CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205834Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	July 18, 2014
Reviewer(s):	Bob Pratt, Pharm.D. Division of Risk Management
Acting Team Leader:	Jamie Wilkins-Parker, Pharm.D. Division of Risk Management
Acting Deputy Division Director:	Reema Mehta, Pharm.D., M.P.H. Division of Risk Management
Subject:	Evaluation to determine if a REMS is necessary
Drug Name(s):	Ledipasvir/Sofosbuvir Fixed Dose Combination, 90/400 mg
Therapeutic Class:	Hepatitis C virus NS5A inhibitor / Hepatitis C virus NS5B polymerase inhibitor
Dosage and Route:	One tablet taken orally once daily
Indication:	Treatment of chronic hepatitis C virus genotype-1 infection
Application Type/Number:	NDA 205834
Applicant/sponsor:	Gilead Sciences, Inc.
OSE RCM #:	2014-354

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity (NME) fixed dose combination of ledipasvir/sofosbuvir (LDV/SOF). On February 10, 2014, the Agency received an original New Drug Application (NDA) from Gilead Sciences for LDV/SOF for the treatment of chronic hepatitis C virus (HCV) genotype 1-infected patients. Ledipasvir is the NME component of the application. Sofosbuvir (Sovaldi®, NDA 204671) is approved for use in combination with other treatments for HCV and does not have a REMS. The applicant did not submit a proposed REMS or risk management plan for LDV/SOF.

1.1 DISEASE BACKGROUND[1-4]

Infection with the single-stranded RNA virus hepatitis C can result in both acute and chronic hepatitis. Approximately 20 to 30 percent of newly infected persons develop signs and symptoms of an acute illness, which can include fever, fatigue, loss of appetite, and other non-specific symptoms. Although the acute disease is usually self-limited, the immune response is mostly insufficient to eradicate the virus such that acute infection leads to chronic infection in 60 to 80 percent of cases. Chronic HCV infection is associated with ongoing liver inflammation and often follows a progressive course over years to decades, increasing the risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma.

HCV lacks a proofreading mechanism during replication that leads to frequent viral mutations and viral heterogeneity. At least seven distinct HCV genotypes and more than 60 subtypes have been identified, with varying geographic distribution. Genotype 1 (GT1) is the most common genotype in the United States, with genotypes 2 and 3 less common. The viral diversity and heterogeneity have prevented the development of a vaccine and also affect the completeness of response to antiviral therapy.

The goal of antiviral therapy in patients with chronic HCV is to see an absence of HCV RNA 12 or 24 weeks after the completion of treatment. This is defined as a sustained virologic response, which is associated with a very low risk of viral reactivation and reduced risk of disease progression. The type and duration of antiviral therapy selected is dependent on the viral genotype, the patient's baseline disease and host factors, the patient's prior treatment experience and response, and other factors.

HCV has been treated with combinations of indirect acting antivirals and direct acting antivirals. The indirect acting agents typically used include interferon alfa and ribavirin, which have broad antiviral activity but are associated with many toxicities and modest efficacy against HCV GT1. Direct acting antivirals are designed to target specific non-structural HCV proteins. Some agents inhibit the NS3/4A serine protease, which cleaves the HCV polyprotein into several polypeptides with distinct functions. Other direct acting antivirals target the NS5A protein necessary for viral assembly and replication, or inhibit the NS5B RNA-dependent RNA polymerase responsible for replication of HCV RNA.

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[1] Chopra S. Clinical manifestations and natural history of chronic hepatitis C virus infection. In:UpToDate, Di Bisceglie AM and Bloom A (Eds), UpToDate, Waltham, MA, 2014.
[2] Chopra S. Characteristics of the hepatitis C virus. In:UpToDate, Edward MS, Di Bisceglie AM, and Bloom A (Eds), UpToDate, Waltham, MA 2014.
[3] Feeney ER and Chung RT. Antiviral treatment of hepatitis C. BMJ 2014; 349:g3308.
[4] Liang TJ and Ghany MG. Current and future therapies for hepatitis C virus infection. NEJM 2013; 368:1907-17.

1.2 PRODUCT BACKGROUND

Ledipasvir is a novel HCV NS5A inhibitor that has demonstrated potent anti-HCV activity against genotype 1a and 1b HCV infection. Sofosbuvir is a nucleotide NS5B polymerase inhibitor that inhibits HCV RNA replication and has been approved for use in combination with other agents for the treatment of chronic HCV infection in adults. The recommended dosage is one tablet once daily for 12 weeks (without cirrhosis). For patients, with cirrhosis, the treatment duration is 24 weeks.

1.3 REGULATORY HISTORY

On February 10, 2014, the Agency received an original New Drug Application (NDA) from Gilead Sciences for LDV/SOF for the treatment of chronic hepatitis C virus genotype 1-infected patients. The Applicant previously received Breakthrough Therapy designation for the treatment on July 22, 2013. The review classification for the application is Priority. The Applicant did not submit a proposed REMS.

2 MATERIALS REVIEWED

- July 3, 2013, Division of Antiviral Products (DAVP) Breakthrough Therapy Designation Request Memorandum, IND 115268
- February 10, 2014, Original NDA 205834 submission
    - Section 2.5, Clinical Overview
- May 8, 2014, slides from NDA 205834 Mid-Cycle Meeting
- June 3, 2014, Mid-Cycle Communication Meeting Minutes
- July 10, 2014, DAVP Clinical Review NDA 205834, Sarah Connelly, M.D.
- July 11, 2014, Draft Prescribing Information LDV/SOF

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

The Applicant completed three phase 3, randomized, open-label clinical trials (ION-1, ION-2, ION-3) of LDV/SOF in patients with chronic HCV GT1 infection in support of the proposed indication. The primary efficacy endpoint was sustained virologic response (SVR) 12 weeks after discontinuation of treatment. Pre-specified historical control rates were used to determine comparative statistical significance.

- In ION-1, the efficacy and safety of LDV/SOF with or without ribavirin for 12 to 24 weeks was evaluated in 865 treatment naïve patients, including those with cirrhosis. Patients in each of the 12-week treatment groups achieved SVR (99% LDV/SOF; 97% LDV/SOF plus ribavirin) compared to a pre-specified historical control rate of 60% ($p<0.001$). Relapse rates were 0.5% in the LDV/SOF arm and 0% in the LDV/SOF plus ribavirin arm.
- The ION-2 study compared LDV/SOF with or without ribavirin for 12 to 24 weeks in 440 patients who had failed prior therapy with an interferon-based regimen of which 53% included an HCV protease inhibitor. Patients in each of the four treatment groups achieved SVR (94% LDV/SOF 12-week; 96% LDV/SOF plus ribavirin 12-week; 99% LDV/SOF 24-week; 99% LDV/SOF plus ribavirin 24-week) compared to a pre-specified historical control rate of 25% ($p<0.001$). Relapse rates were 6.5% in the LDV/SOF 12-week arm, 3.6% in the

LDV/SOF plus ribavirin 12-week arm and 0% in each of the LDV/SOF plus ribavirin 24-week arms.

- ION-3 evaluated 8 weeks of treatment with LDV/SOF with or without ribavirin, and 12 weeks of treatment with LDV/SOF in 647 treatment naïve non-cirrhotic patients. Patients in each treatment group achieved SVR12 (94% LDV/SOF 8-week; 93% LDV/SOF plus ribavirin 8-week; 96% LDV/SOF 12-week) compared to a pre-specified historical control rate of 60% ($p<0.001$). Relapse rates were 5.1% in the LDV/SOF 8-week arm, 4.2% in the LDV/SOF plus ribavirin 8-week arm, and 1.4% in the LDV/SOF 24-week arm.

In summary, ION-1 demonstrated the efficacy of LDV/SOF with or without ribavirin for 12 weeks in treatment naïve patients (including patients with cirrhosis) and ION-2 demonstrated the efficacy of those regimens for 12 or 24 weeks in treatment-experienced patients. ION-3 demonstrated the efficacy of LDV/SOF with or without ribavirin for 8 weeks and LDV/SOF for 12 weeks in treatment naïve patients without cirrhosis.

3.2 SAFETY CONCERNS

For the purpose of this review, serious adverse events associated with LDV/SOF are defined by the regulatory definition of a serious outcome, such as death, a life-threatening reaction, or hospitalization (among other outcomes). Severe adverse events associated with LDV/SOF are defined as Grade 3-4 using the Applicant's Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities.

3.2.1 Serious Adverse Events

Nonfatal serious adverse events (SAEs) of any nature were reported in 51/1952 patients (2.6%) in the pooled phase 3 safety population. No trends were identified, as each SAE occurred in only one or two patients in any given treatment group. The LDV/SOF 24-week group had a higher SAE rate (7.4%) compared with the other LDV/SOF groups (1.9% and 1.1% in the 8-week and 12-week groups, respectively) but the majority of these events occurred during the first 12 weeks of treatment.

One death occurred in the post-treatment period in the ION-1 trial, but was considered not related to study treatment by the investigator. The case involved fatal hepatic failure on post-treatment day 121 in a 63 year-old patient with a history of alcoholism, alcoholic liver disease, and ascites, among other conditions. The DAVP clinical reviewer agreed with the investigator that the events were unlikely related to treatment. Nine other fatal cases have occurred in ongoing studies of LDV/SOF plus ribavirin; one patient died of a cardiac arrest in a foreign trial, and eight patients died in a study of patients who have received liver transplants or have advanced liver disease. The DAVP clinical reviewer noted there was no clustering of events in these fatal outcome cases, and the decompensated liver disease/post-transplant population has known associated comorbidities and is overall a sicker population.

3.2.2 Severe adverse events

The most frequently reported Grade ≥ 3 adverse events (AEs) were fatigue (0.7%), headache (0.6%), and anemia (0.3%). All Grade 3 AEs of anemia occurred in patients in treatment groups receiving ribavirin. Grade 4 AEs were reported in four patients and included events related to a traffic accident; unstable angina; an anaphylactic reaction on post-treatment Day 9; and hypoglycemia. All Grade 4 AEs were considered unrelated to study treatment by the investigator. These assessments seemed reasonable to the clinical reviewer.

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