CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208624Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review	
NDA	208624
Submission Type	505(b)(1)
Applicant	AbbVie, Inc.
Submission Date	11/27/2015
Generic Name	Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir
Trade Name	Viekira XR
Dosage Form (Strength)	Tablet (Dasabuvir[200 mg]/Ombitasvir[8.33 mg]/Paritaprevir[50 mg]/Ritonavir[33.3 mg]
Proposed Indication	Treatment of HCV Genotype 1 Infection
CDTL	Islam R. Younis, Ph.D.
Recommendation	Approval

1. Introduction

Dasabuvir (DAS) is a hepatitis C virus (HCV) NS5B polymerase inhibitor, ombitasvir (OMB) is a HCV nonstructural protein 5A [NS5A] inhibitor, and paritaprevir (PAR) is a HCV NS3/4A protease inhibitor. The three direct acting antivirals were approved, in 2014, as part of the HCV regimen Viekira Pak™ for the treatment of chronic hepatitis C (CHC) infection genotypes (GT) 1a (with ribavirin) and 1b (NDA 206619). Viekira Pak™ is composed of OMB (12.5 mg), PAR (75 mg), and ritonavir (RTV, 50 mg used to increase blood levels of PAR) fixed dose combination (FDC) tablets co-packaged with DAS (250 mg) tablets. The recommended Viekira Pak™ dosage is two OMB, PAR, RTV tablets once daily (in the morning) and one DAS tablet twice daily (morning and evening) with a meal without regard to fat or calorie content.

2. Background

The Applicant developed Viekira XR FDC tablet containing DAS, OMB, PAR, and RTV in order to provide a once-daily dosing alternative to Viekira Pak™. The proposed indication is identical to the approved Viekira Pak™ indication. Viekira XR differs from Viekira Pak™ by the strength of individual drug substances in each tablet and the total number of tablets taken daily (three tablets once daily with food).

The Applicant is seeking approval of the current application based on the results of two relative bioavailability trials:

1. Trial M14-566: DAS, OMB, PAR, and RTV exposures were compared following single dose and multiple dose administration of Viekira XR and Viekira Pak™ under non-fasting conditions.
2. Trial M14-240: DAS, OMB, PAR, and RTV exposures were compared following single dose administration of Viekira XR and Viekira Pak™ under fasting conditions. Also, the effect of a high fat meal on the exposures of Viekira XR components was assessed.

A clinical trial to evaluate the efficacy and safety of Viekira XR FDC was not required because the efficacy and safety of the components of Viekira XR were established previously in six clinical trials enrolling 2,308 CHC patients with and without cirrhosis, as shown in Table 1.

Table 1. Results of Clinical Trials Conducted with Viekira PAK™ With or Without Ribavirin in Subjects with CHC GT1 Infection (Table prepared by the reviewer).

Trial	Population	RBV	Duration	N	SVR12
SAPPHIRE-I	GT1a TN without cirrhosis	Yes	12 weeks	322	96%
	GT1b TN without cirrhosis	Yes	12 weeks	151	98%
SAPPHIRE-II	GT1a TE without cirrhosis	Yes	12 weeks	173	96%
	GT1b TE without cirrhosis	Yes	12 weeks	124	97%
PEARL-II	GT1b TE without cirrhosis	Yes	12 weeks	91	100%
	GT1b TE without cirrhosis	No	12 weeks	88	98%
PEARL-III	GT1b TN without cirrhosis	Yes	12 weeks	210	99.5%
	GT1b TN without cirrhosis	No	12 weeks	209	100%
PEARAL-IV	GT1a TN without cirrhosis	Yes	12 weeks	100	97%
	GT1a TN without cirrhosis	No	12 weeks	204	90%
TURQUOISE-II	GT1a TN & TE with compensated cirrhosis	Yes	12 weeks	140	89%
	GT1a TN & TE with compensated cirrhosis	Yes	24 weeks	121	95%
	GT1b TN & TE with compensated cirrhosis	Yes	12 weeks	68	98%
	GT1b TN & TE with compensated cirrhosis	Yes	24 weeks	51	100%
TURQUOISE-III	GT1b TN & TE with compensated cirrhosis	No	12 weeks	60	100%

3. Product Quality

The NDA is recommended for approval from product quality perspective. Satisfactory information has been submitted to support the quality of the drug substances and drug product. All manufacturing facilities have been determined to be in acceptable status. Please refer to the Office of Pharmaceutical Quality review dated 06/24/2016 for full details.

Drug Substance: The manufacturing and quality attributes of the active pharmaceutical ingredient ingredients (APIs) of the Viekira XR are acceptable because they were previously reviewed and approved by FDA in the cross-referenced NDAs.

Drug Product: The drug product is pale yellow-colored, film-coated, oblong shaped unscored tablets, debossed with "3QD" on one side. The formulation contains an extended release (ER) DAS layer and an immediate release (IR) layer (containing OMB, PAR, and RTV) added [redacted] (b)(4) [redacted] (b)(4) are acceptable. All the excipients used in the formulation meet compendial (USP/NF) quality standards. Excipient quality controls are acceptable, including additional specifications beyond the compendial requirements. [redacted] (b)(4) [redacted] The proposed process controls are acceptable.

Expiration Date and Storage Conditions: Stability data support a 24 month expiration dating period when stored at or below 30°C (86°F).

Dissolution: The applicant provided sufficient information to support the extended release claim of Viekira XR. The color change in the [redacted] (b)(4) film-coating and debossing between the formulation used in the relative bioavailability trials and the proposed commercial formulation are not expected to affect the bioavailability of individual drug substances The proposed dissolution methods for the individual drug substances are acceptable. In vitro dissolution data showed that addition of 40% alcohol in 0.1 N HCl induced a slight increase in the release rate for DAS in the ER layer as well as the APIs in the IR layer. The alcohol induced dose dumping can be prevented by restraining the consumption of alcohol. Therefore, Viekira XR prescribing information states in section 2.2 that "For optimal release of dasabuvir, alcohol should not be consumed within 4 hours of taking VIEKIRA XR".

Packaging: The primary container is a blister package that consists of [redacted] (b)(4) on one side and aluminum foil backing on the other side. The secondary package is a cardboard box; it [redacted] (b)(4) as well as child-resistance. The proposed packaging is expected to provide adequate protection to ensure product quality over the expiration period.

Container Closure: The container closure consists of a monthly carton for a total of 28 days of therapy. Each monthly carton contains four weekly cartons. Each weekly carton contains seven daily dose packs. Each child-resistant daily dose (blister) pack contains three tablets.

4. Nonclinical Pharmacology/Toxicology

All nonclinical information for the current NDA is cross-referenced to the original NDAs and INDs and no additional nonclinical toxicology information is included in the submission package. The information was deemed sufficient during the review of the referenced NDAs.

5. Clinical Pharmacology

The NDA is recommended for approval from clinical pharmacology. Please refer to the clinical pharmacology review dated 06/23/2016 for full details.

Two relative bioavailability trials constitute the basis of approval for this application:

1. Trial M14-566: was a randomized, open-label, cross-over study which compared DAS, OMB, PAR, and RTV exposures following the administration of Viekira XR and Viekira Pak™ as follows:
   a. Part 1 utilized a 2-regimen, 4-period, 2-sequence fully replicated crossover design to assess the relative bioavailability following single dose administration under non-fasting conditions (approximately 40% of the daily calories from fat and up to 45% of daily calories from carbohydrates [approximately 2,200 total calories/day divided over three meals (616-676 Kcal) and a snack (270 Kcal)]).
   b. Part B utilized a two-period, randomized, crossover design to assess the relative bioavailability following multiple doses..

2. Trial M14-240 was a single-dose, open-label, three-period, randomized, complete crossover study which compared DAS, OMB, PAR, and RTV exposures following the administration of Viekira XR and Viekira Pak™ under fasted conditions in addition to the effect of high fat meal on DAS, OMB, PAR, and RTV exposures following the administration of Viekira XR.

Figure 1 depicts relative exposure changes of individual drugs observed in these trials. DAS and PAR exposure were lower by 68% and 21%, respectively following the single dose administration of Viekira XR relative to the single dose administration of Viekira Pak™ under fasting conditions. OMB exposure was similar following the administration of the two formulations. It should be noted that comparing the two formulations under fasting conditions is not relevant to the clinical use of the regimen because Viekira XR is indicated to be administered with food, similar to Viekira Pak™.

Similar exposures of DAS, OMB, PAR were observed following the administration of multiple doses of Viekira XR relative to the administration of multiple doses of Viekira Pak™ under fed conditions (clinical use scenario) except for PAR Cmax (decreased by 28%) and DAS Cmin (decreased by 29%). The decrease in PAR Cmax is not considered clinically relevant because the efficacy of antiviral drugs for the treatment of chronic viral infections such as HIV or HCV is generally driven by AUC and Cmin.

The applicant developed two exposure-SVR_{12} models to characterize the relationship between AUC or Cmin and efficacy in GT1a CHC patients and to assess the clinical relevance of decreases in DAS Cmin. Note that GT1b CHC patients were not included in the model because SVR_{12} rate was > 99% in this patient population. The model utilized data from 4 phase III trials and 2 phase II trials from the Viekira Pak™ development program. The model was evaluated by the clinical pharmacology review team and was found acceptable. The model predicts that a 38% (lower limit of the 90% CI around the mean) decrease in DAS Cmin will produce a 0.6% decrease in SVR_{12} in CHC GT1 patients and 1.0% decrease in patients with factors (including cirrhosis, male, IL28 non CC patients) identified to be associated with lower Viekira Pak™ efficacy.

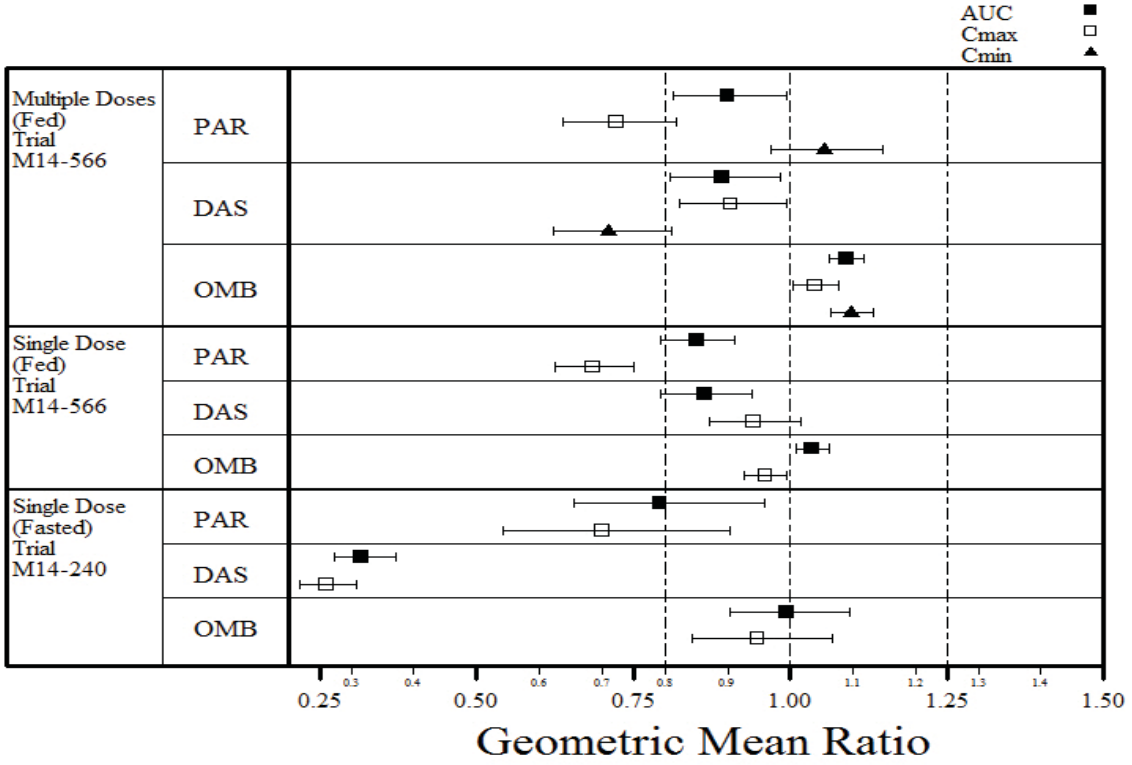

Figure 1. Statistical comparison of DAS, OMB, PAR pharmacokinetic parameters. Points represent the ratio of the geometric mean (Viekira XR/Viekira Pak™) and error bars represent the 90% confidence interval (Figure prepared by the reviewer).

The Applicant evaluated the effect of high fat meal on DAS, OMB, and PAR following the administration of Viekira XR (Figure 2). The AUC of DAS, OMB, PAR was increased by 5.9, 2.0, 4.6 folds, respectively when Viekira XR was administered with high fat meal relative to administration under fasting conditions.

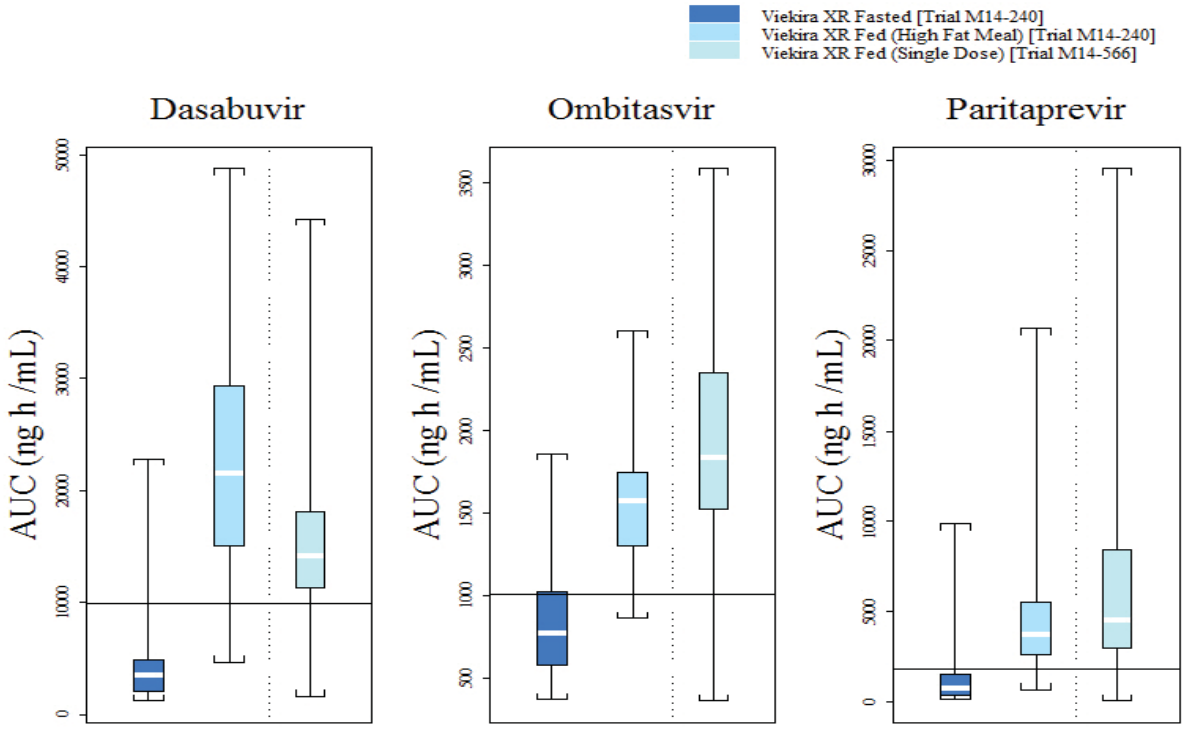

Figure 2. Distribution of DAS, OMB, and PAR AUCs following the administration of Viekira XR under fasting conditions and non-fasting conditions. Solid horizontal line represents median AUC following the admiration of Viekira Pak™ in phase III trials (Figure prepared by the reviewer).

Inspections of the clinical and bioanalytical sites for trial M14-566 were requested. The Office of Study Integrity and Surveillance (OSIS) recommended accepting the bioanalytical and clinical data. Please refer to OSIS memorandum dated 01/08/2016 for full details on clinical site inspection. The inspection of the bioanalytical portion of trial M14-566 was conducted between 02/08/2016 and 02/12/2016. Following the inspection, Form FDA 483 was issued to the applicant. The applicant responded to Form FDA 483 on 03/06/2016 and 03/22/2016 and the responses were deemed satisfactory by OSIS and the issues raised in Form 483 were considered resolved. Please refer to the OSIS memorandum dated 03/24/2016 for full details on bioanalytical site inspection.

6. Clinical Virology

The NDA is recommended for approval from clinical virology perspective. The Applicant did not conduct any new clinical virology studies for this submission. Please refer to the clinical virology review dated 06/21/2016 for full details.

7. Clinical Efficacy and Safety

The NDA is recommended for approval from a clinical perspective. Please refer to the clinical review dated 06/22/2016 for full details.

The applicant did not conduct any clinical efficacy and safety trials with Viekira XR. There is limited safety data generated with Viekira XR during the previously mentioned relative bioavailability trials. Across the two trials, the safety profile of the Viekira XR was generally comparable to Viekira Pak™ with rash and pruritus occurring more frequently in the Viekira XR group. No deaths or serious adverse events (AEs) were reported. Three subjects discontinued due to AEs: one in the Viekira Pak™ arm of trial M12-240 due to headache, and two in the Viekira XR arm of Trial M14-566 due to rash and elevated liver function tests and possible peptic ulcer disease. Rash, pruritus, headache, weight decrease, constipation, nausea and back pain were the most frequently reported AEs regardless of formulation. ALT and bilirubin elevations occurred in similar rates in the Viekira Pak™ and Viekira XR arms. These events have been observed in previous trials of the Viekira Pak™.

8. Advisory Committee Meeting

An Advisory Committee meeting was not held for this application.

9. Pediatrics

There are no pediatric data in the application. This product triggers PREA as a new dosage form. Agreed Initial Pediatric Study Plan (iPSP) for Viekira XR was previously approved on 04/15/2015 and included waiving the requirement to evaluate Viekira XR in pediatric patients younger than 3 years of age. This iPSP is currently under review to expand the waiver to include pediatric patients weighing <42 kg and unable to swallow tablets because the applicant is unable to formulate all the components of Viekira XR into a single formulation for younger children. Further, it is unlikely that pediatric patients who weigh less than 42 kg will be able to swallow the currently available adult Viekira XR formulation. Note that the applicant is developing the components of Viekira XR under the (b)(4) PREA PMR.

10. Other Relevant Regulatory Issues

Financial disclosures were obtained for the relative bioavailability trials for all of the clinical investigators and were reviewed by this reviewer. All investigators reported having no disclosed financial interests/arrangements and, therefore, financial disclosure information does not affect approvability of this application. No additional regulatory issues have been identified.

11. Labeling

The proposed proprietary name Viekira XR was considered acceptable from both a misbranding and safety perspective. Please refer to the Office of Medication Error Prevention and Risk Management, Division of Medication Error Prevention and Analysis memorandum dated 01/14/2016 for full details.

Review and discussions with the applicant regarding the contents of this product prescribing information (PI) are ongoing at the time of this review. DAVP recommended that Viekira XR PI mirrors the approved Viekra Pak™ PI. Also, DAVP recommended listing the components of Viekira XR in alphabetical order throughout Viekira XR PI. Finally, DAVP recommended modifications to the container labels, carton labeling, and (b)(4) to mitigate dosing errors and improve clarity of information.

12. Recommendations/Risk Benefit Assessment

12.1 Recommended Regulatory Action: Approval

12.2 Risk Benefit Assessment: The risk-benefit profile of Viekira XR is acceptable based on the assessment of the review team. Because Viekira XR produced similar exposure to Viekira Pak™ under non-fasting conditions the risks and benefits of Viekira XR is considered similar to those of Viekira Pak™. Efficacy and safety of Viekira Pak™ were established previously in clinical trials in HCV patients.

The only concern this reviewer has is regarding the administration of Viekira XR under fasting conditions. The AUC of DAS, OMB, and PAR from Viekira XR is reduced by 78%, 84%, and 55%, respectively when administered under fasted conditions relative to the administration with moderate or high fat meals. This reduction in exposure is predicted to produce a 9.1% absolute reduction in SVR_{12}. When compared to exposures observed in Viekira Pak™ phase III trials, DAS, OMB, and PAR exposures from Viekira XR under fasting conditions are 67%, 21%, and 49% lower, respectively, which is predicted to produce a 3% absolute reduction in SVR_{12}.

Therefore, this reviewer recommends adding a [redacted] (b)(4) of Viekira XR PI to warn against the administration of Viekira XR under fasting conditions.

12.3 Recommendation for Postmarketing Risk Evaluation and Management Strategies: None

12.4 Recommendation for other Postmarketing Requirements and Commitments: A PMR will be issued for pediatric studies under the Pediatric Research Equity Act (PREA) and consistent with the Agreed Initial Pediatric Study Plan.

12.5 Recommended Comments to Applicant: None

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/s/

ISLAM R YOUNIS
07/07/2016