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APPLICATION NUMBER:

205834Orig1s007, s008, s009

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	February 10, 2016
From	Poonam Mishra, MD, MPH Deputy Director for Safety
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 205834 S007-009
Applicant	Gilead Sciences, Inc.
Date of Submission	August 26, 2015
PDUFA Goal Date	February 26, 2016
Proprietary Name / **Established (USAN) names**	HARVONI ledipasvir, sofosbuvir
Dosage forms / Strength	Fixed Dose Combination Tablet (FDC) containing: Ledipasvir 90 mg Sofosbuvir 400 mg
Proposed Indication(s)	To expand the use in patients with chronic hepatitis C virus infection with 1. Genotypes 1 & 4, who are post liver transplantation with compensated liver disease 2. Genotype 1, with decompensated liver disease regardless of transplantation status
Recommended:	Approval

1. Introduction

The Applicant (Gilead Sciences, Inc.) has submitted three efficacy supplements to NDA 205834 (7, 8, & 9) seeking to expand the indication in patients with chronic hepatitis C virus (HCV) infection, genotypes 1 & 4 who are posttransplantation with compensated liver disease as well as patients with decompensated liver disease with genotype 1 HCV infection, regardless of transplantation status. Specifically, these efficacy supplements include the following subpopulations:

- S-007: Liver transplant recipients with genotype 1 HCV infection
- S-008: Liver transplant recipients with genotype 4 HCV infection
- S-009: Patients with decompensated cirrhosis with genotype 1 HCV infection

Harvoni, a fixed dose combination (FDC) tablet containing ledipasvir 90 mg/sofosbuvir 400 mg, was approved for the treatment of chronic HCV infection in the United States (US) on October 10, 2014. Ledipasvir (LDV) is an HCV inhibitor targeting the HCV nonstructural protein 5A (NS5A) and sofosbuvir (SOF) is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase. SOF was approved for the treatment of chronic hepatitis C (CHC) infection in combination with other HCV agents on

December 6, 2013. The LDV/SOF FDC was initially approved for the treatment of CHC genotype 1 infection in adults without cirrhosis or with compensated cirrhosis. In 2015, the indication was extended to adults with compensated cirrhosis with genotype 4, 5, or 6; and those with HIV-1/HCV genotype 1 or 4 coinfection.

The submission contains data from two Phase 2 trials GS-US-337-0123 (SOLAR-1) and GS-US-337-0124 (SOLAR-2) to support the safety and efficacy of LDV/SOF plus ribavirin (RBV) for 12 weeks in the proposed patient populations - those with HCV genotype 1 or 4 infection who are liver transplant recipients with compensated liver disease as well as those with HCV genotype 1 infection with decompensated liver disease, regardless of transplantation status.

This CDTL review will provide a brief overview of the clinical safety, efficacy, and virology reviews. For detailed assessments, please refer to respective discipline's primary reviews. In particular, this review will focus on the safety and efficacy data in decompensated population as well as in the post liver transplant population as data in these subpopulations has not been previously submitted and reviewed under this NDA.

2. Background

CHC is a global public health problem with an estimated 185 million people worldwide and 3.2 million persons in the US with HCV infection (Mohd Hanafiah 2013, Armstrong, 2006). The natural history of CHC involves progression to cirrhosis, hepatocellular carcinoma (HCC), end stage liver disease, and death. CHC is the most common reason for liver transplantation in the US. By 2007 there were more yearly deaths in the US related to HCV than HIV-1 and, without effective treatment interventions, significant increases in CHC-associated morbidity, mortality, and healthcare costs were predicted (Ly 2012, Wong 2000).

Evaluating clinical outcomes from prospective, randomized controlled clinical trials in patients infected with HCV is challenging and not feasible because of the difficulty of maintaining patients on a randomized arm without intervening therapy for a sufficient duration (many years) to identify late-occurring clinical events such as HCC; therefore, treatment response is defined by virological parameters. The most important virologic parameter has been the sustained virologic response (SVR) which is defined as undetectable HCV RNA in serum after a predefined number of weeks following the completion of therapy.

SVR is an objective endpoint that signifies long-term clearance of hepatitis C and is generally regarded as a "virological cure". Multiple observational cohorts have shown strong correlations between achieving SVR and improved clinical outcomes such as decreased HCC, end-stage liver complications, and mortality. Attainment of SVR in CHC patients has shown to be associated with a decreased progression of fibrosis,

and some studies have even suggested reversal of fibrosis or early cirrhosis (Poynard 2000 & 2002).

With the aging of the infected population, CHC-related complications such as decompensated cirrhosis and HCC are increasing and it is estimated that by 2019-2020 there will be approximately 145,000 annual cases of decompensated cirrhosis and 14,000 cases of HCC (Davis 2010). The ultimate goal of CHC treatment is to reduce the occurrence of end-stage liver disease and its complications including decompensated cirrhosis, liver transplantation and HCC. Without effective treatment, the recurrence of HCV after liver transplantation is universal and is associated with accelerated progression of fibrosis and significant morbidity and mortality.

Interferon (IFN)-based regimens have not been recommended for use in patients with decompensated liver disease and liver transplantation had been the only treatment option. Approval of multiple IFN-free regimens since 2013 has paved the way for treatment of these patients who have been awaiting therapy all these years. Currently approved IFN-free regimens for the treatment of HCV infection include SOF plus RBV; fixed-dose LDV/SOF; simeprevir (SMV, a NS3/4A protease inhibitor) in combination with SOF; a co-packaged triple-DAA regimen (Viekira Pak) consisting of ombitasvir, paritaprevir/ritonavir, and dasabuvir (NS5A inhibitor, ritonavir-boosted NS3/4A PI, and nonnucleoside NS5B-palm polymerase inhibitor, respectively); a regimen consisting of ombitasvir, paritaprevir/ritonavir (Technivie); and a regimen of daclatasvir (DCV, NS5A inhibitor) in combination with SOF. Recent approval of a fixed dose combination of elbasvir, a HCV NS5A inhibitor, and grazoprevir, an HCV NS3/4A protease inhibitor has expanded the available treatment options.

Notably, the majority of the above-mentioned regimens are indicated only in patients with compensated cirrhosis; with limited therapeutic options available to the specific populations such as, those with decompensated cirrhosis or those who are liver transplant recipients. Particularly, HCV protease inhibitor based regimens are either not recommended or contraindicated for use in patients with decompensated liver disease due to risk of liver failure. Specifically, the only approved regimen for decompensated patients is daclatasvir in combination with sofosbuvir taken with or without RBV. For post-transplant patients, available options include the above-mentioned regimen of DCV plus SOF with or without RBV, and Viekira Pak with RBV in patients with normal hepatic function and mild fibrosis (Metavir fibrosis score 2 or lower).

The available data showing the long-term benefits of achieving SVR in HCV patients who have decompensated liver disease and/or post-liver transplantation is limited and needs to be demonstrated in a systematic manner. However, the published data from patients with decompensated cirrhosis due to chronic hepatitis B virus infection suggests that reversal of decompensation is possible with effective therapeutic interventions (Zoulim 2008).

Clinical protocols submitted under IND were reviewed by the review team throughout the course of the product's development, with feedback provided as appropriate. In addition, a pre-NDA meeting was held with the sponsor including the hepatology expert panel convened by the sponsor.

3. CMC/Device

No changes to the chemistry, manufacturing, and controls for the HARVONI tablet are proposed with this application.

4. Nonclinical Pharmacology/Toxicology

No nonclinical safety studies were submitted with these supplements. Refer to original Pharmacology/Toxicology Review for NDA 205834.

Sections 8.1 and 8.2 of the Prescribing Information (PI) were updated to be consistent with the Pregnancy and Lactation Labeling Final Rule. Please refer to Pharmacology/Toxicology Review by Christopher Ellis, Ph.D. for details.

5. Clinical Pharmacology/Biopharmaceutics

No new information for pharmacology; in vitro or nonclinical data; absorption, distribution, metabolism, and elimination (ADME); or pharmacokinetics (PK) profile studies or analyses between healthy and HCV-infected subjects is included with these supplements. New data for population PK analyses was submitted. Please refer to Clinical Pharmacology Review by Dr. Florian for a detailed assessment. In addition, in-depth Clinical Pharmacology/Biopharmaceutics Reviews were conducted during original NDA reviews for sofosbuvir and ledipasvir/sofosbuvir. No new biopharmaceutics information is included within this submission.

As noted in Dr. Florian's review, "The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology information provided in this supplement NDA to support a recommendation of approval of LDV/SOF in patients with decompensated cirrhosis and patients who have received a liver transplant."

Key points from Dr. Florian's review are noted below:

- PK for LDV, SOF, and the predominant circulating metabolite of SOF (GS-331007) were evaluated in SOLAR trials. The data from the SOLAR trials was compared with observations from the original LDV/SOF NDA submission.
- No difference in PK was observed based on liver transplantation status, but differences were observed based on degree of hepatic impairment.

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