CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208624Orig1s000

SUMMARY REVIEW

Summary Review: Deputy Division Director	
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)	Fixed Dose Combination Tablet (FDC): dasabuvir 200mg, ombitasvir 8.33 mg, paritaprevir 50 mg, ritonavir 33.3 mg
Proposed Indication	Treatment of Hepatitis C Virus (HCV) Genotype-1 Infection
Deputy Division Director	Jeffrey Murray, M.D., M.P.H.
Recommendation	Approval

1. Introduction/Background

This is a new drug application for Viekira XR, a FDC tablet of previously approved antiviral drugs containing: dasabuvir (DAS), a HCV NS5B polymerase inhibitor; ombitasvir (OMB), a HCV nonstructural protein 5A (NS5A) inhibitor; paritaprevir (PAR), a HCV NS3/4A protease inhibitor; and ritonavir (RTV), a Cyp3A inhibitor (and HIV protease inhibitor) included to increase exposures of paritaprevir. The three new HCV 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 and 1b. Viekira Pak™ is a co-packaged product of DAS tablets (25 mg) and a FDC tablet containing OMB (12.5 mg), PAR (75 mg), and RTV (50 mg). The recommended Viekira Pak™ dosage is two OMB, PAR, RTV tablets once daily (in the morning) and one dasabuvir tablet twice daily (morning and evening). Therefore, Viekira XR differs from Viekira Pak™ in that all of the HCV antivirals are now combined in one FDC for once daily dosing, the daily mg dose of DAS is higher, and DAS is administered once daily as part of the FDC. However, certain patients need to take twice daily ribavirin with Viekira Pak™ or Viekira XR, depending on GT subtype, so the entire HCV regimen will still be twice daily for those patients. The proposed indication for Viekira XR is identical to the approved Viekira Pak indication because Viekira XR relies on the clinical efficacy and safety data base used to support approval of Viekira Pak™.

As stated in Dr. Younis's Cross Discipline Team Leader (CDTL) review, AbbVie is seeking approval of Viekira XR based on comparability of bioavailability for each of the components in the new formulation compared to that of the previously approved formulations in Viekira Pak™. AbbVie submitted the results of two relative bioavailability trials:

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1. Trial M14-566: DAS, OMB, PAR, and RTV exposures were compared following a 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 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 (refer to the Viekira Pak™ package insert).

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.

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.

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 and to the CDTL review prepared by Dr. Islam Younis.

As stated above, two relative bioavailability trials are the basis of approval for this application. The Office of Study Integrity and Surveillance (OSIS) recommended accepting the bioanalytical and clinical data from trial M14-566. Inspection for Trial M14-240 was not requested. Please refer to OSIS memorandum dated 01/08/2016 for full details on clinical site inspection.

In brief, study results showed that OMB exposures were similar following the administration of the two formulations (Viekira XR and the FDC from Viekira Pak™). However, both DAS and PAR exposures were lower by 68% and 21%, respectively following the single dose

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administration of Viekira XR relative to the single dose administration of Viekira Pak™ under fasting conditions (Trial M14-240). Comparing the two formulations under fasting conditions is not relevant to the clinical use of the regimens because Viekira Pak™ is labeled to be administered with food. In addition, Viekira XR will also be labeled to be given with a meal.

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-as studied in trial M14-566) 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. Thus, the modest reduction in DAS Cmin was the only exposure parameter that needed further justification. To justify the acceptability of the modest reduction in DAS Cmin, AbbVie developed exposure-response (SVR_{12}) models. The model utilized data from four phase 3 and two phase 2 trials from the Viekira Pak™ development program. The clinical pharmacology review team evaluated the model and found it to be acceptable. The model predict 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 baseline or demographic factors associated with lower Viekira Pak™ efficacy.

With respect to food, the AUC of DAS, OMB, PAR was increased by 5.9, 2.0, 4.6 folds, respectively when Viekira XR was administered with a high fat meal. The exposures after a meal are those needed to ensure SVR rates observed in Viekira Pak™ clinical trials; therefore Viekira XR should not be taken in the fasting condition.

6. Clinical Microbiology

The NDA is recommended for approval from clinical microbiology 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. In the two bioavailability trials, the safety profile of the Viekira XR was comparable to Viekira Pak™ with

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rash and pruritus occurring more frequently in the Viekira XR group. No deaths or serious adverse events (AEs) were reported.

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. PREA PMRs will only include pediatric patients weighing at least 42 kg as children of lower weight (and age) would probably have difficulty swallowing the large Viekira XR FDC tablet that includes four drugs. In addition the applicant is developing the components of this drug regimen under the (b)(4) PREA PMR for weight groups less than 42 kg.

10. Labeling

One important statement of note occurs in the Dosage and Administration section of the label in both the full prescribing information and the Highlights, "VIEKIRA XR must be taken with a meal because administration under fasting conditions may result in reduced virologic response and possible development of resistance." Consistently taking Viekira XR on an empty stomach would result in substantial reductions in exposures particularly for PAR and DAS and was estimated to result in an overall reduction in SVR12 of approximately 9% with the potential for emergence of drug resistance of two or more drugs or drug classes.

12. Recommendations/Risk Benefit Assessment

I concur with the review team that the risk-benefit profile of Viekira XR is acceptable and that this application should be approved. Viekira XR allows for once daily dosing (three pills) for patients who don't require addition of ribavirin to the regimen. Therefore it offers a modest convenience benefit for a subgroup of patients compared to Viekira Pak™. Viekira XR produced similar exposures of the component drugs to that of Viekira Pak™ under non-fasting conditions such that the risks and benefits of Viekira XR are expected to be similar to those of Viekira Pak™. One drug, DAS, had a modest Cmin reduction in the Viekira XR formulation that was determined to be clinically insignificant based on exposure response modeling.

The only concern of the review team was the reduction of drug exposures following administration of Viekira XR under fasting conditions. The exposures of DAS, OMB, and PAR from Viekira XR is reduced by 78%, 84%, and 55%, respectively when administered under

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fasted conditions relative to administration with moderate or high fat meals. When compared to exposures observed in Viekira Pak™ phase III trials, DAS, OMB, and PAR exposures from Viekira XR under fasting conditions for every drug administration would be 67%, 21%, and 49% lower, respectively. This would be expected to result in an absolute reduction in SVR12 of approximately 3%, but as stated in Dr. Younis's review SVR reductions could be larger taking into account cross study comparisons. To address this concern a statement was included in the Dosage and Administration section of the Highlights and full prescribing information to stress the importance of taking Viekira Pak with a meal.

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/s/

JEFFREY S MURRAY
07/22/2016