CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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:	October 14, 2014
Reviewer(s):	Felicia Duffy, RN, BSN, MSEd 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):	Viekira Pak
	Ombitasvir, Paritaprevir, and Ritonavir Tablets (12.5 mg/75 mg/50 mg); Copackaged with Dasabuvir Tablets (250 mg)
Therapeutic Class:	NS5A inhibitor, NS3/4 protease inhibitor, and NS5B polymerase inhibitor
Dosage and Route:	Two ombitasvir, paritaprevir, ritonavir tablets once daily by mouth and one dasabuvir tablet twice daily by mouth
Indication:	Treatment of chronic hepatitis C virus genotype-1 infection
Application Type/Number:	NDA 206619
Applicant/sponsor:	AbbVie, Inc.
OSE RCM #:	2014-823

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 ombitasvir, paritaprevir, and ritonavir copackaged with dasabuvir (Viekira Pak). On April 21, 2014, the Agency received an original NDA from AbbVie Inc. (AbbVie) for Viekira Pak for the treatment of chronic hepatitis C virus (HCV) genotype 1-(GT1) infected patients, including patients with cirrhosis. Ombitasvir, paritaprevir, and dasabuvir are the NME components of the application. Ritonavir (Norvir®, NDA 022417) is approved for use in combination with other antiretroviral agents and does not have a REMS. The Applicant did not submit a proposed REMS or risk management plan for Viekira Pak.

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 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

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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.

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.

1.2 PRODUCT BACKGROUND

Paritaprevir is a nonstructural protein [NS] 3/4A protease inhibitor that is essential for viral replication. Ombitasvir is an inhibitor of NS5A, which is another protease essential for viral replication. Dasabuvir is a non-nucleoside inhibitor of HCV RNA-dependent polymerase encoded by the NS5B gene. Ritonavir has no antiviral activity against HCV and is used as a pharmacokinetic enhancer to increase the bioavailability and half-life of paritaprevir[5]. Together, they target and disrupt multiple stages of the HCV life cycle.

The recommended dosage is two tablets of ombitasvir/paritaprevir/ritonavir once daily in the morning, and one tablet of dasabuvir twice daily (morning and evening). The duration of therapy and the addition of ribavirin (RBV) are dependent on the patient population (see Table 1 *Data Source: Draft Package Insert*). Note: the labeling discussions are still underway, and the duration of treatment as proposed by the Applicant is subject to change.

Viekira Pak will be packaged and dispensed in a monthly carton. Each monthly carton contains four weekly cartons. Each weekly carton contains seven daily dose packs. Each dose pack contains four tablets: two ombitasvir/paritaprevir/ritonavir tablets and two dasabuvir tablets, and indicates which tablets need to be taken in the morning and evening so that compliance with the regimen is easier for patients.

Table 1

Treatment Regimen and Duration by Patient Population

Patient Population	Treatment	Duration
Genotype 1b, without cirrhosis	VIEKIRA PAK	12 weeks
Genotype 1a, without cirrhosis	VIEKIRA PAK + ribavirin*	12 weeks
		(b) (4)

[5] AbbVie. Clinical Overview. April 21, 2014.

1.3 REGULATORY HISTORY

On April 21, 2014, the Agency received an original NDA from AbbVie for Viekira Pak for the treatment of GT1 chronic HCV infection, including patients with compensated cirrhosis. The review classification for the application is Priority. The Applicant did not submit a proposed REMS.

The mid-cycle communication with the Applicant occurred on July30, 2014. The Agency communicated the following:

There is currently no anticipated need for a REMS. However, at the present time, there are two major safety concerns with the 3-direct acting antiviral (3-DAA) combination product regimen:

1. The known risk of teratogenicity related to a ribavirin-containing regimen and the need for effective contraception, and

2. Hepatotoxicity with or without concomitant administration of estrogen-containing therapies with the 3-DAA combination.

These safety concerns will require the addition of information to labeling that addresses hepatotoxicity and the use of estrogen-containing therapies. Additionally, the conversion of the proposed Patient Package Insert to a Medication Guide is warranted to help mitigate the potential risk to patients.

2 MATERIALS REVIEWED

2.1 APPLICANT SUBMISSIONS

The following submissions from the Applicant were reviewed for this review:

- AbbVie. Original NDA 206619 submission for Viekira Pak, received April 21, 2014 (S-000/Seq 0003)
    - Section 2.5, Clinical Overview
    - Section 2.7.3, Summary of Clinical Efficacy
    - Section 2.7.4, Summary of Clinical Safety
- AbbVie. Draft Prescribing Information for Viekira Pak, received August 20, 2014 (S-000/Seq 0031)

2.2 OTHER MATERIALS INFORMING OUR REVIEW

- Fleischer, R. DAVP Mid-Cycle Meeting Clinical Slides for Viekira Pak, dated July 8, 2014.
- FDA. Mid-Cycle Communication Meeting Minutes for Viekira Pak, dated July 30, 2014.
- Fleischer, R. DAVP Clinical Review for Viekira Pak, dated September 18, 2014.

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

The Applicant completed six pivotal Phase 3 clinical trials (M11-646, M13-098, M13-099, M13-961, M13-398, and M14-002), and 2 supportive Phase 2 clinical trials (M11-652 and M14-103) of Viekira Pak in patients with chronic HCV GT1 infection in support of the proposed indication. The Phase 3 trials were designed to identify the optimal drug regimen (± RBV) and

duration of treatment. The primary efficacy endpoint was sustained virologic response (SVR) 12 weeks after discontinuation of treatment. All Phase 3 studies had a historical control for the primary efficacy endpoint using a threshold based on telaprevir and pegylated interferon (pegIFN)/RBV SVR rates to determine comparative statistical significance.

3.1.1 Placebo-Controlled Studies (M11-646 and M13-098)

Studies M11-646 and M13-098 were Phase 3, randomized, double-blind, placebo-controlled, multicenter studies. Subjects were randomized to the 3-DAA + RBV vs. placebo for 12 weeks.

- M11-646 (n=631) HCV GT1 treatment –naïve, non-cirrhotic adults. SVR was achieved by 96.2% of subjects with a 95% confidence interval (CI): 94.5% - 97.9% (The lower confidence bound (LCB) was above 70% (non-inferiority threshold) and above 80% (superiority threshold)). Relapse occurred in 7 (1.5%) patients.
- M13-098 (n=394) HCV GT1, pegIFN/RBV treatment-experienced non-cirrhotic adults. SVR was achieved by 96.3% subjects with a 95% CI: 94.1% - 98.4% (The LCB was above 60% (non-inferiority threshold) and above 70% (superiority threshold)). Seven (2.4%) subjects experienced post-treatment relapse.

3.1.2 Regimen-Controlled Studies (M13-389, M13-961, and M14-002)

Study M13-389 was a Phase 3, randomized, open-label, multicenter study. Subjects were randomized to 3-DAA + RBV vs. 3-DAA for 12 weeks.

- M13-389 (n=91) pegIFN/RBV treatment-experienced, non-cirrhotic, HCV GT1b-infected adults. SVR was achieved by 96.6% subjects in the 3-DAA + RBV treatment group (95% CI: 92.8% – 100.0%) and by 91/91 (100%) subjects in the 3-DAA treatment group (95% CI: 95.9% – 100.0%). The LCB was above 64% (non-inferiority threshold) for both treatment groups. Additionally, both regimens demonstrated non-inferiority to the historical control rate for therapy based on telaprevir + pegIFN/RBV.

Studies M13-961 and M14-002 were Phase 3, randomized, double-blind, controlled, multicenter studies. Subjects were randomized to 3-DAA + RBV vs. 3-DAA for 12 weeks. RBV dosing was double-blind and placebo-controlled.

- M13-961 (n=419) treatment-naïve, non-cirrhotic, HCV GT1b-infected adults. Subjects were randomized as follows: 3-DAA + RBV (n= 210) and 3-DAA (n= 209). SVR was achieved by 99.5% subjects in the 3-DAA + RBV treatment group (95% CI: 98.6% – 100.0%) and by 99.0% subjects in the 3-DAA treatment group (95% CI: 97.7% – 100.0%). The LCB was above 73% (non-inferiority threshold) for both treatment groups. Additionally, both regimens demonstrated non-inferiority to the historical control rate for therapy based on telaprevir + pegIFN and RBV. No subject experienced post-treatment relapse.
- M14-002 (n=305) treatment-naïve, non-cirrhotic, HCV GT1a-infected adults. Subjects were randomized as follows: 3-DAA + RBV (n= 100) and 3-DAA (n= 205). SVR was achieved by 97.0% subjects in the 3-DAA + RBV treatment group (95% CI: 93.7% – 100.0%) and by 90.2% subjects in the 3-DAA treatment group (95% CI: 86.2% – 94.3%). The LCB was above 65% (non-inferiority threshold) for both treatment groups.

Additionally, both regimens demonstrated non-inferiority to the historical control rate for therapy based on telaprevir + pegIFN/RBV.

3.1.3 Open Label Study in Compensated Cirrhosis (M13-099)

Study M13-099 was a randomized, open-label, multicenter study. Subjects were randomized to 3-DAA + RBV for 12 weeks vs. 3-DAA + RBV for 24 weeks.

- M13-099 (n= 381) treatment-naïve, and previous pegIFN/RBV treatment experienced HCV GT1 adults with compensated cirrhosis. Subjects were randomized as follows: 3-DAA + RBV for 12 weeks (n= 208) and 3-DAA + RBV for 24 weeks (n= 172). SVR was achieved by 91.8% subjects in the 12-week treatment group (97.5% CI: 87.6% – 96.1%) and by 95.9% subjects in the 24-week treatment group (97.5% CI: 92.6% – 99.3%). For the 12-week and 24-week treatment groups, the LCB was above 43% (non-inferiority threshold) and 54% (superiority threshold). Both 12-week and 24-week treatment with 3-DAA + RBV demonstrated non-inferiority and superiority to therapy based on telaprevir + pegIFN/RBV. In the 12-week treatment group, 12 (5.9%) subjects experienced relapse through post-treatment week 12. In the 24-week treatment group, 1 (0.6%) patient experienced relapse through post-treatment week 12.

3.1.4 Phase 2 Supportive Studies (M11-652 and M14-103)

The M11-652 study was a randomized, open-label, multiple arm, multi-center study. Non-cirrhotic, GT1 treatment naïve and prior pegIFN/RBV null responders (n=571) were randomized to various combinations of the 3-DAAs ± RBV following 8, 12, or 24 weeks of treatment. The primary objectives were to assess the safety of all treatment regimens, and to compare the percentage of subjects achieving 24-week sustained SVR.

- SVR for week 12 was achieved by 455/473 (96.2%) subjects, with a 95% CI: 94.5% – 97.9%. The lower confidence bound (LCB) was above 70% (noninferiority threshold) and above 80% (superiority threshold). One (0.2%) subject experienced on-treatment virologic failure and 7 (1.5%) subjects experienced post-treatment relapse for a total of 8 virologic failures out of 473 ITT subjects (1.7%).

The M14-103 study was an open –label, single-arm, multi-center study of 3-DAA + RBV for 12 weeks in GT1 non-cirrhotic, treatment naïve and experienced subjects (n=38) receiving methadone or buprenorphine.

- SVR for week 12 was achieved by 37/38 (97.4%) subjects, with a 95% CI: 92.3%-100%. The subject who did not receive SVR at week 12 discontinued the study drug after 25 days of treatment due to treatment-emergent serious adverse events. There were no subjects with on-treatment virologic failure or post-treatment relapse.

In summary, the placebo-controlled studies demonstrated the efficacy of 3-DAA +RBV over placebo and telaprevir + pegIFN/RBV for 12 weeks. The regimen-controlled studies demonstrated the efficacy of both 3-DAA+RBV and 3-DAA regimens over the historical control. The compensated cirrhosis trial demonstrated that the 12-week regimen was efficacious for subjects with GT1b, and the 24-week regimen was more efficacious for subjects with GT1a infection.

3.2 SAFETY CONCERNS

Among non-cirrhotic subjects in the Phase 3 trials treated with the 3-DAA+ RBV, ~14% of subjects experienced a moderate or severe treatment-emergent adverse event (AE). Events that occurred in >2% of subjects included fatigue (5%), headache (5%), asthenia (3%), nausea (3%), anemia (2%), insomnia, (2%), and diarrhea (2%). Among subjects treated with the 3-DAA alone, only fatigue (4.5%) and headache (4%) occurred in >2%.

3.2.1 Serious Adverse Events (SAEs)

The frequency of nonfatal SAEs was 3% in Phase 3 trials among subjects treated with the 3-DAA + RBV regimens. Treatment-emergent AEs probably related to the DAA and/or RBV included acute cholecystitis, anemia, and arthralgia.

A total of seven deaths were included in the safety database; six occurred in the post-dosing follow-up period and were due to reasons not related to study drug per the clinical reviewer. There remaining subject had a history of cirrhosis and diabetes [concomitantly receiving metformin and Januvia (sitagliptin)] while on study drug. Her metformin dose was increased and she eventually developed lactic acidosis that required hemodialysis. She developed multi-organ failure with rhabdomyolysis and underwent a liver transplant. After the transplant, the lactic acidosis, rhabdomyolysis and multi-organ failure resolved. She died 81 days post liver transplant. Well-known hepatic pathologist, Dr. Zach Goodman, described the histologic findings were consistent with severe ischemic-hypoxic hepatic necrosis in a patient with underlying cirrhosis and steatosis, and the findings do not suggest a drug-induced or toxic liver injury.

The clinical reviewer commented that: *The metformin label warns against patients with advanced liver disease (including liver failure and cirrhosis) taking metformin as they can be at an increased risk of lactic acidosis. The Applicant was unable to determine why the subject had her metformin dose increased at study entry. Based on review of this case, it is likely that mismanagement of metformin in a patient with high risk of complications was the primary reason for this subject's rapid deterioration, need for a liver transplant, and subsequent death*[6].

3.2.2 Adverse events of special interest

The primary AEs of special interest with this product are teratogenicity (related to RBV), and hepatotoxicity related to 1) paritaprevir, and 2) concomitant use of estrogen-containing medication. Please see Dr. Russell Fleischer's full review of safety and these AEs.

Additionally, Viekira Pak is metabolized as follows:

- Ombitasvir is metabolized via amide hydrolysis followed by oxidative metabolism.
- Paritaprevir is metabolized predominantly by CYP3A4 and to a lesser extent CYP3A5.
- Dasabuvir is predominantly metabolized by CYP2C8 and to a lesser extent by CYP3A.
- Ritonavir is predominantly metabolized by CYP3A and to a lesser extent, by CYP2D6.

Therefore, it is contraindicated to co-administer Viekira Pak with sensitive CYP3A substrates or strong CYP2C8 inhibitors, which may substantially increase plasma concentrations and result in serious AEs. Additionally, it is contraindicated to co-administer Viekira Pak with strong

[6] Fleischer, R. Clinical Review for Viekira Pak, dated September 18, 2014.

inducers of CYP3A or CYP2C8, which may substantially lower the plasma concentrations of Viekira Pak. These drug interactions are described in detail in the prescribing information.

3.2.2.1 Teratogenic events related to ribavirin

Since RBV is a known teratogen, it is contraindicated in pregnancy (Pregnancy Category X). Treatment regimens may include Viekira Pak in combination with RBV; therefore the prescribing information for Viekira Pak will include information regarding this risk for RBV.

With regard to 3-DAA without Ribavirin, there were 11 pregnancies reported during the clinical development program for the 3-DAA regimen. These included 4 deliveries with no complications or birth defects, 3 spontaneous abortions, 2 elective abortions, 1 unknown outcome due to privacy laws, and 1 subject who is due to deliver in December 2014.

The clinical reviewer commented that it does not appear that the 3-DAA alone increases the risk of adverse pregnancy outcomes.

3.2.2.2 Hepatic events related to paritaprevir[7]

Approximately 1% of 3-DAA-treated subjects experienced a post-baseline ALT elevation of >Grade 3. These ALT elevations were generally asymptomatic and occurred during the first 28 days of study drug treatment.

However, due to the identification of 32 additional cases that met the biochemical criteria for Hy's law (ALT or AST >3 x ULN with total bilirubin >2 x ULN), the Applicant convened an Expert Hepatic Review Panel consisting of two hepatologists and another expert in drug-induced liver injury to review the cases. Increases in alkaline phosphatase were typically in the Grade 1 range (>3 x ULN), were asymptomatic, and were not associated with AEs or elevations of other liver enzymes. Additionally, the events resolved with continued DAA dosing and none of the 16 subjects with ALT >3x ULN and bilirubin >2 x ULN had an alkaline phosphatase >2 x ULN.

The panel evaluated 32 subjects: 19 with ALT levels >3 x ULN and total bilirubin >2 x ULN, and 13 with ALT levels >5 x ULN and total bilirubin <2 x ULN:

- Thirty-one subjects received 3-DAA + RBV and one 3-DAA alone
- One subject was in a Phase 2 Study and the others were in Phase 3 trials
- All subjects treated with ABT-450/r 150/100 mg
- The mean time to ALT elevation was 20 days (range 8-57)
- 18 subjects were male and 14 were female
- Eight subjects had cirrhosis
- Seven were females taking an estrogen-containing product (Also see Section 3.2.2.3)
- Twenty-six subjects had no change in their DAA treatment
- Three subjects discontinued study drugs: metformin associated lactic
    - acidosis/death, possible drug toxicity, and acute hepatitis with estrogen use
- Three subjects interrupted study drugs for one to seven days: two due to
    - transaminitis with estrogen use, one for transaminitis, and one for possible
    - steroid toxicity
- Twenty-eight subjects (87.5%) achieved SVR

[7] Ibid

The Panel assessed all cases as hepatocellular drug-induced liver injury with adaptation, but no clinical cases of Hy's law were identified. The Panel concluded that in many cases the elevations in total bilirubin were predominantly indirect and temporally inconsistent with Hy's law in that they preceded the peak serum ALT elevations, a result more likely consistent with inhibition of bilirubin transporters by paritaprevir or exacerbation by RBV-induced hemolysis.

The Panel conducted a separate review of 10 subjects randomized to placebo that met the above criteria and determined that three had possible drug-induced liver injury, four were unlikely to be drug-induced liver injury, and three were unrelated to treatment.

The clinical reviewer agrees with the panel's findings that these cases although biochemically defined as Hy's law cases do not appear to be clinical cases of Hy's law.

3.2.2.3 Hepatic Events related to Concomitant Estrogen-containing Medication

Analysis of Phase 2 and early Phase 3 trials suggested that female subjects receiving estrogen-containing products were experiencing a higher frequency of ≥Grade 3 ALT increases: 6 % (7/113) compared to <1% of females not receiving estrogens.

Due to excessive transaminitis, estrogen-containing oral contraceptives were excluded from use in the ongoing Phase 3 trials. Subsequently, a drug-drug interaction study was initiated with the DAA and an estrogen –containing oral contraceptive (Ortho-Cyclen). The drug-drug study was paused due to ALT elevation (Grade 1-2) observed in the first 4/5 subjects. Subsequently, a low progestin-only oral contraceptive arm was added, and there were no ALT increases or clinically relevant pharmacokinetic interactions between the DAAs and progestin. An additional arm of healthy female volunteers was enrolled and received the DAAs plus an ethinyl estradiol/norethindrone combination oral contraceptive, and the arm was stopped early as 9/12 subjects experienced Grade 1-2 ALT elevations.

These findings support that there is a risk of transaminitis associated with the 3-DAAs, which is increased in females using systemic estrogen-containing medications. Further, ALT elevations were observed in a healthy volunteer study evaluating estrogen-containing oral contraceptives as noted above.

The clinical reviewer indicated that hepatic transaminitis among women taking estrogen-containing products support that estrogen-containing products and paritaprevir probably should not be co-administered. The mechanism of action between paritaprevir and estrogen has not been established, and it would likely be unsafe to conduct additional studies in healthy volunteers.

3.2.3 Postmarketing Requirements[8]

Formal discussions about PMRs and PMCs have not occurred as of the date of this review. Possible postmarketing requirements/commitments could include, but are not limited to:

- A pediatric development program
- A clinical trial in subjects with end-stage renal disease
- A clinical trial in subjects with decompensated (Child-Pugh B) hepatic impairment

[8] Fleischer, R. Clinical Review for Viekira Pak, dated September 18, 2014.

- A clinical trial to determine if RBV is necessary in cirrhotic subjects with GT1b

4 DISCUSSION

Based on the results of the Phase 3 pivotal trials, Viekira Pak provides substantial efficacy in the treatment of chronic HCV GT1 in treatment-naïve and treatment-experienced patients with or without cirrhosis. The once-daily, orally administered 3-DAA ± RVB combination also offers an improved safety profile compared to interferon-based and ribavirin-based HCV regimens, which are difficult for patients to tolerate because of the associated toxicities.

The teratogenicity risk associated with RBV is well documented, and understood by the expected prescriber population for Viekira Pak. The approved RBV labeling includes a Boxed Warning which describes that extreme care must be taken to avoid pregnancy and to use 2 forms of birth control while taking RBV and for 6 months after treatment with RBV has ended. The proposed labeling for Viekira Pak includes also this information in the Warnings and Precautions section of the package insert.

The potential for drug interactions are included in the prescribing information, including in Section 4 Contraindications, which specifies drugs that may substantially increase or decrease the plasma concentrations for Viekira Pak. Prescribers are familiar with similar types of CYP interactions for other antiviral products; therefore, risk communication beyond the label is not warranted at this time.

Additionally, the Phase 2 and Phase 3 studies have shown there is an increased risk of ALT elevation with Viekira Pak, as well as a risk of liver enzyme abnormalities with concomitant use of estrogen-containing medications.

The Applicant's Hepatic Expert Panel concluded that with the exception of women on estrogen, although there is a risk of ALT elevation with Viekira Pak, monitoring of liver enzymes did not have an impact on liver safety. They stated that "the percentage of patients experiencing ALT elevations was relatively low compared to other drug treatments where universal liver chemistry monitoring is recommended, and when monitoring detected ALT elevations, even relatively high elevations, the data suggested that continued drug treatment for the full 12 weeks was generally safe." The panel also raised the concern that routine monitoring may result in the unnecessary discontinuation of treatment in the majority of patients experiencing ALT elevations[9].

Despite the Panel's opinion about not needing to routinely monitor patients for ALT elevations, DAVP raised concerns about transaminitis among male and female subjects not receiving estrogen-containing products becoming concerning to a clinician. Without any guidance or precautionary language in the product labeling about how to manage such patients, clinicians may inappropriately discontinue DAA treatment. Thus, this risk information and the need for monitoring will be included in the label.

In addition, because female patients may be on estrogen containing medications, and those of childbearing potential on the RBV containing regimen must use 2 forms of birth control, (estrogen containing products are one of the most frequently used forms of contraception), it is important that prescribers and patients understand that they must avoid the use these medications while on treatment. The Applicant included the risk of using estrogen-containing medication in

[9] Ibid.

the Warnings and Precautions section; however, DAVP recommends that the co-administration of estrogen-containing products be contraindicated.

Therefore, DAVP, DRISK and the Patient Labeling team recommend a Medication Guide (MG) as a part of the labeling for Viekira Pak. Although the proposed PPI explains the risk of teratogenic effects with RBV and the risk of elevated liver enzymes with the use of estrogen-containing medications, there are further patient-focused messages which need to be communicated.
The Agency can require a Medication Guide in accordance with 21 CFR 208.1(c) when one or more of these situations exist:

> 1) The drug product is one for which patient labeling could help prevent serious adverse effects.
>
> 2) The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use, the product.
>
> 3) The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

The potential for teratogenic effects, elevated liver enzymes with or without concomitant use of estrogen-containing medication, and the need for frequent liver monitoring satisfies all three situations. The MG will be a resource that reinforces the counseling that takes place at the physician's office, and will be given directly to the patient when they pick up the medication from the pharmacy. Since a MG is required to be distributed with the medication at each dispensation, it will facilitate the communication of the risk information to patients each time they receive a prescription, and will serve as a tool to communicate the importance of what preventative measure must be taken weeks or months after the initial counseling takes place. Therefore, DRISK recommends a MG should be included in the labeling (not under a REMS) to communicate this information. The MG will be reviewed under separate cover by the Patient Labeling team.

5 CONCLUSION

To date, no AE's of particular concern or preclinical safety signals have been identified that cannot be effectively communicated through labeling for Viekira Pak.

However, because of the need for effective contraception in women receiving a RBV-containing regimen, and the risk of hepatotoxicity with or without concomitant use of estrogen-containing therapies (and therefore an increase in the need for testing), DRISK recommends that a Medication Guide be included as a part of this product's labeling.

In conclusion, risk mitigation measures beyond approved labeling, which include a MG, are not warranted for Viekira Pak.

Should DAVP have any concerns or questions, feel that a REMS may be warranted for this product, or new safety information becomes available; please send a consult to DRISK.

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/s/

FELICIA DUFFY
10/14/2014

REEMA J MEHTA
10/15/2014