CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208261Orig1s000

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

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	January 22, 2016
Reviewer(s):	Jasminder Kumar, Pharm.D., Division of Risk Management (DRISK)
Acting Team Leader:	Jamie Wilkins Parker, Pharm.D., DRISK
Acting Deputy Director:	Kellie Taylor, Pharm.D., M.P.H.
Subject:	Review evaluates if a REMS is needed for grazoprevir/elbasvir
Drug Name:	grazoprevir 100 mg/elbasvir 50 mg), fixed dose combination (FDC)
Therapeutic Class:	Hepatitis C virus (HCV) NS5A inhibitor (elbasvir), and HCV NS3/4A protease inhibitor (grazoprevir)
Dosage form and route:	Oral tablet
Application Type/Number:	NDA 208261
Applicant/Sponsor:	Merck Sharp and Dohme Corp.
OSE RCM #:	2015-1194

*** This document contains proprietary and confidential information that should not be released to the public. ***

CONTENTS

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) elbasvir/grazoprevir (EBR/GZR) is necessary to ensure the benefits of this product outweigh its risks. Merck Sharp and Dohme Corp. submitted a New Drug Application (NDA 208261) to the Division of Antiviral Products (DVAP) on May 28, 2015. The proposed indication for the fixed dose combination (FDC) of EBR/GZR is for treatment of chronic hepatitis C (CHC) genotypes 1, 4, or 6 infection in adults. The Applicant did not submit a REMS or risk management plan with this application.

2 BACKGROUND

2.1 PRODUCT INFORMATION

The proposed indication for EBR/GZR is for treatment of CHC genotype 1, 4, (b) (4) infection in adults. EBR/GZR is a fixed dose combination product that combines two direct-acting antiviral agents with distinct mechanisms of action and non-overlapping resistance profiles to target hepatitis C virus (HCV) at multiple steps in the viral lifecycle. Elbasvir is an HCV NS5A inhibitor which is essential for viral RNA replication and virion assembly. Grazoprevir is an inhibitor of the HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4B, NS5A, and NS5B proteins and essential for viral replication. EBR/GZR will be available as an oral FDC tablet containing 50 mg elbasvir and 100 mg grazoprevir. The proposed dosing regimen is one tablet taken orally once daily with or without food. Proposed labeling for Genotype 1a, 4, (b) (4) patients who are treatment experienced on treatment virologic failures recommends use of EBR/GZR with ribavirin (RBV). The table below shows the proposed dosage recommendations and durations in patients with or without cirrhosis, per the proposed labeling at the time of the original NDA submission:

Table 1: Proposed Dosage Regimens and Durations for EBR/GZR

Patient Population	Treatment Regimen	Duration
Treatment-naïve or treatment-experienced* relapsers		
Genotype 1, 4, (b) (4)	EBR/GZR	12 weeks (b) (4) (b) (4) (b) (4)
Treatment-experienced*		
Genotype 1b†	EBR/GZR	12 weeks
Genotype 1a, 4, (b) (4)	EBR/GZR with ribavirin¶, #	16 weeks

*Patients who have failed treatment with either peginterferon alfa+ribavirin or peginterferon alfa+ribavirin+boceprevir, simeprevir, or telaprevir

(b) (4)

(b) (4)

¶In clinical trials, the dose of ribavirin was weight-based administered in two divided doses with food. Refer to prescribing information for further details on dosing and dose modifications

(b) (4)

EBR/GZR is contraindicated in patients with severe hepatic impairment. No dose adjustment is recommended in patients with mild, moderate, or severe renal impairment. In patients with severe renal impairment or with end stage renal disease (ESRD), including patients on dialysis, administer EBR/GZR without ribavirin.

Proposed labeling includes a recommendation for baseline NS5A resistance testing in HCV genotype 1a infected patients, due to lower SVR12 rates in patients with one or more baselineNS5A resistance associated polymorphisms at amino acid positions 28, 30, 31, or 93.

2.2 DISEASE BACKGROUND

Hepatitis C is an infection of the liver that results from the HCV, a blood-borne virus. In some, hepatitis C is a short-term illness, but 70%–85% of people who have become infected have a long-term, chronic infection. Chronic HCV infection often follows a progressive course over many years and can result in cirrhosis, hepatocellular carcinoma, the need for liver transplantation, and even death. Chronic HCV infection is the leading indication for liver transplants in the United States (U.S.). An estimated 3-4 million persons in the United States have chronic HCV infection, with half unaware of their status.[1] Today, most people become infected with HCV by sharing needles or other equipment to inject drugs.

There are at least six distinct HCV genotypes (genotypes 1–6) and more than 50 subtypes have been identified. Genotype 1(mostly subtype 1a versus 1b) is the most common HCV genotype in the United States, followed by genotypes 2, 3, 4, 5, and 6, with genotypes 5 and 6 occurring uncommonly in the U.S. but may be more predominant in other parts of the world.[2] Genotype 1 subtypes are regionally very different. In the US, genotype 1a is more prevalent where it accounts for roughly 70% of genotype 1 infections.[3]

In addition, HCV is highly prevalent in patients with chronic kidney disease (CKD) undergoing hemodialysis and kidney transplantation recipients. It is an important cause of morbidity and mortality in these patients. HCV infection has been associated with both liver disease-related deaths and cardiovascular mortality in hemodialysis patients. Left untreated, HCV infection can lead to progressive hepatic dysfunction while also accelerating the deterioration of renal function. Furthermore, chronic HCV infection can limit eligibility for kidney transplant and compromise graft survival in those who do undergo renal transplant. The prevalence rate of HCV among patients undergoing hemodialysis within a U.S. hemodialysis network has been reported as 7.8% (range: 5.5 – 9.8%), and it is estimated that over 60,000 HCV-infected patients will

---

[1] American Associate for the Study of Liver Diseases/Infectious Disease Society of America/International Antivieral Society- USA (AASLD/IDSA/IAS–USA). HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. http://www hcvguidelines.org. Date accessed 13 November 2015.

[2] Gower E, Estes C, Blach, S, Razavi-Shearer K, Razavi H. Globalepidemiology and genotype distribution of hepatitis C infection. Journal of Hepatology. 2014; 61:S45-S57.

[3] News-Medical.Net. Interferon-free treatment for genotype-1b hepatitis C patients: an interview with Professor Wulf Boecher, Boehringer Ingelheim. http://www news-medical net/news/20130730/Interferon-free-treatment-for-genotype-1b-hepatitis-C-patients-an-interview-with-Professor-Wulf-Boecher-Boehringer-Ingelheim.aspx . Date accessed 27 December 2015.

require hemodialysis by 2020.[4] Compared to non-HCV-infected CKD Stage 4 or 5 patients (eGFR < 30 mL/min/1.7 m^2), HCV-infected CKD Stage 4 or 5 patients have poor graft survival and higher overall mortality outcomes following renal transplantation.[5]

The goal of treatment is to eradicate HCV RNA, which is predicted by the achievement of a sustained virologic response (SVR), defined by the absence of HCV RNA by polymerase chain reaction 12 to 24 weeks after stopping treatment. An SVR is associated with a 99% chance of being HCV RNA negative during long-term follow-up and can be considered cure of the HCV infection.

The type and duration of antiviral therapy selected is dependent on the virus 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 as well as variable efficacy against the different HCV genotypes. 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.

Until recently, the treatment for chronic HCV infection has been pegylated interferon and ribavirin (PR), with possible addition of boceprevir (Victrelis™) and telaprevir (Incivek™) (both protease inhibitors) for HCV genotype 1 infection. After given for 24-48 weeks, this treatment resulted in a SVR, defined as undetectable HCV RNA in the patient's blood 24 weeks after the end of treatment in 50%–80% of patients (with higher SVR among persons with HCV genotypes 2 or 3 infections versus infections with HCV genotype 1). More recently, approval of new direct acting antiviral medications, sofosbuvir (Sovaldi) and simeprevir (Olysio) provided new treatment options with improved efficacy. Trials have shown that these medications achieve SVR in 80-95% of patients after 12-24 weeks of treatment.[6,7] In addition, in October 2014, the FDA approved the first combination pill to treat HCV, ledippasvir/sofosbuvir (Harvoni), which offers people with HCV genotype 1 an all-oral treatment regimen with a SVR of 94% after 12 weeks. The FDA approved another combination medication for genotype 1 in December of 2014, Ombitasvir/paritaprevir/ritonavir tablets; dasabuvir tablets (Viekira Pak), with a SVR of 97%. Currently, there are no interferon-free treatment options for HCV genotype 1, 4, (b) (4) in patients receiving hemodialysis.

2.3 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 208261 relevant to this review:

[4] Finelli L, Miller JT, Tokars JI, Alter MJ, Arduino MJ. National Surveillance of Dialysis-Associated Diseases in the United States, 2002. Seminars in Dialysis. 2005;18(1):52-61.

[5] Terrault NA, Adey DB. The kidney transplantation recipient with hepatitis C infection: pre- and post transplantation treatment. Clin J Soc Nephrol. 2007;2:563-557.

[6] Sovaldi® (sofosburvir). [Prescribing information]. Gilead Sciences, Inc. Foster City, CA. August 2015.

[7] Olysio® (simeprevir). [Prescribing information]. Janssen Products, LP. Titusville, NJ. October 2015.

- March 1, 2012: The Agency notified the Sponsor via teleconference that IND 110261 was placed on partial clinical hold because human subjects would be exposed to an unreasonable and significant risk of illness or injury and there was insufficient information to assess risks to human subjects based on the observed dose-related increases in transaminase levels seen in clinical trial PN003.
- March 20, 2012: The Agency sent the Sponsor a Partial Clinical Hold letter outlining specific deficiencies and the information needed to resolve the deficiencies.
- July 25, 2012: The Sponsor submitted Complete Response to the Partial Clinical Hold.
- August 24, 2012: The Agency released the partial clinical hold and concluded that the Sponsor could proceed with proposed studies, provided that daily grazoprevir dose of 100 mg was not exceeded. The Agency recommended specific subject discontinuation criteria based on ALT/AST elevations.
- October 18, 2013: The Sponsor was granted breakthrough therapy designation for EBR/GZR for the treatment of chronic HCV GT1 infection.
- January 30, 2015: The Agency rescinded breakthrough therapy designation for EBR/GZR for the treatment of chronic HCV in GT1 infection based on the recent approval of treatment regimens (Harvoni and Viekira Pak) demonstrating SVR_{12} rates of 94-100% with overall favorable safety profiles.
- April 1, 2015: The Agency granted breakthrough therapy designation for the treatment of chronic HCV GT1 infection in patients with end stage renal disease on hemodialysis, and for the treatment of patients with chronic HCV GT4 infection.
- May 28, 2015: The Agency received a NDA (NDA 208261) submission from Merck Sharp & Dohme Corp. The Sponsor did not submit a proposed REMS.
- July 27, 2015*:* The Agency determined the review classification for this application is Priority.
- September 10, 2015: A Mid-Cycle meeting was held between the Agency and the Sponsor via teleconference. The Agency informed the Sponsor that based on the currently available data a REMS was not needed for EBR/GZR.
- November 19, 2015: A Late-Cycle meeting was held between the Agency and the Sponsor via teleconference. The Agency informed the Sponsor that no issues related to risk management have been identified to date.

3 MATERIALS REVIEWED

The following is a list of materials that informed our review:

- Merck Sharp & Dohme Corp. Summary of Clinical Safety for EBR/GZR, received May 28, 2015.
- Merck Sharp & Dohme Corp. Summary of Clinical Efficacy for EBR/GZR, received May 28, 2015.
- Merck Sharp & Dohme Corp. Clinical Overview for EBR/GZR, received May 28, 2015.

- Merck Sharp & Dohme Corp. Hepatic Safety Evaluation for EBR/GZR (eCTD Sequence 0021), received July 27, 2015.
- Merck Sharp & Dohme Corp. Proposed Prescribing Information for EBR/GZR, received May 28, 2015, updated September 3, 2015.
- Boyd S, Viswanathan P. DAVP. Clinical Review for EBR/GRZ, NDA 208261, dated October 28, 2015.

4 REVIEW FINDINGS FOR EBR/GZR

4.1 Overview of Clinical Program and Efficacy

The efficacy of EBR/GZR was evaluated in five clinical trials consisting of three Phase 3 trials (Study 060 C-EDGE TN, Study 061 C-EDGE COINFECTION, and Study 068 C-EDGE TE), one Phase 2 trial (Study 048 C-SALVAGE), and one Phase 2/3 trial (Study 052 C-SURFER), with a total of 1155 HCV patients with genotype 1, 4, or 6 infection with compensated liver disease (with and without cirrhosis) across all trials. In addition, EBR/GZR was studied in a number of supportive Phase 2 studies. However, these studies were not included in the efficacy analysis due to different doses, different regimens, or shorter durations of study drug received. These supportive Phase 2 studies were included in the safety analysis, further described in section 4.2.

The primary endpoint for all trials was the proportion of patients achieving sustained virologic response 12 weeks after the end of all study therapy (SVR_{12}), defined as HCV RNA < lower limit of quantification (LLOQ) at 12 weeks after treatment. Additional efficacy endpoints included the proportion of patients achieving undetectable (TND) HCV RNA, HCV RNA <LLOQ at various on-treatment time points, and patient reported outcomes (PRO).

C-EDGE TN (Study 060) is a randomized, placebo-controlled, double-blind trial that evaluated EBR/GZR in treatment naïve (TN), HCV genotype 1, 4, or 6 infected patients with or without cirrhosis. HIV co-infected patients were excluded. Patients received either EBR/GZR (immediate treatment group ([ITG], N=316) or placebo (deferred treatment group [DTG], N=105) for 12 weeks. The DTG received EBR/GZR for 12 weeks following the unblinding period. 94.6% of patients in the ITG group achieved SVR_{12}. (b) (4)

(b) (4)

C-EDGE COINFECTION (Study 061) (N=218) is an open-label clinical trial that evaluated EBR/GZR in TN HCV genotype 1, 4, or 6 patients co-infected with HIV, with or without cirrhosis, for 12 weeks. 95% of patients achieved SVR_{12}. (b) (4)

(b) (4)

C-EDGE TE (Study 068) (N=420) is a randomized, parallel-group, open label trial evaluating EBR/GZR with or without ribavirin (RBV) for 12 or 16 weeks among patients with or without cirrhosis, with HCV genotype 1, 4, or 6 infection who experienced virologic failures after prior treatment with pegylated interferon alfa and ribavirin (PR), with or without HIV. The overall

SVR_{12} rate was 92.4%, 94.2%, 92.4%, and 97.2% among the 4 arms EBR/GZR for 12 weeks, EBR/GZR +RBV for 12 weeks, EBR/GZR for 16 weeks, and EBR/GZR +RBV for 16 weeks, respectively. In addition to achieving the highest SVR_{12} rates, the 16 week regimen of EBR/GZR +RBV had no virologic failures. (b) (4) In prior relapsing patients, the 12 week regimen without RBV was highly effective across genotypes, and in all genotype 1b patients, regardless of prior treatment relapse. However, among genotype 1a, 4, or 6, null or partial responders to prior PR treatment, the highest response was achieved with the 16 week +RBV regimen.

C-SALVAGE (Study 048) (N=79) is an open-label, single arm study that evaluated patients with HCV genotype 1 who failed a prior approved direct activing antiviral (DAA) regimen of boceprevir, telaprevir, or simeprevir taken concomitantly with PR. Patients received EBR/GZR +RBV for 12 weeks. Overall, 96.2% of patients achieved SVR_{12}, with only 3 patients experiencing virologic failure.

C-SURFER (Study 052) (N=122) is a randomized, parallel-group, placebo controlled trial of EBR/GZR administered for 12 weeks without RBV, among HCV genotype 1 infected patients with chronic kidney disease (CKD) Stages 4 or 5, with or without cirrhosis, and either TN or had failed prior HCV therapy. RBV was not included because it is contraindicated in patients with advanced CKD. There were 111 patients in the ITG who received EBR/GRZ daily for 12 weeks, 113 patients in the DTG that received placebo during the initial 12 week treatment period and then study drug after the unblinding period, and 11 patients in an open label intensive PK arm (receiving the same treatment as the ITG). Although the Applicant believed that the modified Full Analysis set (mFAS) was appropriate to use given cardiovascular events that may lead to death/withdrawal from the study and remove potential confounders, the Agency believes the Full Analysis set (FAS) was more appropriate and was thus used for Agency's analysis. As a result, 94% of patients in the FAS achieved SVR_{12}, supporting use in subjects with CKD Stages 4/5.

4.2 SAFETY CONCERNS

The overall safety database includes a total of 4143 patients (1439 patients in Phase 1 studies and 2704 patients in Phase 2-3 trials. In addition to the clinical trials discussed in section 4.1, the safety and efficacy of EBR/GZR were also evaluated in number of additional Phase 2 trials: Study 047 C-SCAPE Part B, Study 003, Study 035 C-WORTHY Part A, Study 035 C-WORTHY Part B, Study 035 C-WORTHY Part C, Study 038, Study 029, Study 058 Part A, and Study 059 Part A. These early Phase 2 studies helped to define the dose of GZR and the regimen and populations that were subsequently evaluated in the later Phase 2 and 3 studies. Although these studies are not included in the pooled analysis of efficacy, they are included in the pooled analysis of safety.

Data from these ongoing or completed clinical trials were included in the integrated safety analyses. For a comprehensive safety evaluation, data from the 120 Day Safety Update Report, submitted on July 27, 2015, was also evaluated.

Safety analysis of C-SURFER was not pooled with any trial because patients with underlying CKD Stage 4/5 display a different patient population, with possible different safety concerns.

Common Adverse Events

The most commonly reported adverse reactions (≥10%) in patients taking EBR/GZR for 12 weeks were fatigue and headache. The most commonly reported adverse reactions (≥10%) in patients taking EBR/GRZ with RBV for 16 weeks were fatigue, headache, anemia, and nausea. The majority of patients who received EBR/GZR with or without RBV had one or more AEs, but AEs were less frequent among patients who received EBR/GZR without RBV. Of note, anemia and nausea are known, labeled adverse events associated with RBV. Overall, AEs did not differ among subjects in the 8-, 12-, or 16- week regimens, but were slightly higher in patients that received 18 weeks of treatment.

4.2.1 Serious Adverse Events (SAEs)

In the phase 3 clinical trials, there were 2 treatment-emergent deaths and one death after early treatment discontinuation. There were no deaths in the placebo group. All deaths were considered unlikely to be related to the study drug by the investigator and the clinical reviewer agreed with this conclusion. In the supportive trials, there were was one death during post-treatment follow up and one death after early treatment discontinuation. The investigator ruled these deaths not related to study drug. However, the clinical reviewer felt that one death in Study 059, a study that evaluated patients with Child-Pugh B with or without cirrhosis, which was a result of hepatic failure was difficult to determine whether the event was solely due to the patient's underlying hepatic disease or if study drug contributed. The clinical reviewer notes that although the proposed indication, at the time of the review, is not extended to patients with Child-Pugh B cirrhosis and the death in Study 059 does not impact approvability, it is recommended that EBR/GZR not be used in patients with moderate hepatic impairment (Child-Pugh B). A contraindication may be warranted. [8]

In C-SURFER, there were 5 deaths, all ruled unrelated to study drug by the investigator. The clinical reviewer agreed with this conclusion for all deaths except one, which was determined that the possibility of a medication-related event could not be excluded.

The 120-day safety update also contained two additional deaths in ongoing clinical trials, one of which was in the placebo group. The second death occurred as a result of a suicide, but is of interest because it occurred on treatment without any known confounding factors. However, the clinical reviewer notes that it is difficult to assess causality without any further information which may not be available. Two additional deaths in C-SURFER were reported in the 120 Day safety update report ruled unrelated to study drug by the investigator and agreed upon with, by the clinical reviewer.

SAEs occurred at the same rate for placebo and EBR/GZR treated patients (3%) in C-EDGE TN. In C-EDGE COINFECTION, 1% of subjects receiving EBR/GZR experienced SAEs. Similar rates of SAEs occurred in C-EDGE TE across all groups (3-4%). In C-SALVAGE, 5% of patients experienced an SAE, none of which were related to study drug. In C-SURFER, adverse events occurred more frequently compared to the other Phase 2 and Phase 3 studies, due to multiple co-morbid conditions. In C-SURFER, SAEs occurred in 23% of patients

[8] Boyd S, Viswanathan P. DAVP. Clinical Review for EBR/GRZ, NDA 208261, dated October 28, 2015.

4.2.2 Severe Adverse Events

Severe adverse events occurred in a similarly low rate across studies C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE and C-SALVAGE, ranging from 1-6% of patients experiencing severe AEs, but more frequently in C-SURFER. Overall, the discontinuation rate was also low for patients discontinuing due to an AE. In C-EDGE TN, two patients discontinued due to ALT/AST elevations, as required by protocol and one discontinued due to anxiety and palpitations. There were no discontinuations in C-EDGE COINFECTION. In C-EDGE TE, there were higher rates of discontinuations in patients in the 6 week with RBV arm compared to the other arms (5% vs. 0-1%, respectively). In C-SALVAGE, only one patient discontinued due to dehydration not related to study drug. In C-SURFER, discontinuations were low, with none in the ITG and 5 (4%) in the DTG.

4.2.3 Adverse Events of Special Interest (AESIs)

4.2.3.1 Hepatobiliary Adverse Events

A signal of elevated ALT/AST was noted in the first phase 2 dose-ranging study and therefore, intensive safety monitoring and analysis were conducted. A strong correlation between GZR exposure and the risk of experiencing late ALT/AST elevation events was seen. More specifically, the safety events consisted of ALT elevations >5x upper limit of normal (ULN) with or without concomitant AST elevation >5x ULN.

As a result, discontinuation criteria were also incorporated into Phase 2 and 3 protocols. The hepatic safety population analyzed by the clinical reviewer consisted of 1558 patients (trials 003, 038, 03, 058A, 059A, and 074 were not included). Results showed that treatment with EBR/GZR resulted in a low, but increased incidence of hepatic abnormalities, including late ALT/AST >5x ULN, compared to placebo. No patients in the placebo group experienced elevations in liver enzymes >5x ULN. The event was infrequent with 18 patients who received the proposed dose of GZR 100 mg experiencing a hepatic lab abnormality or event, and 12 patients (0.8%) experiencing late ALT/AST elevations. The events occurred in a dose-related manner and represents approximately 1% of subjects. Most events were first noted at or after treatment week 8 with the majority at or before treatment week 10, which varies from other HCV PIs, in which ALT elevations typically occur within the first 4 weeks of treatment. All events of late ALT/AST elevations completely resolved. The safety update report also revealed two additional patients who experienced late ALT/AST elevation, both of which experienced complete resolution. Additionally, in C-SURFER, there no subjects that experienced late ALT or AST elevations. The clinical reviewer notes that the late ALT elevation event is well characterized in Phase 2 and 3 studies, have not lead to any deaths, and appears manageable with adequate monitoring.[9]

A Hepatic Safety Committee also independently reviewed the events. They concluded there was a low level of concern regarding hepatic safety findings with EBR/GZR administered at doses of 100mg/50mg. The committee determined it was a well-defined pattern and not associated with hepatic dysfunction. In addition, the frequency of late ALT/AST elevations was directly proportional to the magnitude of GZR exposure. Increases GZR exposure and predicted late

[9] Boyd S, Viswanathan P. DAVP. Clinical Review for EBR/GRZ, NDA 208261, dated October 28, 2015.

ALT/AST elevations are seen in patients with: co-administration of GZR with certain medications (boosted HIV protease inhibitors, cyclosporine) and presence of Child-Pugh C hepatic dysfunction. The committee did recommend that more specific recommendations regarding monitoring should be provided.

5 DISCUSSION

Based on results of the Phase 2-3 trials, EBR/GZR was found to be efficacious for the treatment CHC genotypes 1 or 4 infection in adults. (b) (4)

(b) (4)

The most important safety concern associated with EBR/GZR is hepatobiliary events, due to ALT elevations with or without AST elevations. EBR/GZR appears to be associated with late ALT elevations >5x ULN with or without concomitant AST elevation >5x ULN. Late ALT elevations were more frequently seen, compared to AST elevations. However, these all events resulted in resolution of the event, and there have been no hepatic AE that resulted in death. Although there were cases of elevated liver enzymes, the observed safety profile was consistent with the other HCV PIs, with the exception of the time to onset of the events (within the first 4 weeks compared to at or after treatment week 8, for EBR/GZR).

The most likely prescribers of EBR/GZR are specialists who are familiar with the management of HCV, frequently monitor patients including their hepatic function panel, and understand the risks of treatment, specifically the risk of ALT elevations, as seen with other HCV PIs. In addition, this FDC tablet of EBR/GZR offers an alternative treatment option for patients with HCV. Specifically, patients with CKD Stage 4/5 will have a treatment option if approved, as there are no currently approved interferon-free treatment options for HCV genotype 1 or 4, in patients receiving hemodialysis. Furthermore, the proposed Warnings and Precautions section of the labeling for EBZ/GZR will include the risk of ALT elevations with specific recommendations for monitoring. There is no proposed Boxed Warning. The inclusion of the Warning and Precautions labeling recommendations for EBR/GZR are consistent with the current standards of medical care and consistent with treatment guideline monitoring recommendations.[10] Therefore, a REMS is not warranted at this time to ensure the benefits of this drug outweigh its risks.

6 CONCLUSION AND RECOMMENDATIONS

The serious risk of ALT elevations will be included in the Warnings and Precautions section of the proposed labeling. Based on the currently available data, the benefit-risk profile for EBR/GZR is acceptable for the treatment of CHC genotypes 1 or 4 infection in adults, including, for the first time, those with Stage 4 or 5 CKD (including hemodialysis patients). In conclusion, based on the available data, a REMS is not necessary to ensure that benefits of EBR/GZR outweigh the risks of ALT elevations.

[10] American Associate for the Study of Liver Diseases/Infectious Disease Society of America/International Antiviral Society- USA (AASLD/IDSA/IAS–USA). HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. http://www hcvguidelines.org. Date accessed 13 November 2015.

If new safety information becomes available, please consult DRISK, and the need for a REMS can be evaluated.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JASMINDER N KUMAR
01/22/2016

CYNTHIA L LACIVITA
01/23/2016
Concur