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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 1, 2016
From	Kimberly Struble, PharmD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	208341
Applicant	Gilead Sciences
Date of Submission	October 28, 2015
PDUFA Goal Date	June 28, 2016
Proprietary Name / Non-Proprietary Name	Epclusa [(sofosbuvir (SOF) and velpatasvir (VEL)]
Dosage form(s) / Strength(s)	Fixed dose combination tablet containing 400 mg sofosbuvir and 100 mg velpatasvir
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with chronic hepatitis C virus infection
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	SOF/VEL: Treatment of adult patients with chronic hepatitis C virus genotype 1, 2, 3, 4, 5 and 6 infection without cirrhosis or with compensated cirrhosis SOF/VEL/ribavirin (RBV): Treatment of adult patients with chronic hepatitis C virus genotype 1, 2, 3, 4, 5 and 6 infection with decompensated cirrhosis

1. Benefit-Risk Assessment

I am in agreement with the Risk-Benefit Assessment as provided in the Clinical Review by Dr. Prabha Viswanathan and Dr. Sarah Connelly; therefore this section closely mirrors that found in the Clinical Review with the exception of relatively minor revisions that do not substantively impact the overall risk-benefit assessment.

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Benefit-Risk Summary and Assessment

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

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

While great progress has been made in improving SVR12 rates among patients with all stages of hepatic dysfunction
for patients with non-GT1 HCV are needed, especially for HCV GT3. The need for better treatment options is even gr
decompensated cirrhosis regardless of HCV GT. SOF/VEL demonstrated SVR12 rates ranging from 83-100% depen
regimen, HCV GT, cirrhosis stage, and prior treatment history. In addition, SOF/VEL is the first DAA regimen with po
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
compensated liver disease, regardless of HCV GT. Similarly, treatment with SOF/VEL + RBV confers the highest SV
date across HCV GT 1-6 in subjects with decompensated cirrhosis.

Consistent with results from other development programs, HCV GT3- infected subjects with cirrhosis and/or prior trea
lower SVR rates than subjects with any other HCV GT studied. SVR12 rates are 89% for HCV GT3 TE cirrhotic subje
cirrhotics and 90% for HCV GT3 TE subjects. The optimal strategy for improving SVR12 rate in these GT3 subpopul
PMR is recommended to obtain the results from Trial GS-US-342-2097 to assess the role of RBV in HCV GT3 infecte

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

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

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

Dimension	Evidence and Uncertainties	Conclusi
Analysis of Condition	• 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). • 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 (≤ 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 • Once cirrhosis is established, complications such as jaundice, ascites, variceal hemorrhage, and encephalopathy may develop which defines decompensated cirrhosis, or end-stage liver disease. In patients with decompensated cirrhosis, the 5-year survival rate is approximately 50%.	HCV infection is a public health conc HCV infection is a one that affects a and worldwide. P symptoms that are
Current Treatment Options	• The current standard-of-care treatments for CHC are interferon-free, all-oral DAA regimens. Treatment options vary based on HCV GT: ○ GT1: ledipasvir/sofosbuvir; elbasvir/grazoprevir; paritaprevir/ombitasvir/ritonavir + dasabuvir; daclatasvir + sofosbuvir; and simeprevir + sofosbuvir ○ GT2: sofosbuvir + ribavirin ○ GT3: daclatasvir + sofosbuvir; sofosbuvir + ribavirin ○ GT4: ledipasvir/sofosbuvir; elbasvir/grazoprevir; ombitasvir/ paritaprevir/ritonavir + RBV ○ GT5: ledipasvir/sofosbuvir ○ GT6: ledipasvir/sofosbuvir • Treatment with DAAs can result in sustained virologic response determined 12 weeks after the end of treatment (SVR12), considered a virologic cure, in	Patients with chro greatly benefit fro that are well tolera efficacious than cu options. Only one approve GT2, 5 and 6 HCV subjects would be alternative. RBV-free regimen durations (< 16 we

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Dimension	Evidence and Uncertainties	Conclusi
	greater than 93% of CHC patients with compensated liver disease. However, SVR12 rates were lower for certain subpopulations, and some of these regimens require the addition of RBV or longer treatment durations for subjects with cirrhosis and/or prior treatment failure. • During this NDA review cycle, two regimens were approved for treatment of HCV GT 1 or GT 3-infected subjects with decompensated cirrhosis (Child-Pugh-Turcotte [CPT] score B or C) or liver transplant: ○ Treatment with ledipasvir/sofosbuvir + RBV for 12 weeks resulted in SVR12 rates of 87-88% among GT1-infected pre-transplant subjects with decompensated cirrhosis and SVR12 rates of 89% and 57% for post-transplant CPT B and C subjects, respectively. ○ Treatment with daclatasvir + sofosbuvir + RBV for 12 weeks resulted in SVR12 rates 92% for CPT B subjects and 50% of CPT C subjects with GT1; 83% of subjects with GT3 achieved SVR12. • At the time of this review, no DAA regimens are approved for patients with decompensated cirrhosis and HCV GT 2, 4, 5, or 6 infection.	populations that a treat; such regime adherence and mi tolerability issues DAA regimens for decompensated c those infected with unmet medical ne approved regimen
Benefit	• The efficacy of SOF/VEL was established in four Phase 3 clinical trials which cumulatively evaluated 1302 subjects in the SOF/VEL treatment arms. The trial populations varied based on HCV GT and cirrhosis status. ○ ASTRAL-1: TN and TE subjects with compensated liver disease and HCV GT 1, 2, 4, 5, or 6. Subjects received SOF/VEL x 12 weeks or placebo x 12 weeks. ○ ASTRAL-2: TN and TE subjects with compensated liver disease and HCV GT2. Subjects received SOF/VEL x 12 weeks or SOF + RBV x 12 weeks. ○ ASTRAL-3: TN and TE subjects with compensated liver disease and HCV GT3. Subjects received SOF/VEL x 12 weeks or SOF + RBV x 24 weeks. ○ ASTRAL-4: TN and TE subjects with decompensated liver disease (CPT B at screening) with HCV GT 1-6. Subjects received SOF/VEL x 12 weeks, SOF/VEL+RBV x 12 weeks, or SOF/VEL x 24 weeks • The primary efficacy endpoint was SVR12, or virologic cure. As displayed in the tables below, SVR12 results for SOF/VEL for 12 weeks in HCV GT 1, 2, 3, 4, 5, and 6 subjects without cirrhosis or with compensated cirrhosis were 95-100%. The SVR12 rates for SOF/VEL+RBV for 12 weeks in HCV	Four clinical trials evidence of effect treatment of CHC • The recomme with compens SOF/VEL for 1 HCV GT or pri • The recomme with decompe SOF/VEL + RI irrespective of status. The lower SVR12 GT3 subjects, par cirrhosis, merit co adding RBV to op PMR is recommen from Trial GS-US- role of RBV in HC with cirrhosis.

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