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APPLICATION NUMBER:

205834Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Edward Cox, MD MPH
Subject	Office Director Decisional Memo
NDA/BLA #	NDA 205834
Applicant Name	Gilead Sciences, Inc.
Date of Submission (receipt)	April 10, 2014
PDUFA Goal Date	October 10, 2014
Proprietary Name **Established (USAN) Name**	Harvoni ledipasvir (LDV)/sofosbuvir (SOF)
Dosage Forms / Strength	fixed dose combination tablet LDV 90mg/ SOF400 mg
Indication	Harvoni is indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults.
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Sarah Connelly
Product Quality	George Lunn, Rapti Madurawe 7/10/2014; George Lunn, Stephen Miller 9/26/2014
Biopharmaceutics Review	Sandra Suarez, Angelica Dorantes, Richard Lostritto 7/10/2014; Sandra Suarez, Angelica Dorantes 9/26/2014
Statistical Review	Karen Qi, Fraser Smith, Tsae Yun Lin
Pharmacology Toxicology Reviews	Christopher Ellis, Hanan Ghantous, Abigail Jacobs
Clinical Virology	Lisa Naeger, Eric Donaldson, Julian O'Rear
Clinical Pharmacology Review	Jenny Zheng, Leslie Chinn, Shirley Seo, Jeffry Florian, Yaning Wang
OSI	Antoine El-Hage, Susan Thompson, Kassa Ayalew
CDTL Review	Kim Struble
Deputy Division Director's Review	Debbie Birnkrant

OND=Office of New Drugs
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader

Harvoni is a fixed-dose combination tablet of ledipasvir and sofosbuvir developed for the treatment of patients with chronic hepatitis C (CHC) genotype 1 infection. Ledipasvir is a hepatitis C virus NS5A inhibitor. Sofosbuvir is a nucleotide analog hepatitis C virus NS5B inhibitor. Sofosbuvir has been previously approved (December 6, 2013) as Sovaldi (sofosbuvir), a single active ingredient tablet under Gilead's NDA 204671. The ledipasvir component of Harvoni has not been previously approved in the U.S. The combination of

ledipasvir and sofosbuvir received breakthrough therapy designation on July 22, 2013 for treatment of CHC genotype 1 and was granted a priority review.

CHC infection causes a significant burden of disease in the United States and globally. In the U.S. 3.2 million people are estimated to be infected with hepatitis C virus. New therapies to treat CHC offer the promise of important advances in the care of patients with CHC. The development of direct acting antiviral agents has led to significant advances in the treatment of patients with CHC. The new treatments and treatment regimens are yielding sustained virologic response rates considerably higher than what has historically been possible prior to the advent of direct acting antiviral agents for the treatment of CHC.

The review team has reviewed the issues in detail in their respective disciplines with regard to the safety and efficacy of ledipasvir / sofosbuvir. For a detailed discussion of NDA 205834, the reader is referred to the individual discipline specific reviews. In addition, the Cross-Discipline Team Leader's review and the Division Director's review summarize key issues in the NDA submission. This memorandum will focus on select issues from the review.

The NDA is recommended for approval from the CMC perspective (9/26/2014 addendum). The biopharmaceutics review finds the amended procedure for monitoring for (b) (4) ledipasvir satisfactory (9/26/2014 addendum). The Product Quality Microbiology Review identifies no product quality microbiology deficiencies. The manufacturing facilities inspection summary of September 3, 2014 finds the facilities to be acceptable.

The recommendation from the pharmacology/toxicology reviewers is for approval. The general toxicology of sofosbuvir was previously reviewed under Gilead's NDA 204671 and is described in detail in the reviews for Gilead's NDA 204671. The review of the toxicology studies for ledipasvir finds no clear organ of toxicity in studies in mice rats and dogs. There was note of a potential hepatobiliary toxicity signal that was not considered adverse and not dose dependent; the potential toxicity was a slight increase in alkaline phosphatase and/or alanine aminotransferase and increased liver/gall bladder weights (high-dose males only) in the absence of correlating histopathologic changes. Also noted was slight to minimal, random hepatocyte necrosis and bile duct hyperplasia. These findings, classified as non-adverse, were observed at exposures 8 to 30 times higher in mice and rats than the human exposure for ledipasvir. An ophthalmology consultation was requested to evaluate the potential for phototoxicity from ledipasvir. Gilead provided a 3-day multiple oral dose ocular phototoxicity study in pigmented male rats; no eye reactions indicative of phototoxicity were noted in this study. In addition, Gilead provided a single dose oral phototoxicity study in albino female hairless mice; no skin reactions indicative of phototoxicity were noted to have occurred in this study. Harvoni (ledipasvir/sofosbuvir) is categorized as pregnancy category B. Carcinogenicity studies of ledipasvir in mice and rats are ongoing. Two-year carcinogenicity studies of sofosbuvir in mice and rats showed no increase in drug-related neoplasms at the exposures achieved in animals (4- and 18-fold in male and female mice respectively and 8- and 10-fold in male and female rats respectively).

The Clinical Virology Reviewers recommend that the data in NDA 205834 support approval. Ledipasvir is an inhibitor of the HCV NS5A protein. Sofosbuvir acts via inhibition of the

NS5B RNA-dependent RNA polymerase. The product labeling describes resistance mutations associated with decreased susceptibility in HCV replicons in cell culture and treatment emergent mutations from patients experiencing virologic failure.

The Clinical Pharmacology reviewers find there is sufficient clinical pharmacology information to support approval of the application. Following oral administration of Harvoni, ledipasvir median peak concentrations were observed 4 to 4.5 hours after dosing and sofosbuvir was absorbed with a peak plasma concentration approximately 0.8 to 1 hours after dosing. Ledipasvir is >99.8% bound to plasma proteins; sofosbuvir is 61-65% bound to human plasma proteins. Ledipasvir is predominantly eliminated in the feces as the parent drug. Sofosbuvir is extensively metabolized in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. The major elimination pathway is renal excretion with the metabolite GS-331007 representing the predominant metabolite in urine. No dosage adjustment for Harvoni is required in patients with mild and moderate renal impairment. The safety of Harvoni has not been established in patients with severe renal impairment or end stage renal disease; a statement is included in the Dosage and Administration section noting that no dose recommendation can be given for patients with severe renal impairment or with end stage renal disease. No dose adjustment for Harvoni is recommended for patients with mild, moderate, or severe hepatic impairment. The product labeling includes a Warnings and Precautions statement that Harvoni should not be used with rifampin or St. John's wort because they are potent P-gp inducers and may lead to reduced concentrations and therapeutic effect of ledipasvir and sofosbuvir. The labeling also includes information on drug interactions.

Sofosbuvir's efficacy was evaluated in three phase 3 clinical trials and shown to be efficacious in the treatment of CHC infections in patients with genotype 1 as ledipasvir / sofosbuvir 90/400 mg once daily in treatment naive and treatment experienced patients with or without cirrhosis. The trials were historically controlled trials comparing sustained virologic response (SVR) rates from the trials in patients treated with Harvoni to pre-specified SVR rates derived from historical data. Based upon the results of these trials, the duration of treatment for treatment-naïve with and without cirrhosis and treatment experienced patients without cirrhosis is 12 weeks. The labeling also notes that for treatment-naïve, non-cirrhotic patients with a pre-treatment HCV viral load less than 6 million IU/mL, 8 weeks can be considered. The duration of treatment for treatment-experienced patients with cirrhosis is 24 weeks. Using these treatment regimens, the studies did not reveal an increase in response with the addition of ribavirin. With regard to the fixed dose combination of sofosbuvir and ledipasvir, (1) these active moieties have different mechanisms of action; (2) the sofosbuvir component has previously been shown to be effective in the treatment of CHC (3) there is both cell culture and short term in vivo data from patients with CHC showing activity of ledipasvir monotherapy; these data, along with the overall results on SVR in the phase 3 trials for Harvoni, support the role for each component of Harvoni. In addition, as noted in the draft guidance on developing drugs for treatment of patients with CHC, it is important to limit the duration of direct acting antiviral agents as monotherapy because of the concern of developing resistance.[1]

[1] *Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment* (10/16/13) http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225333.pdf

In clinical trials the most common adverse effects reported in clinical study participants treated with Harvoni were fatigue, headache, nausea, diarrhea, and insomnia. The product labeling also describes infrequent elevations of bilirubin, asymptomatic transient lipase elevations, and creatinine kinase elevations that were reported in subjects treated with sofosbuvir (creatinine kinase was not evaluated in phase 3 trials of Harvoni). The labeling also includes Warnings and Precautions statements that sofosbuvir should not be taken with P-gp inducers and should not be taken with other products that contain sofosbuvir (Sovaldi).

NDA 205834 was not presented before the Antiviral Drugs Advisory Committee. There were no particular issues with safety, efficacy, or trial design that warranted presenting the application to an Advisory Committee.

With regard to the required pediatric studies, we are waiving the pediatric study requirement for ages less than 3 years because necessary studies are impossible or highly impractical. Moreover, spontaneous clearance is possible and the risk-benefit balance would not favor treatment in this age group. We are deferring submission of a pediatric study for ages 3 to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed. The required pediatric assessments are enumerated in the approval letter.

In summary, I agree with the review team, CDTL, and the Division Director, that the overall benefits and risks support the approval of NDA 205834 for Harvoni (ledipasvir/sofosbuvir) 90/400 mg for the treatment of patients with CHC genotype 1 as described in the product labeling. The benefits of Harvoni for the treatment of CHC outweigh the risk of treatment with Harvoni. The approval of the combination of ledipasvir/sofosbuvir provides for a treatment regimen, one pill, taken once daily for treatment naive and experienced patients with or without cirrhosis that does not need to be taken in combination with interferon or ribavirin. The product labeling adequately describes the safety and efficacy findings. Postmarketing requirements include studies that will provide additional information on resistance mutations and pediatric safety and efficacy data in children ages 3 to less than 18 years of age.

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Edward Cox, MD, MPH
Director, Office of Antimicrobial Products
OND/CDER/FDA

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