CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206619Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	Dec. 8, 2014
From	Jeffrey S. Murray MD, MPH, Deputy Director
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	206619 Original
Applicant Name	AbbVie, Inc.
Date of Submission	April 21, 2014
PDUFA Goal Date	December 21, 2014
Proprietary Name / **Established (USAN) Name**	Viekira Pak™ (ombitasvir, paritaprevir and ritonavir tablets; dasabuvir tablets)
Dosage Forms / Strength	Co-packaged tablets for oral use: Ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets Dasabuvir 250 mg tablets
Proposed Indication(s)	Treatment, with or without ribavirin, of genotype 1 chronic hepatitis C virus infection
Action/Recommended Action for NME:	Approval, pending final inspection results

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Russell Fleischer
Statistical Review	Joy Mele
Pharmacology/Toxicology	Mark Seaton
CMC Review	Carol Strasinger Maotang Zhou Milton Sloan
Microbiology Review	Patrick Harrington
Clinical Pharmacology Review	Vikram Arya
CDTL Review	Linda Lewis

OND=Office of New Drugs
CMC=Chemistry, Manufacturing, and Controls
CDTL=Cross-Discipline Team Leader

1. Introduction

Treatments for hepatitis C have been rapidly improving with respect to both efficacy and safety. The field is moving away from interferon-based regimens toward all oral regimens to treat all genotypes of HCV infection. This new drug application (NDA) is for a co-packaged product called Viekira Pak. It is comprised of two tablets containing a total of three new molecular entities (NME) that are direct-acting HCV antivirals (DAAs). This is the first time that FDA has received a NDA containing three new molecular entities. One of the tablets also contains a previously approved drug, ritonavir, used as a CYP3A inhibitor to increase

exposures of one of the NMEs, paritaprevir. Viekira Pak is used with or without ribavirin depending on the presence of cirrhosis and genotype subtype as outlined in the prescribing information and in this review. Viekira Pak contains two tablets with the following components:

Fixed Dose Combination Tablet (two tablets once daily)

- ombitasvir 12.5 mg (HCV NS5A inhibitor) +
- paritaprevir 75 mg (HCV NS3/4A protease inhibitor) +
- ritonavir 50 mg (CYP3A inhibitor)

Packaged with,

Single Tablet (one tablet twice daily)

- dasabusvir 250 mg (non-nucleoside HCV RNA polymerase inhibitor)

Paritaprevir is the fourth HCV protease inhibitor that is being recommended for approval and ombitasvir is the second NS5A inhibitor to be recommended for approval. There are no non-nucleoside HCV RNA polymerase inhibitors that have previously received approval.

Ritonavir is an HIV protease inhibitor that was initially approved for the treatment of HIV at a dose of 600 mg twice daily (12 times the dose used in Viekira Pak). However, ritonavir is rarely used as an HIV antiretroviral, but is dosed at lower doses of 100 mg to 400 mg daily, for its ability to increase exposures and reduce dosing frequency of other HIV protease inhibitors (atazanavir, lopinavir, fosamprenavir, saquinavir, darunavir, tipranavir) by inhibiting CYP3A metabolism. Any drug combination containing ritonavir can be expected to have a significant amount of drug-drug interactions as will be discussed in section 5 of this memorandum.

2. Background

This NDA was reviewed under the PDUFA V program with a priority review time clock. The product with the trade name Viekira Pak was granted Breakthrough Therapy Designation in May 2013 and the NDA was accepted for rolling review. The final NDA component that triggered the start of the review clock arrived on April 21, 2014. Because this product has Breakthrough Therapy Designation the Review Team agreed that AbbVie could submit during this review cycle clinical and efficacy data from the following two important trials:

1) Trial M12-999 conducted in post-liver transplant patients.
2) Interim results from Trial M14-004 (TURQUOISE-I) conducted in with HIV/HCV co-infected patients

To support approval, safety and efficacy evaluations were primarily based on six phase 3 trials described in section 7 of this memorandum. In addition, a 14-arm Phase 2 trial was instrumental in showing the contribution toward efficacy of the individual components of Viekira Pak among patients with genotype 1a and 1b. This and other phase 1 and 2 trials showed that each DAA had activity against hepatitis C virus genotype 1 and that each of the drugs were needed in the regimen to provide the highest sustained virologic response (SVR) rate and to reduce the chances of relapse and the emergence of resistance. However, at the end of phase 2 it was still not established whether ribavirin would be needed for patients infected with genotype 1b or for patients infected with genotype 1a who were treatment naive. The safety, efficacy, and optimal treatment duration for patients with cirrhosis were also not established prior to Phase 3 because patients had not been included in the Phase 2 program. Therefore the Phase 3 development program was designed to provide data to resolve these issues as well as to rigorously confirm antiviral efficacy and establish safety. All the Phase 3 trials were randomized, multicenter trials as described in section 7 of this memorandum. Trial designs were consistent with recommendations from the Draft Guidance for Industry, "Chronic Hepatitis C Virus Infection, Developing Direct-Acting Antiviral Drugs for Treatment."

3) CMC (Chemistry, Manufacturing, Controls)

The drug product consists of two immediate-release, film-coated tablets, one co-formulated tablet and one containing a single drug as described above. A single day's dose is packaged in a blister pack in a cardboard wallet configuration containing two FDC tablets to be taken once daily and two dasabuvir tablets to be taken as one tablet twice daily. Seven wallet packs are packaged in a carton and four weekly cartons are packaged in a larger carton to provide a month's supply to the patient. Adequate information was submitted to support the Applicant's proposal for a 24-month expiration dating.

I concur with the conclusions reached by the CMC reviewers. The CMC reviewers concluded that sufficient information was provided in the NDA to assure the quality of the drug substances and the drug product. The Biopharmaceutics reviewer and the Product Quality Microbiology reviewers also recommended approval of the final drug product, the proposed dissolution methods, and the microbiological controls.

Viekira Pak includes four drug substances (including three NMEs) and two final tablet products and, therefore, has multiple manufacturing sites. One of the sites inspected (b) (4) was issued FDA Form 483 based on two observations related to the Quality System. The site is in the process of responding to these observations. At the time of writing this Division Director's Summary Review, the Office of Compliance has not confirmed an Overall Acceptable recommendation.

4) Nonclinical Pharmacology/Toxicology

For a complete discussion of the *in vitro* safety assessments and animal toxicology studies, please refer to the Pharmacology/Toxicology Review performed by Dr. Mark Seaton. Dr. Seaton recommends that Viekira Pak be approved.

Nonclinical studies were conducted with the individual components of Viekira Pak and not the entire regimen. This is consistent with ICH M3(R2) guidance and indication specific draft guidance for hepatitis C drug development[1], which allows foregoing combination animal toxicology studies for certain drugs to treat serious and life-threatening illnesses under certain circumstances. Nonclinical toxicology studies of ritonavir were conducted for its initial development for the treatment of HIV.

Repeat dose toxicology studies of the three NMEs included in this application identified relatively few primary target organs for toxicity. No target organs were identified for ombitasvir at maximal feasible doses that could be administered to animals and at exposures that were 20-40 times higher than clinical trial exposures. Likewise, dasabuvir showed little in the way of organ toxicity in animals aside from inflammation of the ileum in a 6 month rat study. Paritaprevir, administered with ritonavir, produced adverse effects of the gallbladder in two species (mice and dogs). In addition CNS excitation was observed in rat studies of paritaprevir. Previous toxicology studies of ritonavir alone had identified liver toxicity and retinal toxicity. Retinal toxicity has not been observed in clinical trials at higher exposures of ritonavir than will be achieved with Viekira Pak. Ritonavir has been shown to have liver toxicity in humans particularly at the doses initially used for the treatment of HIV.

In summary, animal studies identified the gallbladder, and to a lesser extent the liver, as potential toxicities to be monitored for and reviewed in clinical trials.

Carcinogenicity

Genotoxicity of all three NMEs was evaluated in *in vitro* and *in vivo* assays. Assays were negative for ombitasvir and dasabuvir. Paritaprevir gave positive results in an *in vitro* human chromosome aberration test but was negative in other tests. Based on these results the potential for carcinogenicity with all three of these drugs was considered low; however, carcinogenicity studies were completed given that this product may be given for 6 months in certain populations. No neoplastic lesions were identified in a two-year rat study and a 6-month transgenic mouse study of paritaprevir administered with ritonavir. Ombitasvir and dasabuvir were each evaluated in six-month transgenic mouse carcinogenicity studies and no neoplastic lesions were observed.

Reproductive toxicology

As stated in product prescribing information, Viekira Pak is designated pregnancy Category B. In animal reproduction studies, no evidence of teratogenicity was observed with the administration of ombitasvir (mice and rabbits), paritaprevir/ritonavir (mice and rats), or

[1] Draft Guidance for Industry, "Chronic Hepatitis C Virus Infection, Developing Direct-Acting Antiviral Drugs for Treatment."

dasabuvir (rats and rabbits) at exposures higher than those for the recommended clinical doses of these drugs.

5) Clinical Pharmacology/Biopharmaceutics

For a complete discussion of the clinical pharmacology issues, please refer to the Clinical Pharmacology Review submitted by Dr. Vikram Arya and the collaborating team of reviewers. I concur with Dr. Arya's review which states that the information in the application supports the approval of Viekira Pak. In addition, the Clinical Pharmacology Review resulted in labeling recommendations that differed from the applicant's initial label proposal. These are outlined in Dr. Arya's Executive Summary of the Clinical Pharmacology Review.

Paritaprevir is metabolized primarily by CYP3A in humans and has been shown to inhibit several hepatic transporters, the most clinically relevant being inhibition of OATP1B1 which is critical in bilirubin transport. In humans this causes bilirubin elevation driven by an elevation of the indirect bilirubin fraction.

According to Dr. Arya and the Review team's conclusions regarding exposure-response relationships for both efficacy and safety, "a change in the exposure within a window of 0.5 to 2.0 fold from the population mean exposures for all three direct acting antivirals (paritaprevir, ombitasvir, dasabuvir) are not anticipated to alter the efficacy or safety profile to an extent that necessitates dosing changes." Recommendations for labeling based on changes in exposures related to intrinsic or extrinsic factors used this exposure window as a benchmark for the three HCV antivirals. Exposure changes in ritonavir are not considered critical as long as paritaprevir exposures are within the 0.5 to 2.0 fold window because ritonavir is not present as an active antiviral and because there are adequate safety data from previous ritonavir trials conducted in HIV-infected patients to support much higher exposures of ritonavir.

Pertinent clinical pharmacology issues for Viekira Pak summarized briefly in my memorandum include: 1) an exposure-response relationship for paritaprevir for transaminase elevations and other safety parameters, 2) food effect, 3) increased exposures with hepatic impairment, 4) multiple drug-drug interactions, and 5) a drug-drug interaction with estrogen based oral contraceptives (of unknown mechanism) that increases the frequency of transaminase elevations.

<u>Exposure response</u>

The exposure-response analyses for safety identified positive relationships for drug-induced rash, ALT elevations, total bilirubin elevations and hemoglobin reductions with paritaprevir/ritonavir. However the potential increases in frequencies of drug-induced rash, bilirubin elevations and hemoglobin reductions from increasing paritaprevir AUC exposures by 2 fold are predicted to be small with a clinically negligible effect. A 2-fold increase in paritaprevir exposure increased the odds of ALT > 3 times the upper limit of normal by 1.6-fold. This has clinical implications for subjects with hepatic impairment or any other condition or concomitant medication that substantially increases paritaprevir exposure. A 2-fold exposure threshold increase was also used to guide dosing recommendations when interpreting drug-drug interactions.

Food-effect

Exposures of all four component drugs are increased by administration with a moderate or high fat meal but the highest increases were observed for paritaprevir and ombitasvir. AUC increases for paritaprevir ranged from 180% to 210% and AUC increases for ombitasvir ranged from 76- 81% when administered with a moderate or high fat meal. The prescribing information will recommend that Viekira Pak be taken with a meal (without regard to fat or calorie content) as was done in all phases of clinical trials. Therefore, safety and efficacy was established for exposures achieved when Viekira Pak is taken with a meal.

Hepatic Impairment

Compared to subjects with normal hepatic function, there were only mild decreases or slight increases in AUCs for all three of the direct acting HCV antivirals in Viekira Pak in mild hepatic impairment. In moderate (Child Pugh B) hepatic impairment paritaprevir AUCs increased by 62%. However, in subjects with severe hepatic impairment, paritaprevir and dasabuvir AUCs increased by approximately 945% and 325%, respectively, and ombitasvir AUCs decreased by 54%. Given the substantially increased exposures of paritaprevir and dasabuvir, and the exposure-response relationship of paritaprevir and ALT elevations, Viekira Pak will be contraindicated in patients who have severe hepatic impairment (Child-Pugh C). In addition, treatment of patients with Child Pugh B hepatic impairment will not be recommended because there are no safety and efficacy data in this population to support its use in this population. In addition, it is possible that paritaprevir, with its known effects of transaminase elevations may present a safety risk in this population even though AUC increases were relatively modest (less than 2-fold) in the single dose hepatic impairment study. AbbVie is conducting Trial M14-227 entitled "An Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 and ABT-333 with Ribavirin in Adults with Genotype 1 Chronic Hepatitis C Virus Infection and Decompensated Cirrhosis" in patients with Child Pugh B hepatic impairment. This will be a post-marketing requirement because this is a vulnerable population that could present a safety risk. Other dosing configurations or regimens of these drugs would be needed for studying patients with severe hepatic impairment.

Drug-Drug Interactions

AbbVie anticipated many clinically relevant drug interactions, primarily because paritaprevir is extensively metabolized by CYP3A4, and ritonavir is a potent inhibitor of CYP3A4. In addition, CYP2C8 plays a major role in dasabuvir metabolism. The drugs in Viekira Pak also inhibit P-gp and OATP transporters further increasing the possibility of drug-drug interactions. Consequently, AbbVie conducted extensive drug-drug interaction studies (25 drug-drug interaction studies) with the component drugs of Viekira Pak and other drugs that were likely to be co-administered in the indicated population. One should refer to Tables 2, 5, 6, and 7 in the product labeling to see results of numerous drug-drug interactions studies and recommendations for when to avoid use or how to manage interactions. Noteworthy drug interactions summarized in Dr. Lewis's CDTL memorandum are with the calcineurin inhibitors tacrolimus and cyclosporine, which are indicated in the prevention of organ rejection in the liver transplant setting. Exposures of both drugs are markedly increased in the presence of Viekira Pak and both must be significantly dose reduced to avoid toxicities.

Concomitant administration of Viekira Pak with several types of oral contraceptives (OC) was evaluated in a specific drug-drug interaction study conducted in healthy volunteers. OCs included: ethinyl estradiol (EE) and norgestimate (NGM), norethindrone (NET), and EE and NET. A majority of healthy volunteers receiving OCs containing EE developed ALT elevations, some greater than three times the upper limit of normal (ULN). None of the subjects receiving only NET dosed with Viekira Pak developed ALT elevations. EE containing contraceptives moderately decreased exposures of the components of Viekira Pak (3%-52% decreases in AUC). Viekira Pak had minimal effects on EE exposures. Therefore, it appears that the ALT elevations resulting from co-administration of EE and Viekira Pak are not mediated by plasma levels of EE or paritaprevir. Clinical implications of this drug interaction are discussed further under Section 8 of this memorandum pertaining to safety.

Intrinsic Factors Not Resulting in Labeling Recommendations

In addition, differences in clinical pharmacology with respect to age, race, ethnicity, gender, or renal function did not result in recommendations for dose adjustments or restrictions. Neither race nor ethnicity was found to be a significant covariate for drug exposure. Exposures in female subjects were found to be 1.2 to 1.8-fold higher than in male subjects; however, these differences were not considered clinically relevant. Slightly higher exposures were noted in subjects at least 65 years of age compared to those younger than 65 years old. In subjects with severe renal impairment but not on dialysis, AUC for paritaprevir and dasabuvir were increased by 45% and 50%, respectively, and ombitasvir AUC was not changed compared to subjects with normal renal function. None of these observations warranted labeling recommendations because they fell within the exposure-response window described above.

Viekira Pak was studied in a thorough QT study. Supratherapeutic doses of the components did not show a significant QTc interval prolongation effect.

6) Clinical Microbiology

I concur with the Clinical Microbiology Review prepared by Patrick Harrington, Ph.D., who concludes that the NDA should receive approval from a virology perspective. In an Addendum to the Virology Review, Dr. Harrington provided his analysis of the interim virology data from Study M14-004 submitted late in the review cycle.

Based on similar viral targets, treatment emergent substitutions observed in *in vitro* replicon systems, and treatment emergent substitutions observed in patients with virologic failure in clinical trials, both paritaprevir and ombitasvir are expected to be cross resistant to previously approved products in their respective classes. Substitutions at NS3 positions R155 and D168 emerged in patients failing therapy with paritaprevir and were also observed with other approved NS3 protease inhibitors (boceprevir, telaprevir, and simeprevir). Substitutions at NS5A positions M/L28, Q/R30, H/P58 or Y93 are associated with reduced susceptibility to ombitasvir and have also been observed in patients failing treatment with the other approved NS5A inhibitor (ledipasvir) and some NS5A inhibitors under development. Cross-resistance

between both paritaprevir or ombitasvir and drugs in other DAA classes, RBV, or interferon is not expected.

Cross-resistance is expected between dasabuvir and other non-nucleoside NS5B-palm polymerase inhibitors in development but no other drugs of this class are currently approved. Cross-resistance is not expected between dasabuvir and interferon, RBV or other DAA classes, including other classes of NS5B polymerase inhibitors.

Dr. Harrington concludes that a baseline NS3 Q80K polymorphism (shown to reduce the SVR rate to simeprevir when used in combination with interferon) and certain NS5A polymorphisms may have some effect on HCV GT1a response to Viekira Pak plus ribavirin but given the overall low rates of virologic failure in the clinical trials this effect was not substantial.

Using data pooled from Phase 2 and 3 clinical trials, 81/2498 (3.2%) subjects receiving Viekira Pak with or without RBV for treatment durations of 8 to 24 weeks experienced virologic failure: 5.4% (74/1363) in GT1a and 0.6% (7/1131) in GT1b. This included regimens that are shorter or contain fewer drugs than will be recommended. Among those with GT1b HCV, virologic failure and emergence of resistance was uncommon. Over 90% of GT1a subjects experiencing virologic failure with a 12 or 24 week treatment duration (the proposed regimens) developed a resistance-associated substitution in at least one antiviral target and over 50% developed resistance-associated substitutions in all three antiviral targets. Choosing a regimen and duration that minimized virologic failure and multiple class resistance was a major priority of the NDA review and labeling recommendations.

7) Clinical/Statistical-Efficacy

For more detailed descriptions of the Phase 3 trial designs supporting efficacy, please refer to the Clinical Review provided by Senior Clinical Analyst Russell Fleischer, the Statistical Review prepared by Joy Mele and the CDTL memorandum prepared by Dr. Linda Lewis.

As displayed in other reviews and the product label, the basic designs of the six Phase 3 trials are shown in Table 1. In addition to the phase 3 trials, two smaller trials in post-liver transplant patients and HIV co-infected patients were reviewed to support labeling statements describing use in those populations. The primary efficacy endpoint in all clinical trials was the proportion of subjects achieving SVR12 defined as HCV RNA below the lower limit of quantitation (LLOQ) assessed 12 weeks after the end of study treatment. In all trials, the endpoint was measured using the COBAS TaqMan HCV test (version 2.0) with an LLOQ of 25 IU/mL. Two of the Phase 3 trials were placebo-controlled trials where the safety and efficacy of the entire treatment regimen in Viekira Pak plus ribavirin were compared to placebo. However, as stated in Joy Mele's statistical review, the primary efficacy comparison in all 6 trials was to the historical sustained virologic response (SVR) rate of telaprevir plus pegylated interferon (pegIFN) with RBV therapy. All of the phase 3 trials used the to-be–marketed formulations contained in Viekira Pak and ribavirin was dosed twice daily by weight consistent with doses used in combination with pegIFN for the treatment of HCV genotype 1 infection.

The "PEARL" trials were designed to compare treatment with Viekira Pak+RBV to Viekira Pak alone in non-cirrhotic subjects.

Table 1. Randomized, Multicenter Trials Conducted with VIEKIRA PAK With or Without Ribavirin (RBV) in Subjects with Chronic HCV GT1 Infection

Trial	Population	Study Arms (Number of Subjects Treated)
SAPPHIRE I (double-blind)	GT1 (a and b) TN[a] without cirrhosis	• Viekira Pak + RBV (12 wks) (473) • Placebo (158)
SAPPHIRE II (double-blind)	GT1 (a and b) TE[b] without cirrhosis	• Viekira Pak + RBV (12 wks) (297) • Placebo (97)
PEARL II (open-label)	GT1b TE without cirrhosis	• Viekira Pak + RBV (12 wks) (88) • Viekira Pak (12 wks) (91)
PEARL III (double-blind)	GT1b TN without cirrhosis	• Viekira Pak + RBV (12 wks) (210) • Viekira Pak (12 wks) (209)
PEARL IV (double-blind)	GT1a TN without cirrhosis	• Viekira Pak + RBV (12 wks) (100) • Viekira Pak (12 wks) (205)
TURQUOISE II (open-label)	GT1 (a and b) TN & TE with cirrhosis	• Viekira Pak + RBV (12 wks) (208) • Viekira Pak + RBV (24 wks) (172)

a. TN, treatment-naïve was defined as not having received any prior therapy for HCV infection.
b. TE, treatment-experienced subjects were defined as either: prior relapsers, prior partial responders, or prior null responders to pegIFN/RBV treatment.

Results

Notably, only four subjects in the phase 3 data base were missing HCV data to make a determination for the primary endpoint (SVR12) making imputation of missing data essentially unnecessary.

Demographics/Baseline Characteristics

Pooling from the Phase 3 trials, important demographic factors and baseline characteristics are summarized in Table 2 by genotype and the presence or absence of a diagnosis of cirrhosis.

Table 2. Demographics and Baseline Characteristics of Trial Participants in Phase 3 Trials By Genotype and Presence of Cirrhosis.

	Without Cirrhosis		Cirrhosis
	Genotype 1a	**Genotype 1b**	**GT 1a and 1b**
Age (median)	53 years	52 years	58 years
Male (%)	63%	47%	70%
Race: White (%), Black (%)	90% White 7% Black	93% White 7% Black	95% White 3% Black
IL28B CT,TT	85%	83%	86%
HCV-RNA > 800,000	85%	77%	86%

Other than race, the trials enrolled a diverse population of HCV infected patients and included people with poorer prognostic factors, such as non-CC genotypes, higher HCV RNA levels, and previous null responders. As stated above, patients with cirrhosis were enrolled in a separate trial (TURQUOISE II). The percentage of Black participants was much less than desirable and meaningful subgroup analyses were not possible; however numerical point estimates for Black trial participants are summarized below.

Efficacy results are shown in Tables 3 and 4 below for patients with and without cirrhosis, respectively. SVR12 rates range from 95-100% for label-recommended regimens/durations. The lower confidence bounds for these point estimates exceed both noninferiority and superiority thresholds, as prospectively defined in the protocols, for the historical benchmarks of pegIFN and telaprevir in the various populations.

Table 3. SVR12 Results for Patients Without Cirrhosis By Genotype Subtype.
Shaded boxes are for recommended regimens/durations

Genotype/Treatment History	Viekira Pak 12 wks SVR (lower bound)	Viekira Pak + RBV 12 wks SVR (Lower Bound)
GT1a		
TN	90% (86%)	96-97% (93%)*
TE	ND	96% (92%)
GT1b		
TN	100% (98%)	99.5% (97%)
TE	100% (96%)	98% (92%)

*Range is for two trials, lower bound is the lowest of the confidence bounds from the two trials.

Table 4. SVR12 Results for Patients With Cirrhosis By Genotype Subtype
Shaded boxes are for recommended regimens/durations

	Viekira Pak +RBV 12 wks (L.B.)	Viekira Pak + RBV 24 wks (L.B.)	Treatment Diff. 24-12 wks
Overall 1a and 1b	92% (87%)	96% (92%)	4% (0.07%, +10%)
GT1a	89% (81%)	95% (89%)	6% (-0.6%, +13%)
GT1b	99% (91%)	100% (92%)	--

For patients without cirrhosis who were infected with Genotype 1b, adding ribavirin did not appear to improve SVR12 rates as is evident in the Table 3 above. Viekira Pak without ribavirin was not studied in genotype 1b participant with cirrhosis. Extending the treatment duration of Viekira Pak and ribavirin to 24 weeks in patients with cirrhosis and genotype 1b infection also did not improve SVR12 rates (Table 4).

For genotype 1a patients, the addition of ribavirin to Viekira Pak improved SVR12 response rates by approximately 7%. The additional ribavirin toxicities for 12 weeks of duration were considered acceptable and manageable to achieve this incremental improvement in SVR12 given the potential consequences of drug resistance associated with treatment failure. Deciding on the best treatment duration for genotype 1a patients with cirrhosis was a somewhat more difficult issue. The difference in SVR12 was 6% favoring the longer treatment

duration of 24 weeks; given that relapse is most often associated with resistance to one or more drug (and currently, drug class), this margin of improvement in efficacy is meaningful. However, a 24-week treatment duration recommendation for all genotype 1a cirrhotics means doubling the treatment duration for approximately 90% of those initiating therapy for no additional benefit. The difference in SVR12 between patients receiving 12 and 24 weeks of treatment appeared to be driven primarily by patients who were previous null responders to pegIFN and ribavirin; however, subgroup analyses were not robust because of small numbers for any given subgroup. Section 12 discusses how labeling addresses flexibility in dosing duration in genotype 1a cirrhotics given limitations of subgroup analyses.

Efficacy in Blacks/African Americans

In the six Phase 3 trials, representation of Blacks was much less than the percentage of HCV infected patients who are Black in the United States; however, a large proportion of patients were enrolled in Europe and other parts of the world. In treatment naïve and treatment experienced genotype 1a and 1b Black patients receiving Viekira Pak plus ribavirin (from SAPPHIRE I, II, and PEARL IV) the pooled SVR12 rate was 97% (58/60). In PEARL II and III none of the 30 Genotype 1b Black participants relapsed after receiving Viekira Pak with or without ribavirin. Only 11 Black participants with cirrhosis were studied in TURQUOISE II; 92% (10/11) achieved SVR12. Although the numbers are small, the SVR12 point estimates are similar to the overall trial population and do not appear to present a signal for decreased efficacy.

Post-Liver Transplant: M12-999

This trial enrolled post-transplant patients with recurrent HCV, but did not include patients with an aggressive form of post-transplant disease.

Pertinent inclusion criteria were:

- at least 1 year post-transplant,
- had not received treatment for recurrent HCV infection since transplant,
- had minimal hepatic impairment (Childs-Pugh A),
- had liver fibrosis score ≤ F2 on a biopsy performed within 6 months of screening.

All subjects received 24 weeks of Viekira Pak plus ribavirin. Thirty-three of 34 enrolled (97%) achieved SVR. The only subject who failed to achieve SVR discontinued treatment prematurely due to an adverse event. No episodes of rejection were identified during the trial and all subjects remained on calcineurin inhibitor medications. The lower confidence bound for the treatment effect was 85%. The results show that response rates in the post-transplant patients enrolled in this trial are comparable to response rates in patients who have not undergone transplant.

HIV/HCV Co-infected Subjects (M14-004) – Interim Results

This trial is an ongoing phase 2/3 trial with multiple parts. Results from Part 1a were submitted during the review cycle of this application. Part 1a enrolled HIV/HCV co-infected patients who had virologic suppression of their HIV on an antiretroviral regimen (specifically raltegravir or atazanavir plus emtricitabine/tenofovir) and who had a CD4+ cell count > 200

cells/mm^3. Patients could be either HCV treatment-naïve or interferon-based treatment-experienced, including those with compensated cirrhosis.

Sixty-two patients were randomized to Viekira Pak with ribavirin for either 12 or 24 weeks. Approximately two-thirds were treatment naïve to HCV treatment and 19% had cirrhosis. Approximately 90% were genotype 1a. SVR12 rates were 93.5% for those receiving 12 weeks of treatment and 91% for those receiving 24 weeks. All subjects with GT1b HCV achieved SVR. Treatment for HCV did not appear to interfere with maintaining HIV suppression. The SVR12 rate in non-cirrhotic patients with 12 weeks of treatment was 96% (24/25). Although the data submitted from this trial are limited, virologic response appears to be comparable to that observed in HCV mono-infected patients and these data are important to include in labeling.

8) Safety

The safety data base in this application was large enough to identify relatively uncommon adverse reactions. As enumerated in the Dr. Lewis' CDTL memorandum the safety database included 2,964 subjects who received at least one dose of Viekira Pak in the Phase 2 and 3 clinical trials. The Phase 3 trials contributed 2,060 subjects, 1,888 receiving 12 weeks of Viekira Pak and 172 receiving 24 weeks; 1,551 subjects received Viekira Pak+RBV and 509 received Viekira Pak alone.

The most common adverse reactions observed with Viekira Pak administered with ribavirin were fatigue, nausea, pruritus, insomnia and asthenia. Fatigue, asthenia, nausea and pruritus are known to be associated with ribavirin. Nausea, pruritus, insomnia and asthenia were less when Viekira Pak alone was compared to Viekira Pak plus ribavirin in comparative trials in this drug development program. For the most part, adverse events did not result in drug discontinuation. Dose modifications of ribavirin occurred and did not appear to impact SVR12 rate.

Marked transaminase elevations (at least Grade 3 in severity), occurred at a frequency of 1% or less in the overall drug development population. This is the adverse reaction of most potential concern in that it could represent a signal for potentially serious adverse reactions when administered to a broader population postmarketing. In addition, Grade 3 or greater transaminitis occurred with greater frequency (approximately 9%) in females using estrogens in phase 3 trials and ALT elevations (at least Grade 1) occurred in the majority of healthy volunteers receiving EE-containing oral contraceptives in a drug interaction study with Viekira Pak and oral contraceptives. When ALT elevations were observed in the drug interaction study, use of estrogen-containing oral contraceptives in Phase 3 trials was no longer allowed. Table 5 (excerpted from Dr. Arya's review) shows how EE products in particular greatly increase the risk of Grade 3 or greater transaminase elevations. By contraindicating EE-containing oral contraceptive use it is hoped that the rate of transaminase elevations will be closer to 1%.

Table 5. Post-baseline Grade 3+ ALT elevations in Phase 2 and 3

	No. Patients with Grade 3+ ALT elevations	Total No. Patients	Percentage
Ethinyl Estradiol	6	23	26.1%
Other Estrogens	1	89	1.1%
No Estrogens	28	2927	1.0%

Upon thorough review, no cases of transaminase elevations were associated with liver failure that was attributed to Viekira Pak. In addition, no cases appeared to meet criteria for Hy's Law. The applicant, an expert review commissioned by the applicant, and FDA were in general agreement on this.

As previously discussed in Section 4, paritaprevir caused gall bladder erosions in mice and dogs. In the clinical safety data base, there were only five subjects identified with serious adverse events related to gall bladder disease. As stated in Russ Fleischer's review, 4/5 had a history of gallbladder disease prior to entry, 2/5 interrupted study drugs and all achieved SVR. At this time there does not appear to be a clinical signal for clinically significant gallbladder disease in humans; however, FDA will watch for cases that might occur postmarketing in the post-marketing period.

9) Advisory Committee Meeting

There was no advisory committee meeting for this NDA because this drug product was designated Breakthrough and there were no major issues that needed additional advisory committee input. The treatment regimen included in this application demonstrated robust virologic response rates exceeding 95%, overall, and FDA and the applicant were able to reach consensus on labeling for safety issues particularly those relating to transaminase elevations and drug interactions as discussed above.

10) Pediatrics

Dr. Lewis summarized pediatric issues in her CDTL Review. In brief, this NDA "triggers" required pediatric trials under PREA. The applicant will be required to evaluate the pharmacokinetics, treatment response and safety (including long-term safety) in pediatric patients with chronic hepatitis C infection ages 3 to 18 years. AbbVie has agreed to accomplish this within the context of the two Pediatric Requirements listed in the Approval Letter.

11) Other Relevant Regulatory Issues

The only unresolved regulatory issue at the time of writing this memorandum is final recommendations from the Office of Compliance regarding inspections of manufacturing facilities as discussed in section 3 above.

12) Labeling

One of the more difficult labeling issues for this NDA was providing the best recommendations for dosing duration in genotype 1a patients with cirrhosis.

FDA and the applicant agreed on the recommendations outlined in the table below, excerpted from the prescribing information. The primary treatment duration recommendation in genotype 1a patients with cirrhosis is for 24 weeks; however, a footnote acknowledges that consideration for a 12 week dosing duration may be appropriate for certain patients as described in the Clinical Studies Section of the label. Basically, patients who are treatment naïve would be reasonable candidates for the shorter duration; previous null responders to pegylated interferon and ribavirin would not.

Table 6. Treatment Regimen and Duration by Patient Population (Treatment-Naïve or Interferon-Experienced)

Patient Population	Treatment*	Duration
Genotype 1a, without cirrhosis	VIEKIRA PAK + ribavirin	12 weeks
Genotype 1a, with cirrhosis	VIEKIRA PAK + ribavirin	24 weeks**
Genotype 1b, without cirrhosis	VIEKIRA PAK	12 weeks
Genotype 1b, with cirrhosis	VIEKIRA PAK + ribavirin	12 weeks

*Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.
**VIEKIRA PAK administered with ribavirin for 12 weeks may be considered for some patients based on prior treatment history *[see Clinical Studies (14.3)]*.

Another important labeling issue was related to recommendations (in Warnings and Precautions) with respect to the development of significant transaminase elevations during treatment. As stated above, EE-containing medications are contraindicated for use with Viekira Pak. EE medications can be restarted 2 weeks following completion of treatment with Viekira Pak. The label states, "Women using estrogens other than ethinyl estradiol, such as estradiol and conjugated estrogens used in hormone replacement therapy had a rate of ALT elevation similar to those not receiving any estrogens; however, due to the limited number of subjects taking these other estrogens, caution is warranted for co-administration with VIEKIRA PAK." In addition the label includes some general guidance regarding monitoring:

"Hepatic laboratory testing should be performed during the first 4 weeks of starting treatment and as clinically indicated thereafter. If ALT is found to be elevated above baseline levels, it should be repeated and monitored closely:

- Patients should be instructed to consult their health care professional without delay if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice or discolored feces.
- Consider discontinuing VIEKIRA PAK if ALT levels remain persistently greater than 10 times the ULN.
- Discontinue VIEKIRA PAK if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR."

In addition, labeling will include a medication guide. The decision to include a medication guide was based, in part, on the contraindication of EE containing medications to reduce the risk of transaminase elevations and to make patients familiar with prescribing information warnings with respect to potential liver toxicity.

13) Decision/Action/Risk Benefit Assessment

- Regulatory Action
  I recommend that Viekira Pak with or without ribavirin (depending on HCV genotype subtype and cirrhosis status) for the treatment of chronic hepatitis C virus infection with genotype 1 be granted approval, pending final recommendations from manufacturing site inspections.

- Benefit-Risk Assessment

  The Benefit-Risk of Viekira Pak appears to be highly favorable and much improved over the previously approved interferon based regimens for chronic hepatitis C with genotype 1. SVR12, which is considered a virologic cure, is nearly universal in noncirrhotic genotype 1b patients treated with Viekira Pak alone for 12 weeks, and also in cirrhotic genotype 1b patients treated with Viekira Pak plus ribavirin for 12 weeks. SVR12 for genotype 1a patients treated with Viekira Pak plus ribavirin for 12-24 weeks (duration depending on cirrhosis and treatment history) yielded response rates of 95% and greater with tight lower confidence bounds. Previous interferon-based treatments that included a single DAA did not yield treatment effects that approached a 95-99% SVR12 for any population and yielded rates far below these for cirrhotics and treatment-experienced patients. In brief, Viekira Pak's virologic treatment effects are unambiguously robust and the virologic success rate clearly surpasses expectations for DAA regimens just a year or two ago. The correlations between achieving SVR and reductions in complications of cirrhosis including hepatocellular carcinoma and liver transplant are significant and compelling and are addressed in FDAs Draft Guidance for Industry for HCV drug development mentioned above. Thus, the long-term clinical benefit in patients achieving SVR12 is expected to be substantial, realizing that some people with highly advanced disease may still develop complications but at a lower rate than would have otherwise been expected in patients not able to achieve SVR.

The strong efficacy of Viekira Pak is balanced with a favorable tolerability profile; less than 1% of patients prematurely discontinued therapy related to adverse events and there were relatively few concerning safety signals. The safety signal of primary concern is elevations in transaminases (of at least Grade 3) in approximately 1% that signifies some degree of liver injury. However, most patients who experienced this were asymptomatic and resolved while continuing on treatment. Overall the benefit to risk is highly favorable for the treatment of this serious and potentially life-threatening disease.

In addition to pediatric trials required under PREA, FDA is requesting submission of the following clinical data as postmarketing requirements (PMR):

1. A trial evaluating the use of the drugs in Viekira Pak in patients with decompensated cirrhosis (Trial M14-227) entitled, "An Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 and ABT-333 with Ribavirin in Adults with Genotype 1 Chronic Hepatitis C Virus Infection and Decompensated Cirrhosis." This will be a PMR because patients with Child-Pugh B cirrhosis are a vulnerable population that could present a safety risk if Viekira Pak is used (off-label). Paritaprevir levels are modestly increased, but even a modest increase in patients with this level of liver dysfunction could pose an increased safety risk specifically with respect to liver toxicity.
2. A clinical trial or observational study in Blacks/African American HCV-infected patients that will evaluate safety and efficacy and allow for comparative analyses with White enrollees in the same trial or observational study. This will be a PMR because the safety data base for Blacks/African Americans was insufficient to identify potential unexpected toxicities in this subgroup which may be more vulnerable to drug toxicity based on increased frequencies of certain comorbidities.
3. A clinical trial in HCV-infected patients with severe renal impairment (Trial M14-226) entitled, "An Open-Label Study to Evaluate the Safety and Efficacy of Ombitasvir/ABT-450/Ritonavir and Dasabuvir with or without Ribavirin (RBV) in Treatment-Naïve Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection, with Severe Renal Impairment or End-Stage Renal Disease."

In addition nonclinical studies evaluating resistance will also be conducted as a PMR as outlined in the approval letter.

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/s/

JEFFREY S MURRAY
12/11/2014