proposed proprietary name, Vosevi, was found acceptable in a previous review[1] performed by DMEPA; therefore, the FPI should be updated to incorporate "Vosevi" in place of the placeholder "[Tradename]" throughout.

[1] Wilson, V. Proprietary Name Review for Vosevi (NDA 209195). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 FEB 28. 22p. OSE RCM No.: 2016-12029788.

Reference ID: 4069021

Container Label

Our assessment of the container label revealed the following discrepancies and deficiencies:

1. The established name for this multi-ingredient tablet is listed in a manner that is inconsistent with the Agency's recommended presentation of established names for antivirals. The Applicant correctly lists the active ingredients in alphabetical order, "(sofosbuvir, velpatasvir, voxilaprevir)," but does not include "and" between velpatasvir and voxilaprevir. The established name on the container label should be revised to read (sofosbuvir, velpatasvir, and voxilaprevir).
2. An area for the expiration date has not been designated on the container label. To prevent medication errors relating to administration of expired medication the expiration date is required on the immediate container label per 21 CFR 201.17. Additionally, we note an area for the lot number has not been designated but is required to appear on the immediate container label per 21 CFR 201.10(i)(1).
3. The proposed proprietary name, Vosevi, was found acceptable in a previous review[1] performed by DMEPA; therefore, the container label should be revised to incorporate "Vosevi" in place of the placeholder "Tradename."

4 CONCLUSION & RECOMMENDATIONS

Our review of the Full Prescribing Information and container label determined the FPI and container label requires revision. We provide our recommendations to the Division in section 4.1 and recommendations in letter-ready format to the Applicant in section 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

1. The proposed proprietary name, Vosevi, was found conditionally acceptable; therefore, the FPI should be updated to incorporate "Vosevi" in place of the placeholder "[Tradename]".

4.2 RECOMMENDATIONS FOR GILEAD SCIENCES, INC.

We have completed a review of the proposed container label for NDA 209195 and have identified the following concerns to be addressed prior to the approval of this NDA:

1. Revise the established name on the container label, "(sofosbuvir, velpatasvir, voxilaprevir)," to read "(sofosbuvir, velpatasvir, and voxilaprevir)" to be consistent with the Agency's recommended presentation of established names for multi-ingredient antivirals.

2. Add the lot number and expiration date on the immediate container label per 21 CFR 201.10(i)(1) and 21 CFR 201.17, respectively. Ensure that the lot number is clearly differentiated from the expiration date to reduce the risk of medication errors resulting from administration of expired medication.

Reference ID: 4069021

3. Replace “Tradename” with the proprietary name, Vosevi, found conditionally acceptable per Agency letter dated March 1, 2017.

APPEARS THIS WAY ON ORIGINAL

Reference ID: 4069021

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vosevi that Gilead Sciences, Inc. submitted on December 8, 2016.

Table 2. Relevant Product Information for Vosevi	
Initial Approval Date	N/A
Active Ingredient	Sofosbuvir, velpatasvir and voxilaprevir
Indication	indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) infection
Route of Administration	Oral
Dosage Form	Tablet
Strength	400 mg/100 mg/100 mg
Dose and Frequency	One tablet once daily with food
How Supplied	Bottles of 28
Storage	Store below 30 °C (86 ºF). Dispense only in original container.
Container Closure	Child-resistant closure

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 4069021

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/s/

VALERIE S WILSON
03/13/2017

BRENDA V BORDERS-HEMPHILL
03/14/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 209195	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Under Review Established/Proper Name: sofosbuvir, velpatasvir, and voxilaprevir Dosage Form: tablet Strengths: 400mg/100mg/100mg Route(s) of Administration: Oral		
Applicant: Gilead Sciences, Inc Agent for Applicant (if applicable):		
Date of Application: 12/8 /16 Date of Receipt: 12/8/16 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: 8/8/17	Action Goal Date (if different):	
Filing Date: 2/6/17	Date of Filing Meeting: 1/17/17	
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Treatment of genotype 1, 2, 3, 4, 5, and 6 chronic hepatitis C infection		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	

Reference ID: 4049117

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☐ Fast Track Designation ☒ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 106739, 115268, 118605, 125751, 115670, 119926	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.***	☒	☐		

Reference ID: 4049117

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov)*: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☐	☒		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		

Reference ID: 4049117

• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [**see 21 CFR 314.54(b)(1)].**	☐	☐		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [**see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☐		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

• If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement **[see 21 CFR 314.50(i)(1)(i)(C) and 314.54]**? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If no,** include template language in the 74-day letter. ***Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]*** ***Note: Pharmaceutical equivalents*** *are drug products in identical dosage forms and route(s) of administration that:* ***(1)*** *contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period;* ***(2)*** *do not necessarily contain the same inactive ingredients;* ***and*** ***(3)*** *meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.*	☐	☐		

Reference ID: 4049117

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: 5 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

Reference ID: 4049117

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	

[1] http://www fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

Reference ID: 4049117

Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	

Reference ID: 4049117

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		PeRC scheduled 5.3.17
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required***[3]	☐	☒		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

Reference ID: 4049117

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	Sponsor submitted proprietary name Vosevi
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☐	☒	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☐	☐ ☒	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm

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Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 09/30/2015	☐	☐		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 06/02/2016	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐			Not needed for voxilaprevir

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ATTACHMENT

MEMO OF FILING MEETING

DATE: 1/17/2017

BACKGROUND: Gilead Sciences, Inc., submitted an NDA on December 8, 2016 for the treatment of chronic hepatitis C virus (HCV) , genotype 1, 2, 3, 4, 5, and 6, virus infection in adults without cirrhosis or with compensated cirrhosis (b) (4) (b) (4). This application is an NME NDA consisting of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) as a fixed dose combination tablet with a dosage strength of 400mg/100mg/100mg. SOF/VEL/VOX combines sofosbuvir (SOF), a nucleotide NS5B polymerase inhibitor, velpatasvir (VEL), a NS5A inhibitor, and voxilaprevir, a macrocyclic NS3/4A protease inhibitor.

SOF/VEL/VOX was granted Fast Track designation on June 12, 2015 and Breakthrough Therapy (BT) designation on February 19, 2016 for the treatment of chronic HCV genotype 1 infection in patients who have previously failed an NS5A inhibitor containing DAA regimen.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Andrew Gentles	Y
	CPMS/TL:	Karen Winestock	Y
Cross-Discipline Team Leader (CDTL)	Kim Struble		Y
Division Director/Deputy	Debra Birnkrant Jeff Murray		Y
Office Director/Deputy	John Farley		Y
Clinical	Reviewer:	Kirk Chan-Tack	Y
	TL:	Kim Struble	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Lisa Naeger Eric Donaldson	Y
	TL:	Julian O'Rear	Y
Clinical Pharmacology	Reviewer:	Qin Sun	Y

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	TL:	Shirley Seo	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:	Jeffrey Florian	Y
Biostatistics	Reviewer:	Karen Qi	Y
	TL:	Thamban Valappil	N
Nonclinical Pharmacology/Toxicology)	Reviewer:	Mark Powley	Y
	TL:	Hanan Ghantous	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Steve Miller	Y
	RBPM:	Luz Rivera	N
• Drug Substance	Reviewer:	Sithamalli Chandramouli	N
• Drug Product	Reviewer:	Shrikant Pagay	N
• Process	Reviewer:	Ying Wang	N
• Microbiology	Reviewer:	Ying Wang	N
• Facility	Reviewer:	Christina Capacci-Daniel	N
• Biopharmaceutics	Reviewer:	Min Li	N
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)	EA James Laurenson		N
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Morgan Walker	N
	TL:	Barbera Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Wendy Lubarsky	N
	TL:	Sam Skariah	N
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Valerie Wilson	N
	TL:	Vicky Borders-Hemphill	N
OSE/DRISK (REMS)	Reviewer:	Elizabeth Everhart	N
	TL:	Naomi Redd	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

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Bioresearch Monitoring (OSI)	Reviewer:	Antonio El-Hage	N
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees			
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

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CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: ***the application did not raise significant safety or efficacy issues***
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

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CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	☒ YES ☐ NO
Environmental Assessment • Categorical exclusion for environmental assessment EA) requested? **If no**, was a complete EA submitted? **Comments**:	☒ YES ☐ NO ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**: No inspections needed at this time.	☐ Not Applicable ☒ YES ☐ NO

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<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review</u> (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☐ YES ☒ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

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REGULATORY PROJECT MANAGEMENT
Signatory Authority: John Farley, MD, Deputy Director, OAP **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): March 3, 2017 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:

	REGULATORY CONCLUSIONS/DEFICIENCIES
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☒ Priority Review

	ACTION ITEMS
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☒	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

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

/s/

ANDREW A GENTLES
01/31/2017

KAREN D WINESTOCK
01/31/2017

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 209195

Application Type: New NDA

Drug Name(s)/Dosage Form(s): sofosbuvir/velpatasvir/voxilaprevir fixed dose combination 400mg/100mg/100mg tablet

Applicant: Gilead Sciences, Inc

Receipt Date: December 8, 2016

Goal Date: August 8, 2017

1. Regulatory History and Applicant's Main Proposals

Gilead Sciences, Inc., submitted an NDA on December 8, 2016 for the treatment of chronic hepatitis C virus (HCV) infection in adults without cirrhosis or with compensated cirrhosis (b) (4) This application is an NME NDA consisting of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) as a fixed dose combination tablet with a dosage strength of 400 mg/100mg/100mg.

SOF/VEL/VOX combines sofosbuvir (SOF), a nucleotide NS5B polymerase inhibitor, velpatasvir (VEL), a NS5A inhibitor, and voxilaprevir, a macrocyclic NS3/4A protease inhibitor.

SOF/VEL/VOX was granted Fast Track designation on June 12, 2015 and Breakthrough Therapy (BT) designation on February 19, 2016 for the treatment of chronic HCV genotype 1 infection in patients who have previously failed an NS5A inhibitor containing DAA regimen.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

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4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

NO 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment: *Original NDA application. No RMC at this point.*

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required

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Selected Requirements of Prescribing Information

• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term

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"**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

YES 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

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Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

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Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

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Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]."*

Comment:

N/A

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33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

YES 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

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PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

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Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

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2 DOSAGE AND ADMINISTRATION
2.1 Subsection Title
2.2 Subsection Title
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Subsection Title
5.2 Subsection Title
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Immunogenicity
6.2 or 6.3 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Subsection Title
7.2 Subsection Title
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)
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12 CLINICAL PHARMACOLOGY
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13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
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14.1 Subsection Title
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15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

Reference ID: 4049132

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/s/

ANDREW A GENTLES
01/31/2017

KAREN D WINESTOCK
01/31/2017