CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204671Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Sofosbuvir Risk Management Review

Date:	September 12, 2013
Reviewer(s):	Yasmin Choudhry, M.D., Medical Officer, Division of Risk Management (DRISK) Kendra Worthy, Pharm. D., Team Leader, DRISK
Division Director	Claudia Manzo, Pharm. D., DRISK
Drug Name(s):	Sofosbuvir Tablet 400 mg
Therapeutic Class:	Hepatitis C virus NS5B polymerase inhibitor
Indication(s):	Indicated in combination with ribavirin (RBV) for the treatment of chronic hepatitis C in adults with genotype 2 or 3 infection and in combination with pegylated (PEG) interferon and ribavirin in treatment-naïve adults with genotype 1 or 4 infection
Dose(s):	Sofosbuvir 400 mg tablet orally once a day
Subject:	To evaluate the need for a Risk Evaluation and Mitigation Strategy (REMS)
Application Type/Number:	NDA 204671 received April 8, 2013; Sequence 0000
Applicant/sponsor:	Gilead Sciences Inc.
OSE RCM #:	2013-876

1 INTRODUCTION

This review documents the Division of Risk Management (DRISK) evaluation of the New Drug Application (NDA) 204671 for sofobuvir (GS-7977) Tablets to assess the need for a Risk Evaluation and Mitigation Strategy (REMS).

The clinical reviewer in the Division of Antiviral Products (DAVP) is recommending approval[1] for NDA 204671 for the use of sofosbuvir in combination with ribavirin (RBV) in treatment-naive and treatment experienced subjects with genotype 2 or 3 hepatitis C virus (HCV) infection and sofosbuvir in combination with pegylated (PEG) interferon and RBV in treatment-naïve subjects with genotype 1 or 4 HCV infection.

2 MATERIALS REVIEWED

- Gilead's sofosbuvir NDA 204671 original application received April 8, 2013
- Gilead's Summary of Efficacy and Safety for sofosbuvir received April 8, 2013
- Clinical review by Poonam Mishra, M.D., dated September 6, 2013.

3 BACKGROUND

Sofosbuvir is a first in class, new molecular entity, pan-genotypic inhibitor of the Hepatitis C virus (HCV) NS5B RNA-dependent RNA polymerase, which is essential for viral replication.

The proposed indication for sofosbuvir is for use in combination with ribavirin for the treatment of chronic hepatitis C virus infection in adults with genotype 2 or 3 infection and in combination with PEG and RBV in treatment-naïve adults with genotype 1 or 4 infection. It is not indicated for monotherapy. The recommended dosage is 400 mg tablet once daily.

According to the sponsor[2], an estimated 3.2 million people have chronic HCV infection which leads to significant morbidity and mortality; approximately 10,000 deaths occur each year in the US, and 20% develop cirrhosis, end-stage liver disease, and hepatocellular carcinoma. Additionally, among the patients with HCV infection worldwide, an estimated 4-5 million people are co-infected with HIV which further leads to an increased rate of liver fibrosis progression and failure.

The currently available drugs for HCV infection are: PEG subcutaneous injection given once-weekly, and RBV oral tablets given as twice-daily.

The sponsor's rationale for developing sofosbuvir includes that the current treatment options for chronic HCV infection:

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[1] Clinical Review NDA 204671 Sofosbuvir by Poonam Mishra dated September 6, 2013.

[2] Summary of safety by Gilead Sciences Inc. dated April 8, 2013.

- offer limited efficacy
- are associated with significant toxicities; and
- are either given as subcutaneous injection, or orally on a more than once-daily regimen.

3.1 OVERVIEW OF CLINICAL PROGRAM

3.2 EFFICACY

Efficacy of sofosbuvir for the treatment of Hepatitis C was demonstrated in four pivotal Phase 3 studies (see below). The primary endpoint was sustained virologic response defined as HCV RNA < LLOQ (limit of quantitation) 12 weeks after the discontinuation of treatment or active therapy (SVR12).

- Study P7977-1231: A Multicenter, randomized, active-controlled study evaluated efficacy and safety of sofosbuvir + RBV for 12 weeks compared with PEG + RBV for 24 weeks in treatment naïve subjects with genotype 2 or 3 HCV infection.
- Study GS-US-334-0107: A multicenter, randomized, double-blind, placebo-controlled study evaluated efficacy and safety of sofosbuvir + RBV for 12 weeks versus placebo in subjects with genotype 2 or 3 HCV infection who were interferon intolerant/ineligible or unwilling to take interferon.
- Study GS-US-334-0108**:** A multicenter, randomized, double-blind study evaluated efficacy and safety of sofosbuvir + RBV for 12 or 16 weeks in treatment experienced subjects with genotype 2 or 3 HCV infection.
- Study GS-US-334-0110: An ongoing, multicenter, open-label study evaluated efficacy and safety of sofosbuvir + PEG + RBV treatment for 12 weeks in treatment naïve subjects with genotype 1, 4, 5, or 6 HCV infection.

3.3 SAFETY

The safety data was derived from 2885 subjects treated in the four pivotal Phase 3 clinical trials and 23 additional trials (Phase 1 & 2). The safety profile of sofosbuvir and RBV regimens was consistent with the known safety profile of RBV; the safety profile of PEG and RBV containing regimen was similar to the well documented adverse event profile of PEG and RBV containing regimens. Additionally, an exacerbation of the known toxicities or expected side effects associated with PEG use was not seen.

The incidence of serious adverse events was low. Malignant hepatic neoplasm (a known complication of cirrhosis in this patient population) was seen in 4 subjects (0.5%), and pyrexia and cellulites was seen in 2 subjects each (0.4%). Mild elevations of serum lipase, creatine kinase and bilirubin (consistent with hemolytic anemia with RBV therapy) were noted which did not raise significant concerns (clinical review). Additionally, no safety signals related to hepatotoxicity, bone marrow suppression, acute hypersensitivity reactions, cardiac or renal toxicity were identified. A total of four deaths were reported in sofosbuvir pivotal trials; none of these deaths were considered related to the study treatment.

The most frequently reported adverse events included fatigue, headache, insomnia and nausea.

The pediatric trials to assess safety and efficacy of sofosbuvir for the treatment of chronic hepatitis C in pediatric subjects will be required under Pediatric Research Equity Act (PREA).

4 RISK MANAGEMENT PROPOSED BY APPLICANT

The sponsor did not submit a risk management plan, REMS or a pharmacovigilance plan.

5 DISCUSSION

As of September 9, 2013, the preliminary recommended regulatory action for sofosbuvir by the clinical reviewer is approval. The clinical reviewer is not recommending a REMS at this time. Based on the clinical review of the available data, the benefits of sofosbuvir for the proposed indication outweigh the risks of sofosbuvir. Additionally, the safety profile of sofosbuvir did not raise concerns in regards to hepatic, cardiac or renal toxicity warranting measures beyond labeling.

Moreover, the risks associated with the currently available drugs for HCV infection (PEG and RBV) are managed via labeling only. An Antiviral Drugs Advisory Committee (AC) Meeting is scheduled for October 25, 2013. Based on the clinical review, we are not anticipating serious safety concerns from members of the AC at this time.

6 CONCLUSION

DAVP and DRISK agree that the risks associated with sofosbuvir can be managed at this time through labeling and routine pharmacovigilance and that a REMS for sofosbuvir is not necessary to ensure the benefits outweigh the risks.

Should DAVP raise further concerns (after the AC) regarding safety of sofosbuvir we will reevaluate our recommendation. DRISK will continue to follow this NDA.

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/s/

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09/12/2013

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09/13/2013
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