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APPLICATION NUMBER:

205834Orig1s000

SUMMARY REVIEW

Decisional Review for NDA 205834

Date	September 23, 2014
From	Debra Birnkrant, M.D.
Subject	Division Director's Summary Review
NDA/BLA # Supp #	NDA 205834/Original Submission
Proprietary / Established (USAN) names	Harvoni™ [ledipasvir (LDV)/sofosbuvir (SOF)]
Dosage forms / strength	Fixed-dose combination, 90 mg/400 mg tablets, once daily
Proposed Indication(s)	Indicated for the treatment of chronic hepatitis C (CHC) in adults with Genotype 1 infection
Action	Approval

1. Introduction to Review: This Division Director's memorandum provides a topline summary of NDA 205834 for Gilead Sciences' New Drug Application (NDA) for the fixed-dose combination of ledipasvir, an NS5A inhibitor and sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor for treatment of adult patients with Genotype 1 (GT1) infection. This decisional review summarizes pertinent findings from the original NDA submission and FDA's multidisciplinary reviews and product labeling.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Division of Scientific Investigations (DSI) Status:
Chronic hepatitis C viral infection is a public health burden. Based on NHANES data from 2003-2010, it is estimated that 2.7- 3.9 million people in the United States are infected with the virus. Most are unaware that they are infected and consequently treatment is not reaching those in need. With chronic infection, it is projected that there will be an increase in cases of hepatocellular carcinoma (HCC) with an estimated peak incidence in 2019 of 14,000 cases/year and decompensated cirrhosis with a projected peak incidence in 2020 of >145,000 cases/year (Davis, et al., Gastroenterology 2010) because the epidemic began decades ago with 75% of those with HCV in the United States born between 1945-1965 (CDC).

Treatment regimens have improved over the years based on better tolerability and enhanced effectiveness. In 2013, two new direct-acting antivirals were approved from two different classes. SOF, an HCV nucleotide analog NS5B polymerase inhibitor was approved in combination with ribavirin, with and without pegylated interferon for treatment of chronic hepatitis C (CHC) GT 1- 4 infection. SVR12 rates increased to 89% with this new direct-acting antiviral in combination with pegylated interferon and ribavirin (P/R) for CHC GT 1 viral infection. Simeprevir (SIM), an NS3/4A protease inhibitor was also approved for use in

combination with P/R in 2013. Overall SVR12 rates were 80% for GT1a and GT1b patients naïve to treatment. Off-label use of the combination of SOF and SIM in the COSMOS trial was recently published. Overall SVR rates from the COSMOS trial were 93% for the populations enrolled (Lawitz, et al., Lancet, 2014).

Treatment of CHC infection allows for a chance of virologic cure. Virologic cure as measured by sustained virologic response (SVR) 12 weeks after completion of treatment is associated with histologic benefit, a decrease in all-cause and liver-related mortality, and decreases in rates of HCC and hepatic decompensation (van der Meer, et al. JAMA 2012). Regarding treatment for CHC, current standards are outlined in the 2014 American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) treatment guidelines that were recently revised as of August 11, 2014.

The NDA for the FDC was submitted on February 8, 2014 and reviewed under the PDUFA V program. As previously mentioned, SOF was approved in 2013. LDV is the first drug in its class and the FDC is recommended for use in HCV GT1 patients based on Phase 3 clinical trials that enrolled both treatment-naïve and treatment-experienced patients. Duration of treatment is dependent on whether cirrhosis is present and other baseline factors. For example, the FDC is recommended for use for 12 weeks duration for GT1 patients who are treatment-naïve. A treatment duration of 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL based on an analysis of baseline predictors of relapse. A 24-week treatment duration is recommended for treatment-experienced patients with cirrhosis; treatment-experienced is defined as those patients who have failed treatment with either P/R or an HCV protease inhibitor plus P/R. See Table 1 below that is excerpted from product labeling.

Table 1 Recommended Treatment Duration

Patient Population	Treatment Duration
Genotype 1 Treatment-naïve +/- cirrhosis	12 weeks*
Genotype 1 Treatment-experienced** without cirrhosis	12 weeks
Genotype 1 Treatment-experienced** With cirrhosis	24 weeks

The FDC for 8 weeks can be considered in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA < 6 million IU/mL

The safety and efficacy of LDV/SOF in pediatric patients have not been studied.

The application was granted a priority review because CHC is a serious and life-threatening disease and the FDC appeared to provide improvement in safety and effectiveness. In addition, the FDC was designated as a Breakthrough Therapy under FDASIA,Title IX because preliminary clinical evidence indicated substantial improvement over available therapies in the treatment of CHC-infected adults including the first ribavirin-free regimen for GT1.

The original NDA submission contained clinical data from three Phase 3 trials in GT1 CHC viral infection and Phase 2 trials as well as other studies that supported dose selection. ION-1 and ION-3 trials were conducted in treatment-naïve patients and ION-2 was conducted in patients who had previously failed a P/R regimen including subjects who may have failed a PI-based regimen.

Per Dr. El-Hage, Office of Scientific Investigations (OSI), six domestic Phase 3 clinical trial sites underwent inspection. Overall, the data submitted from these six sites are considered acceptable in support of the pending application.

The application was not presented before the Antiviral Drugs Advisory Committee because a preliminary review of the NDA, including labeling did not reveal any significant clinical or safety issues that would benefit from an advisory committee discussion.

3. Chemistry/Manufacturing/Controls (CMC): The CMC reviewers of the LDV/SOF NDA are: Drs. George Lunn, Sandra Suarez and Steven Donald. Dr. Rapti Madurawe supervised the CMC review with Dr. Stephen Miller serving as CMC-Lead. The CMC team reviewed data to assure the identity, strength, purity and quality of the FDC; complete SOF drug substance data was provided in approved NDA 204671 and was incorporated in this NDA by reference. The CMC team is in agreement with the Applicant that the FDC contains 90 mg of LDV and 400 mg SOF and concluded the following:

The composition, manufacturing process and specifications for the FDC tablets are appropriate. Specifically, for LDV, there are two isolated intermediates that have acceptable specifications. Per Dr. Lunn's review, a reasonable specification that includes tests for appearance, identity, acetone content, water, assay, impurities, residual solvents, and elemental impurities is also provided.

The stability data contained in the FDC NDA support an expiry date of 24 months when stored at or below 30 degrees centigrade. Further, the container-closure system and labeling are appropriate.

An inspectional report has been completed and the outcome is satisfactory.

4. Pharmacology/Toxicology: Please see review of submitted nonclinical toxicology studies by Dr. Christopher Ellis, supervised by Dr. Hanan Ghantous.

The nonclinical safety profile of SOF has been previously reviewed under NDA 204671 with the exception of two-year carcinogenicity studies that were reviewed with this application. Per Dr. Ellis' review, the nonclinical safety profile of LDV has been evaluated in: safety pharmacology studies in rats and dogs; repeat-dose toxicology studies in mice, rats and dogs for up to 1, 6 and 9 months duration, respectively; up to two-week repeat-dose toxicology studies to qualify impurities; phototoxicity studies in mice and rats; fertility and pre- and post-natal developmental studies in rats; embryo-fetal developmental studies in rats and rabbits; and genetic toxicology studies (Ames, *in vitro* chromosomal aberration and *in vivo* rat micronucleus assays). In addition, numerous *in vitro* and *in vivo* nonclinical pharmacokinetic studies evaluating the absorption, distribution, metabolism and excretion of LDV have been conducted; rat and mouse carcinogenicity studies with LDV are currently in progress.

Myocardial inflammation and degeneration occurred in rats administered oral GS-9851 doses, a 1:1 mixture of SOF and its diasteriomer, of 2,000 mg/kg/day in a 7-day toxicology study. Cardiac toxicity was not observed in rats administered oral doses of SOF up to 750 mg/kg/day for approximately 20 months, or in dogs and mice administered SOF up to 500 and 1,000 mg/kg/day for 9 and 3 months respectively, with corresponding exposures approximately 9-fold (rat), 17-fold (dog) and 24-fold (mouse) that in humans at the recommended SOF dose of 400 mg once daily. Nonetheless, cardiac effects seen in nonclinical studies were further examined in clinical trials and are summarized in Dr. Sarah Connelly's clinical review.

As described in Dr. Ellis' review, no clear target organs of toxicity were identified in repeat-dose toxicology studies in mice, rats and dogs administered LDV doses of up to 300, 100 and 30 mg/kg/day for 1, 6 and 9 months, respectively. Therefore, no specific overlapping toxicity of potential significant clinical concern was identified in animals administered LDV or SOF alone. However, a potential LDV-related mild hepatobiliary toxicity signal (not considered adverse and not clearly dose-dependent) was noted, with slight increases in ALP and/or ALT associated with increased liver/gall bladder weight (high-dose males only) without correlating histopathology changes observed in mice following oral administration of LDV at up to 300 mg/kg/day ($AUC_{0\text{-}24hr}$~164 & 271 μg.h/ml for LDV in females and males, respectively). In addition, minimal-to-slight random foci of hepatocyte necrosis (males) and bile duct hyperplasia (males and females) were noted in rats following oral administration of LDV at up to 100 mg/kg/day ($AUC_{0\text{-}24hr}$~56 μg.h/ml for LDV). These non-adverse hepatobiliary findings were observed at LDV AUC exposure ~8- and 30-fold higher, in rats and mice respectively, than in humans at the recommended LDV dose. In addition, slight increases in cholesterol and triglycerides were noted in rats at 100 mg/kg/day. In dogs, no clear clinically relevant LDV-related findings were

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