APPLICATION NUMBER:

209195Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
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<td>PDUFA Goal Date</td>
<td>August 08, 2017</td>
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<td>OSE RCM #</td>
<td>2016-2983/2985</td>
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<tr>
<td>Reviewer Name(s)</td>
<td>Elizabeth Everhart, MSN</td>
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<td>Cynthia LaCivita, Pharm D</td>
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<tr>
<td>Review Completion Date</td>
<td>May 5, 2017</td>
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<tr>
<td>Subject</td>
<td>Evaluation of the need for a REMS</td>
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<tr>
<td>Established Name</td>
<td>Sofosbuvir, Velpatasvir, Voxilaprevir</td>
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<tr>
<td>Trade Name</td>
<td>Vosevi</td>
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<tr>
<td>Name of Applicant</td>
<td>Gilead Sciences, Inc.</td>
</tr>
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<td>Therapeutic Class</td>
<td>Direct-acting Hepatitis C anti-viral; sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor; velpatasvir, an HCV NS5A inhibitor; voxilaprevir, an HCV NS3/4A protease inhibitor</td>
</tr>
<tr>
<td>Formulation(s)</td>
<td>Fixed Dose Combination (FDC) tablet; 400 mg sofosbuvir/100 mg velpatisavir/100 mg voxilaprevir</td>
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<tr>
<td>Dosing Regimen</td>
<td>1 tablet once daily</td>
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Reference ID: 4094680
EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Vosevi (sofosbuvir, velpatasvir, and voxilaprevir FDC) is necessary to ensure the benefits outweigh its risks. Gilead submitted a New Drug Application (NDA) #209195 for Vosevi, a direct-acting antiviral (DAA) with the proposed indication for the treatment of chronic hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) in:

The risks associated with Vosevi include the possibility of hepatitis B virus (HBV) reactivation in patients co-infected with HBV and HCV, as well as the risk of symptomatic bradycardia with co-administration of amiodarone and sofosbuvir taken in combination with another DAA. The applicant did not submit a proposed REMS or risk management plan with this application; the applicant proposes to communicate risks of HBV reactivation in patients receiving a DAA who are HBV/HCV co-infected and the risk of symptomatic bradycardia in patients who are co-administered amiodarone and sofosbuvir with another DAA through product labeling.

DRISK and the Division of Antiviral Products agree that a REMS is not needed to ensure the benefits of Vosevi outweigh its risks. Eradicating chronic hepatitis C with direct-acting antiviral (DAA) medications such as Vosevi decreases morbidity and mortality from advanced liver disease. Vosevi has been shown to be efficacious in achieving a sustained virologic response at 12 weeks post-treatment (SVR 12) and has a safety profile similar to other DAAs currently approved with risks that are managed through professional labeling and routine pharmacovigilance.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Vosevi (sofosbuvir, velpatasvir, and voxilaprevir FDC) is necessary to ensure the benefits outweigh its risks. Gilead submitted a New Drug Application (NDA) #209195 for Vosevi with the proposed indication for the treatment of chronic hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) in:

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* Child-Turcotte-Pugh Classification for Severity of Cirrhosis
This application is under review in the Division of Antiviral Products (DAVP). The applicant did not submit a proposed REMS or risk management plan with this application but proposes to communicate risks through product labeling.

2 Background

2.1 PRODUCT INFORMATION

Vosevi (sofosbuvir/velpatasvir/voxilaprevir) is a fixed-dose combination (FDC) of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor; velpatasvir, an HCV NS5A inhibitor; and voxilaprevir, an HCV NS3/4A protease inhibitor indicated for the treatment of chronic hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis (Child-Pugh A)

Sofosbuvir and velpatasvir are approved as a FDC (Epclusa); hence voxilaprevir is the drug in this FDC that is a new molecular entity (NME). Sofosbuvir is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is required for viral replication. Velpatasvir is an inhibitor of the HCV NS5A protein, which is also required for viral replication. Voxilaprevir is an inhibitor of the HCV NS3/4A protease and acts as a noncovalent, reversible inhibitor of the NS3/4A protease, another important component of viral replication.

Vosevi is proposed as one tablet (400 mg sofosbuvir/100 mg velpatisavir/100 mg voxilaprevir) by mouth once daily for 12 weeks. If approved, Vosevi will have a Box Warning that is part of DAA class labeling for the risk of reactivation of hepatitis B in patients treated with DAAs who also have a history of infection with hepatitis B. Because of the increased concentration of voxilaprevir with co-administered rifampin, rifampin co-administration with Vosevi is contraindicated. Vosevi is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 209195 relevant to this review:

- 06/12/2015: Fast track designation granted
- 12/08/2016: NDA 209195 submission for the treatment of adult patients with chronic HCV infection received
- 03/21/2017: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for Vosevi

Section 505-1 (a) of the FD&C Act: FDAAA factor (F): Whether the drug is a new molecular entity.

Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.
3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition
Hepatitis C (HCV) is a blood-borne virus that affects the liver. The virus may be silent for many years after infection, as 70-85% of people with HCV develop chronic infection. Of the estimated 2.7 – 3.9 million people in the United States with chronic HCV, the majority are unaware of the infection. When left untreated, HCV can lead to chronic liver disease, including cirrhosis and decompensated liver disease, hepatocellular carcinoma, and death; according to the Centers for Disease Control and Prevention, for every 100 persons infected with HCV, 75-85 will develop chronic infection, 60-70 will develop chronic liver disease, 5-20 will then go on to develop cirrhosis over 20-30 years, and 1-5 will die from consequences of HCV (i.e., hepatocellular carcinoma and/or complications of cirrhosis). HCV is also the leading indication for liver transplantation in the United States. Hepatitis C has currently six known genotypes; they are numbered 1-6 and have further delineation into subtypes (genotype 1a and genotype 1b, for example). In the US, genotype 1 is the most common genotype (approximately 70%), followed by genotype 2 (15-20%), GT 3 (10-12%), and GT 4 (1%); genotypes 5 and 6 are quite uncommon (roughly ≤ 1%) in the US.

3.2 Description of Current Treatment Options
Treatment for chronic HCV has evolved dramatically over the past 5 years from pegylated interferon + ribavirin-based therapy with high toxicity and low efficacy to all-oral direct acting anti-viral (DAA) treatments. There are currently nine brand name DAAs approved, many are in combination (either as FDC or combined treatment) to avoid development of viral resistance, as well as to successfully treat different genotypes; Table 3 (see Appendix 1) summarizes the currently approved DAAs. As the treatment of HCV has moved to all-oral DAA treatment with a better understanding of the virus and the non-structural proteins the DAAs target (i.e., NS3/4A protease inhibitors, NS5B nucleoside polymerase inhibitors, NS5B non-nucleoside polymerase inhibitors, and NS5A inhibitors), HCV eradication is achieved in the majority of patients receiving treatment. There remains an unmet medical need for patients who have failed treatment with a DAA.

4 Benefit Assessment
The goal of HCV treatment is sustained virologic response at 12 weeks post-treatment (SVR 12), defined as undetectable HCV RNA 12 weeks post-treatment; SVR 12 is considered a virologic cure. Eradicating the virus reduces the progression to end-stage liver disease and the complications of cirrhosis, including

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\(^d\) Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

\(^e\) Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*
the development of hepatocellular carcinoma; all-cause mortality is also decreased. The two pivotal clinical trials submitted by the applicant and described below demonstrated good efficacy, with high SVR 12 rates across all arms of the trials.

**Pivotal Study #1: GS-US-367-1171 (POLARIS-1):** Phase 3, randomized, double-blind, placebo-controlled study to investigate the antiviral efficacy, safety, and tolerability of SOF/VEL/VOX compared with placebo for 12 weeks in NS5A inhibitor-experienced subjects with genotypes 1, 2, 3, 4, 5, or 6 chronic HCV infection. Subjects with genotype 1 HCV infection were randomized 1:1 to each group. Subjects with genotype 2, 3, 4, 5, or 6 HCV infections were enrolled to the VOSEVI group. Randomization was stratified by the presence or absence of cirrhosis. Table 1 below, modified from the draft product label, presents the SVR 12 results by genotype for POLARIS-1; no subjects who received placebo achieved SVR 12.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Vosevi 12 Weeks (N=263)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GT-1a (N=101)</td>
</tr>
<tr>
<td>SVR12</td>
<td>96% (253/263)</td>
</tr>
</tbody>
</table>

GT: genotype

a. One subject with undetermined genotype achieved SVR12.
b. Four subjects had GT-1 subtypes other than GT-1a or GT-1b; all 4 subjects achieved SVR12.

**Pivotal Study #2: GS-US-367-1170 (POLARIS-4):** Phase 3, randomized, open-label study to investigate the antiviral efficacy, safety, and tolerability of 12 weeks of SOF/VEL/VOX compared with 12 weeks of SOF/VEL in subjects with genotypes 1, 2, 3, or 4 chronic HCV infection with or without cirrhosis who had previously failed a DAA-containing regimen that did not include an NS5A inhibitor. Subjects with genotypes 1, 2, or 3 infections were randomized in a 1:1 fashion to each group. Subjects with genotype 4 infection were enrolled in the Vosevi group. Subjects whose only past exposure to a DAA-containing regimen was an NS3/4A protease inhibitor were excluded from the trial; no subjects with genotypes 5 or 6 were enrolled. Table 2, modified from the draft product label, presents the SVR 12 results by genotype for POLARIS-4; no subjects who received placebo achieved SVR 12.

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† Section 505-1 (a) of the FD&C Act: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.
5 Risk Assessment & Safe-Use Conditions

The safety of Vosevi was evaluated from a pooled data from the two registrational, Phase 3 clinical trials, POLARIS – 1 and POLARIS – 4. Adverse reactions considered related to study drug occurring in >10% of patients were headache (22%), fatigue (18%), diarrhea (13%), and nausea (12%); of these subjects, most had events that were considered mild or moderate, with the adverse reactions occurring at similar or more greater frequency than patients who received placebo.6,8

A concern for hepatic toxicity seen in some patients, mainly with advanced liver disease, in the approved DAAs, Technivie and Viekira Pak/Viekira Pak – XR, prompted FDA to require updates to those drug labels.9 As part of the clinical development of Vosevi, an Independent Adjudication Committee (IAC) of hepatologists was convened to review all cases of potential hepatotoxicity identified in the integrated Phase 3 and Phase 2 safety populations. There were 46 potential cases identified, with 1 case being identified as possibly drug-induced liver injury (DILI) and one case identified as probably DILI. Both cases were in patients with cirrhosis and both cases resolved without sequelae after stopping study drug.10

In addition to the drug-drug interaction (DDI) with a contraindication for use of rifampin with Vosevi mentioned previously, drugs that are inducers of P-glycoprotein (P-gp) and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, St. John’s wort, carbamazepine) may significantly decrease plasma concentrations of sofosbuvir, velpatasvir, and/or voxilaprevir, thereby potentially leading to reduced therapeutic effect of Vosevi. These DDIs will be communicated in the Warning and Precaution section of the product label, as well as being further described in Section 7 (Drug Interactions) of the label.

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6 Section 505-1 (a) of the FD&C Act: FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
The main serious risks with Vosevi, risk of hepatitis B reactivation and serious symptomatic bradycardia are discussed in the two sections below.

5.1 **Risk of Hepatitis B Virus Reactivation in Patients Co-infected with HCV and HBV**

Hepatitis B virus (HBV) reactivation has occurred in patients taking DAAs who are co-infected with HCV and HBV and who are not receiving HBV antiviral therapy. HBV reactivation is characterized by rapidly increasing HBV DNA (marker of viral activity) which can be accompanied by increases in liver aminotransferase levels (e.g., AST and ALT elevations) and, in severe cases, increases in bilirubin levels, liver failure, and death.

To mitigate this risk, all DAA labels were updated with a Box Warning for risk of HBV reactivation in patients co-infected with HBV and HCV. If approved, Vosevi will include the same Boxed Warning. The label includes a recommendation for testing all patients for evidence of current or prior HBV infection. If a patient has evidence serologically of HBV infection, the label recommends monitoring the patient both clinically and via labs for any signs of HBV reactivation during treatment with Vosevi and during post-treatment follow-up.

5.2 **Serious Symptomatic Bradycardia When Sofosbuvir Is Co-administered with Amiodarone and Another HCV Direct-Acting Antiviral**

There have been postmarketing cases of symptomatic bradycardia, including cases requiring pacemakers, when amiodarone is co-administered with sofosbuvir (one of the drugs in Vosevi FDC) in combination with another DAA. There was also a fatal cardiac arrest reported in a patient taking amiodarone as well as the DAA Harvoni (ledipasvir/sofosbuvir).

To mitigate this risk, the drug label for Vosevi will include a Warning and Precaution to communicate this risk and will further recommend against co-administration of amiodarone with Vosevi. In patients taking amiodarone who will be prescribed Vosevi, the label has recommendations for patient counseling about the risk of symptomatic bradycardia, as well as recommendations for in-patient cardiac monitoring for the first 48 hours of co-administration of amiodarone and Vosevi. This recommendation applies to patients taking Vosevi who need to be co-administered amiodarone, as well as to patients who discontinue amiodarone just prior to starting Vosevi, due to the long half-life of amiodarone.

6 **Expected Postmarket Use**

If approved, Vosevi will be used in the outpatient clinic setting by healthcare providers, the likely prescribers are hepatologists and gastroenterologists, who typically see and treat patients with HCV. Patients will be prescribed the medication to take at home.
7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Vosevi beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Vosevi on the basis of the efficacy and safety information currently available. Chronic HCV is a serious condition that can lead to the development of cirrhosis and hepatocellular carcinoma. Eradicating chronic hepatitis C with DAAs such as Vosevi decreases morbidity and mortality from advanced liver disease. Vosevi has been shown to be efficacious in achieving SVR 12 and has a safety profile similar to other DAAs currently approved with risks that can be handled via professional labeling and routine pharmacovigilance.

9 Conclusion & Recommendations

Based on the available data, DAVP and DRISK have determined that a REMS is not necessary to ensure the benefits of Vosevi outweigh its risks. The safety concerns associated with Vosevi will be communicated via labeling and, in general, healthcare providers who treat chronic hepatitis C should be familiar with the risks of HBV reactivation in patients co-infected with HBV and HCV, as well as the risk of symptomatic bradycardia with co-administration of amiodarone and sofosbuvir taken in combination with another DAA. As of the date of this review, labeling discussions with the applicant are ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Materials Reviewed

The following is a list of materials informing this review:


11 References


5 Spach, D. HCV Epidemiology in the United States. Module 1, Lesson 1, from University of Washington; Hepatitis C Online: http://www.hepatitisc.uw.edu/go/screening-diagnosis/epidemiology-us/core-concept/all, accessed 4/18/17


7 Gilead. Modified from draft product label. December, 2016


9 FDA. Drug Safety Communication: FDA warns of serious liver injury risk with hepatitis C treatments Viekira Pak and Technivie. October 22, 2015

10 Gilead. Summary of Clinical Safety, pp 72-76

11 FDA. Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C. October 4, 2016
## 12 Appendices

### 12.1 Appendix 1

**Table 3 – List of Approved DAAs for Hepatitis C**

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Active ingredient(s)</th>
<th>Year Approved</th>
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<td>Daklinza</td>
<td>daclatasvir</td>
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<td>Epclusa</td>
<td>sofosbuvir and velpatasvir</td>
<td>2016</td>
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<tr>
<td>Harvoni</td>
<td>ledipasvir and sofosbuvir</td>
<td>2014</td>
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<tr>
<td>Olysio</td>
<td>simeprevir</td>
<td>2013</td>
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<tr>
<td>Sovaldi</td>
<td>sofosbuvir</td>
<td>2013</td>
</tr>
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<td>Technivie</td>
<td>ombitasvir and paritaprevir and ritonavir</td>
<td>2015</td>
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<td>Viekira Pak</td>
<td>dasabuvir and ombitasvir and paritaprevir and ritonavir</td>
<td>2014</td>
</tr>
<tr>
<td>Viekira Pak XR</td>
<td>dasabuvir and ombitasvir and paritaprevir and ritonavir</td>
<td>2016</td>
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<tr>
<td>Zepatier</td>
<td>elbasvir and grazoprevir</td>
<td>2016</td>
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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/

ELIZABETH E EVERHART
05/05/2017

CYNTHIA L LACIVITA
05/07/2017
Concur