CENTER FOR DRUG EVALUATION AND RESEARCH

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® Sofusbuvir (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 Connelly 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.

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

Division Director's Review
Debra Birnkrant, MD
NDA 208341
Epclusa (sofosbuvir and velpatasvir)

1. **Benefit-Risk Assessment**

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

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Consistent with results from other development programs, HCV GT3- infected subjects with cirrhosis and/or prior trea slightly lower SVR rates than subjects with any other HCV GT studied. SVR12 rates are 89% for HCV GT3 TE cirrhot GT3 cirrhotics and 90% for HCV GT3 TE subjects. The optimal strategy for improving the SVR12 rate in these GT3 s unclear. The Applicant has agreed to a PMR to obtain the results from Trial GS-US-342-2097 to assess the role of RI subjects with cirrhosis.

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

(1) SOF/VEL for 12 weeks: Subjects with HCV GT 1, 2, 3, 4, 5, or 6 infection and without cirrhosis or with con
(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) (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 (≤ 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.	HCV monoinfectio coinfection are a s public health conc increase in new ca Appalachia and S to injection drug u If untreated, chron threatening condit population in the U Patients can expe severe and debilit

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