CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204671Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Edward Cox, MD MPH
Subject	Office Director Decisional Memo
NDA/BLA #	NDA 204671
Applicant Name	Gilead Sciences, Inc.
Date of Submission	April 6, 2013
PDUFA Goal Date	December 8, 2013
Proprietary Name / Established (USAN) Name	Sovaldi sofosbuvir
Dosage Forms / Strength	tablets, 400 mg
Indication	SOVALDI is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for the treatment of chronic hepatitis C (CHC) infection as a component of a combination antiviral treatment regimen. • SOVALDI efficacy has been established in subjects with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection The following points should be considered when initiating treatment with SOVALDI: • Monotherapy of SOVALDI is not recommended for treatment of CHC. • Treatment regimen and duration are dependent on both viral genotype and patient population • Treatment response varies based on baseline host and viral factors
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Poonam Mishra
Product Quality	Fuqiang Liu, George Lunn, Rapti Madurawe Krishna Ghosh, Tara Gooen Steven P. Donald, Stephen Langille
Biopharmaceutics Review	Minerva Hughes, Angelica Dorantes
Statistical Review	Karen Qi, Wen Zeng, Dionne Price
Pharmacology Toxicology Reviews	Christopher Ellis, Hanan Ghantous, Abigail Jacobs
Clinical Virology	Lisa Naeger, Eric Donaldson, Jules O'Rear
Clinical Pharmacology Review	Jenny Zheng, Su-Young Choi, Shirley Seo, Jeff Florian, Yaning Wang, Sarah Dorff, Michael Pacanowski
OSI	Antoine El-Hage, Susan Liebenhaut, Janice Pohlman
CDTL Review	Sarah Connelly
Deputy Division Director's Review	Debbie Birnkrant

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

Sovaldi (sofosbuvir) is a nucleotide analog hepatitis C virus NS5B polymerase inhibitor that has been developed for the treatment of chronic hepatitis C (CHC) as a component of a combination antiviral treatment regimen. This will be the first approved drug for the treatment of chronic hepatitis C that is an NS5B polymerase inhibitor. Sofosbuvir received breakthrough therapy designation and was granted a priority review. Chronic hepatitis C 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 review team has reviewed the issues in detail in their respective disciplines with regard to the safety and efficacy of sofosbuvir. For a detailed discussion of NDA 204671, 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 Office of New Drug Quality Assessment (ONDQA) finds that the Chemistry, Manufacturing, and Controls (CMC) information in the NDA as amended is adequate and recommends approval of Sovaldi (sofosbuvir) tablets, 400 mg. The recommendation from the Office of Compliance (OC) regarding NDA 204671 is for approval. During the review of the NDA, ONDQA, OC, and the review division worked closely to address the cGMP issues identified at some sites that were originally included in the NDA. Gilead's Foster City site, the initially proposed testing laboratory for the API and the finished dosage form for sofosbuvir, was found to have several deficiencies with regards to testing procedures. Gilead has removed

the Foster City site from the NDA; they will use an alternative cGMP compliant testing facility in the NDA. In addition, the (b) (4) API site has been removed from the application because of data integrity violations reported by EDQM. With the removal of (b) (4) drug substance is being manufactured and tested by (b) (4) Testing is also carried out by (b) (4) The Product Quality Biopharmaceutics Reviewer recommends approval. The Product Quality Microbiology Review recommends approval. The application is recommended for approval from the standpoint of CMC.

The recommendation from the pharmacology/toxicology reviewers is for approval. Sofosbuvir is a nucleotide pro-drug that is converted intracellurlarly to the active uridine triphosphate form (GS-461203). Sofosbuvir (GS-7977) is one of two diastereoisomers that are in the mixture designated GS-9851. The target organs identified in the nonclinical studies included the heart and gastrointestinal tract. At an estimated AUC exposure for the sofosbuvir metabolite GS-331007 that is 14-fold the human exposure myocardial inflammation and degeneration were observed in rats in a 7-day toxicology study receiving 2000mg/kg/day of the diastereoisomeric mixture. Cardiac toxicity was not observed in rats that were administered sofosbuvir (GS-7977) at doses up to 500 mg/kg/day for 6 months, or in dogs or mice administered sofosbuvir (GS-7977) at up to 500 and 1000 mg/kg/day in 9 and 3 month studies. The animal AUC exposures of GS-331007 in the 6-month rat, 3-month dog, and 9-month mouse studies relative to human exposures were 9-fold (rat), 27-fold (dog), and 41-fold (mouse) higher. A postmarketing requirement will be included to conduct a 7-day rat study using sofosbuvir (GS-7977) to evaluate its contribution to the findings noted with GS-9851. Gastrointestinal hemorrhage was observed in dogs receiving sofosbuvir for 3 to 6 months at exposures 29- to 39-fold the human exposure.

The labeling categorizes sofosbuvir use with ribavirin and peginterferon as pregnancy category X because of reproductive toxicity of ribavirin (birth defects and/or fetal deaths) and peginterferon alfa (an abortifacient). The product labeling describes in the Warnings and Precautions section the risk of embryo-fetal toxicity, that a pregnancy test with a negative result should be obtained before initiating therapy, that 2 effective contraceptive methods must be used during treatment and for 6 months after completing treatment and pregnancy tests should be monitored during this time period. The labeling also provides information on the ribavirin pregnancy registry. Sofosbuvir itself is categorized as pregnancy category B.

The Clinical Virology Reviewer recommends that the data in NDA 204671 support approval. The labeling describes treatment emergent substitutions in patients with virologic failure. Product labeling also describes treatment-emergent substitutions that were associated with reduced sofosbuvir susceptibility. Sofosbuvir was evaluated for possible mitochondrial toxicity. No decrease in mitochondrial DNA was noted in multiple cell lines incubated with sofosbuvir. Sofosbuvir and its metabolites showed no inhibition of mitochondrial biogenesis.

The Clinical Pharmacology reviewers find the data in the application are acceptable and recommend approval for the application. Following oral administration sofosbuvir was absorbed with a peak plasma concentration approximately 0.5 to 2 hours after dosing. Sofosbuvir is 61-65% bound to human plasma proteins. 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 is required in patients with mild and moderate renal impairment. The safety of sofosbuvir has not been established in patients with severe renal impairment or end stage renal disease; a statement is included in the Warnings and Precautions section noting that no dose recommendation can be given for patients with severe renal impairment or with end stage renal disease because of higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite. No dose adjustment for sofosbuvir is recommended for patients with mild, moderate or severe hepatic impairment. Sofosbuvir is a substrate of the drug transporter P-gp and the breast cancer resistance protein. The product labeling includes a Warnings and Precautions statement that sofosbuvir 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 sofosbuvir.

Sofosbuvir's efficacy was evaluated in six clinical trials and shown to be efficacious in the treatment of chronic hepatitis C virus (CHC) infections in patients with genotype 1 and 4 in combination with peginterferon alfa and ribavirin and in patients with genotype 2 and 3 in combination with ribavirin. Based on the results of these trials, the recommended duration of the treatment regimen is 12 weeks for genotypes 1, 2, and 4; for genotype 3 the recommended duration of treatment is 24 weeks with sofosbuvir and ribavirin because shorter duration regimens achieved lower response rates than the 24 week regimen in patients with genotype 3 CHC. Data supporting the efficacy of treatment of patients with hepatocellular carcinoma meeting Milan criteria (patients awaiting liver transplantation) were provided. In addition the efficacy of sofosbuvir in the treatment of CHC in the setting of HIV co-infection supports the efficacy of sofosbuvir for treatment of CHC in HCV/HIV co-infection. For patients with genotype 1 infection who are not eligible for treatment with an interferon-based regimen, the data support that sofosbuvir plus ribavirin for 24 weeks is a therapeutic option. The labeling provides dosing and administration instructions for each of these different types and patient populations with CHC infection.

Over 1,500 HCV infected subjects received sofosbuvir in phase 3 trials. The data from the clinical trials and the toxicology studies were carefully reviewed with a particular emphasis on evaluating for potential cardiac toxicity. A different NS5B polymerase inhibitor has been associated with significant cardiac toxicity; however, the molecule associated with cardiac toxicity is a guanosine analog, while sofosbuvir is a uridine analog. Careful review of the clinical cases of cardiac events did not reveal an association with cardiac toxicity for sofosbuvir. In the controlled trials, there was not an excess of cardiac toxicity. Limited cases of cardiac disorders that were identified in sofosbuvir-treated patients were confounded and an association with sofosbuvir could not be made. As noted in the pharmacology/ toxicology section, a postmarketing requirement for a follow-up rat toxicology study with sofosbuvir

rather than the diastereoisomeric mixture will be conducted to further investigate the animal findings. The findings from this diastereoisomeric mixture animal study are also described in the product labeling. In addition, the potential for cardiac toxicity is an adverse event that will be closely monitored in the postmarketing setting.

In clinical trials the most common adverse effects reported in clinical study participants treated with Sovaldi and ribavirin were fatigue and headache. In participants treated with Sovaldi, ribavirin and peginterferon-alfa, the most common side effects reported were fatigue, headache, nausea, insomnia and anemia. The product labeling includes statements in the Warnings and Precautions section on embryo-fetal toxicity noting that ribavirin may cause birth defects or death of the exposed fetus and that peginterferon is an abortifacient. The labeling also includes Warnings and Precautions statements that sofosbuvir should not be taken with potent P-gp inducers.

NDA 204671 was presented before the Antiviral Drugs Advisory Committee. On the question of whether the data support approval of sofosbuvir in combination with ribavirin for treatment of chronic hepatitis C in adult patients with genotype 2 and 3 infection the committee voted Yes 15; No 0; abstain 0. On the question of whether the data support approval of sofosbuvir in combination with pegylated interferon and ribavirin for treatment of chronic hepatitis C in adult patients with genotype 1 and 4 infection the committee voted Yes 15; No 0; abstain 0. The committee expressed a range of views on the strength of evidence for use of sofosbuvir in combination with pegylated interferon and ribavirin for treatment of chronic hepatitis C in patients with genotype 1 infection who are nonresponders to a prior course of pegylated interferon and ribavirin. Some Committee members recommended that additional data could help to clarify the appropriate treatment duration in patients with genotype 1 infection who are nonresponders to a prior course of pegylated interferon and ribavirin while other members were in agreement that the extrapolation from the HCV genotype 1 treatment-naïve population with baseline factors predictive of lower responses to a pegylated interferon/ribavirin regimen supported sofosbuvir use in a treatment-experienced population based on the strength of the analysis results. On the strength of evidence for use of sofosbuvir in combination with ribavirin in patients with hepatocellular carcinoma patients meeting Milan criteria (awaiting liver transplantation), the committee expressed the need to have effective treatments for this patient population. There was concern as to whether the data involving subjects with relatively low MELD scores would be applicable to the broader pre-transplant population; that having undetectable HCV viral load prior to transplant appears to predict a more favorable outcome post-transplant; that more studies in the population with higher MELD scores could provide additional information to guide therapy in this difficult to treat population. In response to the question on postmarketing studies the committee recommended additional studies in different patient populations, studies in combination with other direct acting antiviral agents, studies evaluating longer term follow-up, and additional information on antiviral resistance.

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.

In summary, I agree with the review team, CDTL, and the Division Director, that the overall benefits and risks support the approval of NDA 204671 for Sovaldi (sofosbuvir) 400 mg tablets as a component of a combination antiviral treatment regimen for the treatment of chronic hepatitis C genotypes 1, 2, 3, 4 infection as described in the product labeling. The approval of sofosbuvir represents the first drug in a new class of antiviral drugs for the treatment of patients with chronic hepatitis C infection. 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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Director, Office of Antimicrobial Products
OND/CDER/FDA

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EDWARD M COX
12/06/2013