CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208341Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration Center for
Drug Evaluation and Research Office of
Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	April 18, 2016
Reviewer:	Erin Hachey, PharmD, Division of Risk Management (DRISK)
Acting Team Leader:	Jamie Wilkins Parker, PharmD, DRISK
Acting Division Director:	Kellie Taylor, PharmD, MPH, DRISK
Subject:	Evaluation to determine if a REMS is necessary
Drug Name(s):	Sofosbuvir/Velpatasvir 400 mg / 100 mg fixed-dose combination (FDC)
Therapeutic Class:	Nucleotide analog inhibitor of Hepatitis C virus (HCV) nonstructural protein 5B (NS5B) polymerase and nonstructural protein 5A (NS5A) inhibitor
Dosage and Route:	One tablet orally once daily
Proposed Indication:	Treatment of hepatitis C virus (HCV) infection in adult patients with HCV genotypes (GT) 1, 2, 3, 4, 5, or 6
Application Type/Number:	NDA 208341
Sponsor:	Gilead Sciences, Inc.
OSE RCM #:	2015-2434

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) fixed-dose combination (FDC) of sofosbuvir/velpatasvir (SOF/VEL) is necessary to ensure the benefits of this product outweigh its risks. A new drug application (NDA 208341) for SOF/VEL was received on October 28, 2015, from Gilead Sciences, Inc. (Gilead). The proposed indication for SOF/VEL is the treatment of adult patients with chronic Hepatitis C virus (HCV) genotypes (GT) 1, 2, 3, 4, 5, or 6. Velpatasvir is the NME component of the application and will be available only in the FDC product currently under review. Sofosbuvir is approved for use as a single entity (Sovaldi, NDA 204671) and in combination with ledipasvir in an FDC tablet (Harvoni, NDA 205834) for the treatment of chronic HCV in adults, and does not have a REMS. The Sponsor did not include a proposed REMS or risk management plan for SOF/VEL in this submission.

1.1 Background

1.1.1 Disease Background

HCV infection is a serious and potentially life-threatening disease. It affects 3-5 million people in the U.S. Infection with the single-stranded RNA virus hepatitis C can result in both acute and chronic hepatitis. Approximately 20 to 30 percent of newly infected persons develop signs and symptoms of an acute illness, which can include fever, fatigue, loss of appetite, and other non-specific symptoms. Although the acute disease is usually self-limited, the immune response is mostly insufficient to eradicate the virus such that acute infection leads to chronic infection in 60% to 80% of cases. Chronic HCV infection is associated with ongoing liver inflammation and often follows a progressive course over years to decades, increasing the risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma.

HCV lacks a proofreading mechanism during replication that leads to frequent viral mutations and viral heterogeneity. At least seven distinct HCV genotypes and more than 60 subtypes have been identified, with varying geographic distribution. Genotype 1 (GT 1) is the most common genotype in the United States (72%), with GT 2 (11%), GT 3 (9%), and GT 4 (6%) being less common, and GT 5 and 6 occur uncommonly (≤ 1%) in the U.S. The viral diversity and heterogeneity have prevented the development of a vaccine and also affect the completeness of response to antiviral therapy.

The standard measure of efficacy for antiviral therapy is the absence of detectable HCV RNA, termed sustained virologic response (SVR), documented 12 weeks after the end of treatment (SVR12)[1], and considered a virologic cure. The type and duration of antiviral therapy selected is dependent on the viral genotype, the patient's baseline disease and host factors, the patient's prior treatment experience and response, among other factors.

[1] Viswanathan P and Connelly S. Division of Antiviral Products, Clinical Review of SOF/VEL, NDA 208341, dated March 29, 2016.

HCV has been treated with combinations of indirect acting antivirals and direct acting antivirals (DAA). The indirect acting agents typically used include interferon alpha and ribavirin (RBV), which have broad antiviral activity, but are associated with many toxicities and modest efficacy against HCV. DAA are designed to target specific non-structural HCV proteins involved in RNA replication. Some agents inhibit the non-structural protein (NS) 3/4A serine protease, which cleaves the HCV polyprotein into several polypeptides with distinct functions. Other DAAs target the NS5A protein necessary for viral assembly and replication, or inhibit the NS5B RNA-dependent RNA polymerase responsible for replication of HCV RNA. Various DAAs of the same class may have similar targets; however, their degrees of activity across the HCV GTs may differ.[2]

Great progress has been made in improving SVR12 rates among patients with all stages of hepatic dysfunction. However, at this time, no DAA regimens are approved for patients with decompensated cirrhosis and GT 2, 4, 5, or 6 HCV infection. Therefore, a need exists for well-tolerated and cost-effective DAA combinations that provide the highest rates of viral eradication in all patients (including those with advanced liver disease), the broadest spectrum of action on viral genotypes showing minimal or no clinical resistance, and the shortest treatment duration.[3]

1.1.2 Product Background

Sofosbuvir/velpatasvir (SOF/VEL) is a fixed dose combination (FDC) tablet containing two direct acting antiviral (DAA) agents which interfere with the replication of HCV. Velpatasvir is a novel HCV NS5A inhibitor that has demonstrated potent antiviral activity against GT 1, 2, 3, 4, 5, and 6 HCV infection. Sofosbuvir is an HCV nucleotide analog NS5B polymerase inhibitor that has been approved for use in combination with other agents for the treatment of chronic HCV infection in adults, in the United States, the European Union, and more than 20 other countries worldwide.

The Sponsor's proposed indication is treatment of patients with chronic HCV infection; intended subpopulations include treatment-naïve (TN) and treatment-experienced (TE) patients, and patients with compensated and decompensated cirrhosis. The Sponsor's recommended dosage and treatment duration for non-cirrhotic patients and patients with compensated cirrhosis (Child-Pugh Class A) is one (400 mg/ 100 mg) tablet by mouth once daily for 12 weeks. The recommended treatment regimen for patients with decompensated cirrhosis (Child-Pugh Class B or C) is one tablet by mouth once daily, in combination with ribavirin (RBV), for 12 weeks. When administered with SOF/VEL, the recommended dosage of RBV is based on weight: 1000 mg per day for patients < 75 kg, and 1200 mg per day for patients weighing at least 75 kg, divided and administered twice daily with food. The Sponsor has not proposed a different dose or duration of SOF/VEL based on HCV GT or prior treatment experience. At this time, dosing recommendations are still under review. A dosage recommendation cannot be made for patients with severe renal impairment or end stage renal disease. The combination regimen of SOF/VEL and RBV is contraindicated in patients for whom RBV is contraindicated.

[2] Viswanathan P and Connelly S. Division of Antiviral Products, Clinical Review of SOF/VEL, NDA 208341, dated March 29, 2016.
[3] Aghemo, A., & De Francesco, R. (2013). New horizons in hepatitis C antiviral therapy with direct-acting antivirals. Hepatology, 58(1), 428-438.

1.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 208341 relevant to this review:

September 30, 2013: The Sponsor was granted Fast Track designation for SOF/VEL for the treatment of chronic HCV GT 1, 2, 3, 4, 5, and 6.

May 15, 2015: The Sponsor was granted Breakthrough Therapy designation for SOF/VEL for the treatment of chronic HCV GT 3, 4, 5, and 6 infection in treatment naïve patients.

May 26, 2015: A Pre-NDA meeting was held between the Agency and the Sponsor via teleconference. One agreement resulting from this meeting was the involvement of an Independent Adjudication Committee (IAC) to screen for potential cases of drug-induced liver injury (DILI) in the pivotal Phase 2 and 3 trials for SOF/VEL.

October 28, 2015: An original NDA submission was received by the Agency from Gilead for SOF/VEL (NDA 208341) for the treatment of adult patients with chronic (HCV) genotypes 1, 2, 3, 4, 5, or 6. The Sponsor did not submit a proposed REMS.

February 11, 2016: The Mid-Cycle communication was held between the Agency and the Sponsor via teleconference. The Agency informed the Sponsor that, based on the currently available data, the review team had not identified any major safety concerns for SOF/VEL.

There is no Advisory Committee planned for this application.

2 MATERIALS REVIEWED

The following is a list of materials that informed our review:

- Gilead. Proposed Prescribing Information for SOF/VEL, dated October 28, 2015.
- Gilead. Clinical Overview for SOF/VEL, dated October 28, 2015.
- Gilead. Summary of Clinical Efficacy for SOF/VEL, dated October 28, 2015.
- Gilead. Summary of Clinical Safety for SOF/VEL, dated October 28, 2015.
- Gilead. Proposed Prescribing Information for SOF/VEL, dated October 28, 2015.
    - Updated March 31, 2016.
- Viswanathan P and Connelly S. Division of Antiviral Products, Clinical Review of SOF/VEL, NDA 208341, dated March 29, 2016.
- Pratt, B. DRISK, REMS Review for Ledipasvir/Sofosbuvir, dated July 18, 2014.

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