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APPLICATION NUMBER:

208341Orig1s000

SUMMARY REVIEW

Decisional Review for NDA 208341

Date	June 16, 2016
From	Debra Birnkrant, M.D.
Subject	Division Director's Summary Review
NDA#	NDA 208341
Applicant Name	Gilead Sciences, Inc.
Date of Submission	October 28, 2015
PDUFA Goal Date	June 28, 2016
Proprietary Name / Established (USAN) Name	Epclusa® Sofosbuvir (SOF) and velpatasvir(VEL)
Dosage Forms / Strength	Fixed dose combination tablet containing 400 mg SOF and 100 mg VEL
Proposed Indication(s)	Treatment of adult patients with chronic hepatitis C virus infection
Recommended Action	Approval

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Drs. Prabha Viswanathan and Sarah Connolly supervised by Dr. Kim Struble
Statistical Review	Drs. Karen Qi and Thamban Valappil supervised by Dr. Dionne Price
Pharmacology Toxicology Review	Dr. John Dubinion supervised by Dr. Hanan Ghantous.
CMC Review	Drs. Larry Bai, George Lunn, Sithamalli Chandramouli, and Ying Wang with Dr. Stephen Miller, CMC- Lead
Microbiology Review	Drs. Lisa Naeger and Eric Donaldson supervised by Dr. Jules O'Rear
Clinical Pharmacology/Pharmacometrics Review	Drs. Jenny Zheng and Abhay Joshi supervised by Dr. Shirley Seo; Dr. Fang Li supervised by Dr. Jeffry Florian
DDMAC	Kemi Asante, Pharm.D.
OSI	Dr. Antoine El Hage
CDTL Review	Dr. Kim Struble
OSE/DMEPA	Mónica Calderón, PharmD, BCPS
OPM/DMPP	Morgan Walker, PharmD, MBA
OSE/DRISK	Erin Hachey, Pharm.D.

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OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

APPEARS THIS WAY ON ORIGINAL

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1. Benefit-Risk Assessment

I am in agreement with the benefit-risk assessment summarized in the multidisciplinary reviews of [REDACTED] in agreement with the summary contained in the benefit-risk framework that contains an analysis of [REDACTED] viral infection, current treatment options, and the benefit, risk and risk management for the pangenotypic regimen SOF/VEL. My recommendation is for approval of NDA 208341 for the fixed-dose combination of SOF/VEL for the treatment of adult patients with chronic hepatitis C viral infection for genotypes 1-6 without cirrhosis or compensated cirrhosis and for SOF/VEL/ribavirin (RBV) for the treatment of adult patients with chronic hepatitis C viral infection for genotypes 1-6 with decompensated cirrhosis.

Benefit-Risk Summary and Assessment

Sofosbuvir (SOF) is a hepatitis C virus (HCV) NS5B nucleotide analog polymerase inhibitor and velpatasvir (VEL) is a NS5A inhibitor. SOF/VEL is a fixed-dose combination tablet with a proposed indication for treatment of patients with chronic HCV infection. Subpopulations include treatment-naïve (TN) and treatment-experienced (TE) patients and patients with compensated or decompensated cirrhosis.

HCV infection is a serious disease, affecting an estimated 3-5 million people in the US and 170 million people worldwide (<http://www.epidemic.org/theFacts/theEpidemic/worldPrevalence/>). Although often asymptomatic in early stages, if untreated, HCV can lead to debilitating and life-threatening liver problems, including hepatocellular carcinoma, liver failure, and death. Treatment options for hepatitis C (CHC) have changed dramatically over the past 5 years as oral direct-acting antiviral (DAAs) agents have become available. Regimens, resulting in markedly improved efficacy rates. The standard measure of efficacy is the absence of detectable HCV RNA (SVR), sustained virologic response (SVR), documented 12 weeks after the end of treatment (SVR12); SVR12 is considered the primary endpoint. DAA regimens were approved during this NDA review cycle that confer SVR12 rates greater than 93% for HCV genotype 1 (GT1) infected patients with compensated liver disease, defined as the absence of cirrhosis or compensated cirrhosis (Child-Pugh class A). The first approvals of DAA regimens in HCV GT 1 or 3-infected subjects with decompensated cirrhosis or liver transplant recipients occurred during this review cycle, with SVR12 rates ranging from 50-92% among HCV GT1 subjects and 83% for HCV GT3 subjects.

While great progress has been made in improving SVR12 rates among patients with all stages of hepatic dysfunction, additional data for patients with non-GT1 HCV are needed, especially for HCV GT3. The need for better treatment options is even greater for patients with decompensated cirrhosis regardless of HCV GT. SOF/VEL demonstrated SVR12 rates ranging from 83-100% depending on regimen, HCV GT, cirrhosis stage, and prior treatment history. In addition, SOF/VEL is the first DAA regimen with data for GT 1, 2, 3, 4, 5 and 6. SOF/VEL is a highly effective, RBV-free, single tablet, once daily treatment option for TN and TE patients with compensated liver disease, regardless of HCV GT. Similarly, treatment with SOF/VEL + RBV confers the highest SVR12 rates across HCV GT 1-6 in subjects with decompensated cirrhosis.

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Consistent with results from other development programs, HCV GT3- infected subjects with cirrhosis and/or prior treatment had slightly lower SVR rates than subjects with any other HCV GT studied. SVR12 rates are 89% for HCV GT3 TE cirrhotic subjects, 90% for HCV GT3 TE subjects, and 90% for HCV GT3 subjects without cirrhosis. The optimal strategy for improving the SVR12 rate in these GT3 subjects is unclear. The Applicant has agreed to a PMR to obtain the results from Trial GS-US-342-2097 to assess the role of RBV in subjects with cirrhosis.

No major safety issues unique to SOF/VEL were identified in this review. The most frequent adverse drug reactions were headache and nausea. SOF has been associated with serious bradycardia when co-administered with amiodarone and another treatment was prohibited in the four pivotal trials and no cases of serious bradycardia were observed. RBV is associated with adverse reactions and serious risks, but these safety issues are well known and are not exacerbated by concomitant administration of SOF/VEL.

Approval of SOF/VEL for treatment of adult patients with CHC infection is fully supported by the available evidence. The following regimens are recommended based on thorough analysis of efficacy, safety, and virology data overall, and in the following populations:

- (1) SOF/VEL for 12 weeks: Subjects with HCV GT 1, 2, 3, 4, 5, or 6 infection and without cirrhosis or with compensated cirrhosis
- (2) SOF/VEL + RBV for 12 weeks: Subjects with HCV GT 1, 2, 3, 4, 5, or 6 infection and decompensated cirrhosis

Dimension	Evidence and Uncertainties	Conclusion
Analysis of Condition	<ul style="list-style-type: none"> Chronic infection with hepatitis C virus (HCV) causes inflammation of the liver that can lead to long-term health problems or death. Globally, an estimated 170 million people are infected with HCV, including approximately 3 to 5 million people in the United States (US) (Edlin, et al, Hepatology, 2015). At least seven distinct HCV genotypes (GTs) exist. GT 1 is the most common among US patients (72%), followed by GT 2 (11%), GT 3 (9%), and GT 4 (6%). GTs 5 and 6 occur uncommonly ($\leq 1\%$) in the US but may predominate in other parts of the world. HCV infection is typically asymptomatic in its early stages. However, if left untreated, HCV infection can lead to cirrhosis, hepatocellular carcinoma, liver failure, and death. HCV infection is a leading cause of chronic liver disease in the US. 	<p>HCV mono-infection and HCV/HIV co-infection are a significant public health concern. There has been a significant increase in new cases of HCV in the US, particularly in Appalachia and the South. Injection drug use is a major risk factor for HCV infection.</p> <p>If untreated, chronic HCV infection is a life-threatening condition. The estimated population in the US with chronic HCV infection is 3 million. Patients can experience severe and debilitating health problems.</p>

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