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APPLICATION NUMBER:

208624Orig1s000

MEDICAL REVIEW(S)

NDA 208624

Medical reviewer: Tanvir Bell, MD

Subject: Amendment to Pediatrics (Section 10) of Clinical Review dated June 22, 2016

Sponsor: AbbVie

Product: Viekira XR

This amended clinical review serves to document the agreed upon changes regarding the pediatric plan to include PREA deferrals and waivers, and PREA PMR submission dates.

PREA Deferrals and Waivers

In the original NDA application submitted on September 28, 2015, the applicant included their Agreed PSP that outlined the pediatric development plan utilizing Study (b) (4). AbbVie had originally requested (b) (4).

After review by the Division and the Pediatric Review Committee (PeRC), further clarification with AbbVie occurred around an appropriate weight estimate for who may be able to swallow a tablet, instead of an age cut-off. AbbVie proposed 42kg.

The Applicant will be issued a PREA PMR to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response as the primary endpoint) of ombitasvir, paritaprevir, ritonavir, dasabuvir in pediatric patients with chronic hepatitis C virus infection, who weigh at least 42 kg and are able to swallow tablets. (b) (4)

(b) (4)
AbbVie was granted a deferral for the studies in pediatric patients who weigh at least 42 kg and are able to swallow tablets. The final report is due 8/31/2022.

Studies in pediatric patients less than 3 years of age have been waived because necessary studies would be impossible or highly impractical and there is no expected benefit for this age group.

PREA PMR Submission Dates

This amended clinical review documents discussions that occurred between DAVP and AbbVie to agree to new deferral timetable submission dates, as they were different than what was submitted in the original NDA application (Agreed PSP). During the review of the NDA, PREA PMR (b) (4)

(b) (4)

AbbVie was requested (b) (4) Viekira XR (b) (4)

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/s/

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07/15/2016

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07/15/2016

Clinical Review
Tanvir Bell, MD
NDA208624
3QD (dasabuvir/ ombitasvir/ parataprevir/ ritonavir)

Clinical Review

Date	
From	Tanvir Bell, M.D. Medical Officer
Subject	Clinical Review
NDA	NDA 208624
Applicant	AbbVie, Inc.
Date of Submission	11/27/15
PDUFA Goal Date	7/28/16
Proprietary Name	Proposed name Viekira XR
Dosage Form/Strengths	Single tablet containing 200 mg dasabuvir/8.33 mg ombitasvir/50 mg parataprevir/33.3 mg ritonavir
Proposed Indication(s)	Treatment of genotype 1 Hepatitis C virus infection including those with compensated cirrhosis, with or without ribavirin
Recommendation	Approval

1. Executive Summary

In summary, the 3QD fixed-dose formulation of dasabuvir, ombitasvir, parataprevir, and ritonavir demonstrated similar exposure to the previously approved individual components (3-DAA) and approval is recommended. The 3-DAA regimen is marketed under the trade name Viekira Pak® and consisted of a fixed-dose tablet containing ombitasvir, paritaprevir and ritonavir co-packaged with dasabuvir. The overall dasabuvir exposures with the fixed-dose formulation are about 20% less, but loss of efficacy against Hepatitis C virus is not expected. Dasabuvir was previously administered separately twice daily whereas it is now included as a component of the new 3QD formulation. No new safety signals were identified. The most frequently reported adverse events in the relative bioavailability studies were headache, nausea, chills and fatigue, which have been observed in large clinical trials of the regimen. Similar ALT elevation and alkaline phosphatase elevations were also observed in subjects who received the 3QD as with 3-DAA in these small studies.

2. Introduction

The Applicant is proposing a new co-formulated fixed-dose combination (FDC) containing dasabuvir, ombitasvir, paritaprevir, and ritonavir to replace its currently approved combination of the same drugs that are administered as a FDC of ombitasvir, paritaprevir, ritonavir administered with separate dasabuvir (3-DAA).

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The components of the 3-DAA and 3QD regimens are dasabuvir, a hepatitis C virus non-nucleoside NS5B polymerase inhibitor; ombitasvir, a hepatitis C virus NS5A inhibitor; paritaprevir, a hepatitis C virus NS3/4A protease inhibitor; and ritonavir, an HIV protease inhibitor, which is also a CYP3A inhibitor being used to boost levels of paritaprevir. The 3-DAA regimen is approved for use in combination with ribavirin in patients with genotype 1a infection with or without cirrhosis.

The prior 3-DAA approved co-formulation consists of two tablets of ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablet given once daily with a separate tablet of dasabuvir 250mg administered twice daily. The combination is currently copackaged as Viekira® Pak, (NDA 206619). This new formulation ["3QD"] contains all the agents in a single formulation of dasabuvir, ombitasvir, paritaprevir, ritonavir 200/8.33/50/33.33 mg. The proposed regimen is three tablets taken once daily with a meal without regard to fat or calorie content. The development program for 3QD is dependent on the results of two relative bioavailability studies M14-566 and M14-240. The proposed 3QD FDC contains an additional 100 mg of dasabuvir to equal a total daily dose of 600 mg.

3. CMC

The 3QD dosage form is a bilayer tablet with dasabuvir in the extended release (ER) layer and ombitasvir, parataprevir, and ritonavir formulated within the immediate release (IR) layer. The ER layer of dasabuvir has the (b)(4) form but has copovidone added to (b)(4). The commercial formulation of this bilayer tablet will be pale yellow. The tablets are packaged in a blister pack with 3 tablets per card. It will be dispensed as monthly cartons. The instructions on the blister pack are to take the three tablets once-daily at same time with a meal. The cartons need to be stored at or below 30°C (86°F). Please refer to the Product Quality review for complete details.

4. Nonclinical Pharmacology/Toxicology

Extensive programs of nonclinical studies were previously conducted and fully reviewed under NDA 206619. In view of nonclinical safety profiles for each of these compounds, additional nonclinical combination safety studies with dasabuvir, ombitasvir, parataprevir, and ritonavir were not necessary to support this application. Therefore, no new nonclinical pharmacology/toxicology data were submitted by the sponsor.

5. Clinical Pharmacology/Biopharmaceutics

Please refer to Clinical Pharmacology Review for details.

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The applicant conducted two pivotal relative bioavailability studies to support approval of the 3-QD formulation.

Comparative Bioavailability Studies Using dasabuvir/ombitasvir/parataprevir/ritonavir: Studies M14-566 and M14-240

Study M14-566 was a Phase 1, non-fasting, open-label, two-part study. Part 1 was a single dose study, and Part 2 was a 14-day multiple dosing regimen that compared the 3QD regimen (3 pills dasabuvir, ombitasvir, paritaprevir, ritonavir 200/8.33/50/33.3 mg) to the 3-DAA regimen (2 pills ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg with dasabuvir 250 mg dosed morning and evening).

In Part 1, 88 subjects were enrolled. Each subject received a single daily dose of the 3QD regimen and the 3-DAA regimen in a two occasion 4-period, 2-sequence replicated crossover study design. The primary objective was to evaluate the bioavailability of the 3QD regimen compared to 3-DAA regimen after one day of dosing. The results showed that 3QD had comparable bioavailability to the 3-DAA regimen.

Four subjects were withdrawn from Part 1 due to non-AE related issues: one failed to come for study visits; two had a positive urine cotinine test and were withdrawn at the investigator's discretion; and one withdrew for personal reasons.

In Part 2, 66 subjects were enrolled in a two period, crossover design. Each subject received fourteen days of treatment in each period. The primary objective was to evaluate the bioavailability of 14 day dosing. Both regimens had comparable bioavailability for components when measuring the C_{max} and AUC.

Exposures of 3QD compared with 3-DAA were as follows:

- Bioavailability for all components were comparable when measuring the C_{max} and AUC.
- Dasabuvir mean C_{24} exposures decreased by 29%.
- Parataprevir mean C_{24} exposures decreased by 27%.
- Ritonavir mean C_{24} exposures decreased by 21%
- Ombitasvir mean C_{24} exposures were equivalent.

Five subjects were withdrawn from Part 2; two withdrew consent, one was lost to follow-up, and two subjects with AEs and are described in the AE section below.

Study M12-240 was a Phase 1, single dose, open-label, three period, randomized crossover study. The primary objective of M12-240 was to evaluate the effects of food on the 3QD regimen versus the 3-DAA and to evaluate the bioavailability of both regimens. Forty-six subjects were enrolled in the study.

Exposures in the 3QD compared with 3-DAA were as follows:

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- In the fasting condition, dasabuvir had 70% lower exposures, parataprevir had 21%-30% lower exposures, and ombitasvir and ritonavir had exposures that were comparable.
- In the fed condition versus the fasted condition, dasabuvir had 600% higher exposures, ombitasvir had 100% higher exposures, parataprevir had 360% to 500% higher exposures, and ritonavir had 100% higher exposures.
- The greater magnitude on dasabuvir and parataprevir in fed conditions is because of lower exposures in the fasted condition.

A total of four subjects withdrew from the study. Two subjects had positive urine drug screen during period two and were withdrawn by the investigator; one subject withdrew consent; and one subject failed to return for the second period of the study.

6. Clinical Microbiology

No clinical microbiology data was submitted for these relative bioavailability studies, which enrolled healthy volunteers. For more information regarding the microbiology and virology of these products, please see NDA 206619.

7. Clinical/Statistical-Efficacy

No clinical trials with the 3QD formulation were conducted. Please refer to NDA 206619 for details regarding efficacy of dasabuvir, ombitasvir, parataprevir, and ritonavir.

8. Safety

Safety Summary

Limited safety data from the BA/BE studies did not generate any new safety concerns for the 3QD regimen. Across the two studies, the safety profile of the 3QD was generally comparable to 3-DAA with rash and pruritus occurring more frequently in the 3QD groups. No deaths or SAEs were reported. Three subjects discontinued due to adverse events: one in the 3-DAA arm of Study M12-240 due to headache, and two in the 3QD MAD portion of Study M14-566 due to rash and elevated liver function tests and possible peptic ulcer disease.

Across the studies, rash, pruritus, headache, weight decreased, constipation, nausea and back pain were the most frequently reported adverse event regardless of

formulation. These events have been observed in previous trials of the 3-DAA formulation.

Liver function changes have been observed with this regimen of drugs and ALT and bilirubin elevations occurring similar rates in the 3-DAA and 3QD arms of these small studies.

AE's

The most common AE that occurred in the single dose study M12-240 was headache: 1/45 (2.2%) in the 3QD group and in 2/45 (4.4%) in the 3-DAA group. In M14-566 Part 1, headache occurred in 6/87 (6.9%) of subjects in the 3QD group versus 9/87 (10.3%) in the 3-DAA group.

In Study M14-566 Part 2, adverse events were generally mild to moderate in severity. Table 1 below shows AEs reported in at least two subjects. AE groups are created by this medical reviewer to help organize the constellation of MedDRA preferred terms to clinically meaningful categories.

Table 1. AEs in M14-566 Part 2.

AE groups	MedDRA Preferred Term	Regimen A 3-QD N=63, n(%)	Regimen B-3-DAA N=65, n(%)
Possible allergic reaction	Rash papular	7 (11)	3 (4.6)
	Pruritus	6 (9.5)	6 (9.2)
	Pruritus generalized	3 (4.8)	1(1.5)
	Throat irritation	0	3 (4.6)
	Ocular hyperemia	2 (3.2)	0
Generalized reaction	Headache	4 (6.3)	11 (16.9)
	Chills	1(1.6)	3 (4.6)
	Fatigue	1 (1.6)	2 (3.1)
	Dizziness	0	3 (4.6)
	Presyncope	0	3 (4.6)
	Nervousness	3 (4.8)	0
	Weight decreased	6 (9.5)	6 (9.2)
GI disturbance	Constipation	8 (12.7)	11 (16.9)
	Nausea	1 (1.6)	6 (9.2)
	Abdominal pain upper	2 (3.2)	0
	Flatulence	0	2 (3.1)
Musculoskeletal	Back pain	5 (7.9)	1 (1.5)

Two subjects discontinued M14-566 Part 2 due to an AE; and both were on the 3QD regimen when the AEs occurred.

- Subject 226 had rash, pruritus and moderate abdominal discomfort with a Grade 3 elevation in ALT to 301 U/L and grade 2 elevation in AST to 169 U/L reported on day 14, and study drug was discontinued. The total bilirubin was 1.4 mg/dL and was within normal limits for the duration of the study period. On day 17 his ALT peaked to 451 U/L with an AST 225 U/L. On Day 21 the subject experience bilateral upper quadrant abdominal pain with papular rash and pruritus in axillae and suprapubic area. On day 24 the abdominal pain resolved, but on Day 30 (post treatment day 16), the subject experienced a second event of abdominal pain of moderate intensity, ALT was 90 U/L. Secondary causes of hepatitis were ruled out. On Day 37 (post-treatment Day 23), the event of ALT elevation was considered resolved.

Reviewer comment: This subjects' constellation of findings can be consistent with drug allergy evidenced by the rash, elevated ALT and abdominal pain. Elevated ALTs can contribute to abdominal pain as a consequence of hepatic congestion. Transaminitis is known to be related to paritaprevir and this single incidence does not equate to a new safety signal.

- Subject 258 discontinued due to symptoms consistent with a peptic ulcer. On day 33 the subject presented with nausea, vomiting and dizziness. She discontinued study drugs on day 34. Her symptoms were treated with clear soda, saltines, calcium carbonate and ranitidine, and the event resolved on post treatment day 10 (day 44). The investigator considered this event to have a reasonable possibility of being related to study drug. The subject already completed taking the 3-DAA regimen prior to being on 3QD and occurrence of the peptic ulcer.

Reviewer comment: It is challenging to determine causality as no diagnostic studies were undertaken and abdominal pain, nausea and vomiting have been reported in other clinical trials of these DAAs.

Lab abnormalities

In Study M14-566, Part 2, five subjects experienced clinically significant changes laboratory values and are described herein. Four subjects had elevations in total bilirubin values that were greater than 2 times the upper limit of normal. Two subjects had the elevation occur with both the 3QD and 3-DAA regimen; and in each the bilirubin level normalized on therapy. Two additional subjects had the elevation with the 3-DAA regimen; those elevations also normalized on therapy. All four elevations were elevations in indirect bilirubin without clinical jaundice. The subject with the grade 3 ALT elevation and grade 2 AST elevation was an SAE and is described above.

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Reviewer comment: One of the components of the 3-DAA regimen, paritaprevir, is a known inhibitor of the bilirubin transporter OATP1B1, which is associated with asymptomatic elevations of predominantly indirect bilirubin levels.

In M14-566, Part 1, two subjects on the 3QD regimen had laboratory abnormalities that were isolated and not clinically significant. One had an isolated elevation of total bilirubin on 63.28 mcM/L on day 2, and one subject had a single triglyceride elevation of 12.88 mmol/L on day 9. One subject on the 3-DAA regimen had an isolated elevation of white blood count of $22.5 \times 10^9/L$. None of these three abnormalities were associated with any adverse events.

In Study M12-240, one subject had neutropenia in the 3QD non-fasted arm, which was also observed when the subject received the 3-DAA regimen in the fasted state. The subject started with a neutrophil count of 1,180/L and decreased to approximately 900 both times and recovered to at or above 1,170/L. Neither incident of neutropenia was associated with an adverse event.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics

There is an agreed iPSP for Viekira Pak and assessments (b) (4)
currently ongoing. (b) (4)

The Applicant received a waiver for subjects under 3 years of age since this clinical trials in this age group would be difficult and the population is described as lacking clinical benefit.

11. Other Relevant Regulatory Issues

No additional regulatory issues have been identified.

12. Labeling

The proposed labeling changes by company include changes in dosages in section 2.1 and section 3. References within labeling to the combination of dasabuvir, ombitasvir,

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parataprevir, and ritonavir occur throughout the document. When describing the combination, previous versions with 3-DAA combination had dasabuvir listed last, whereas the new labelling of 3QD has the drugs listed in alphabetical order with dasbuvir listed first. [REDACTED] (b) (4)

[REDACTED] Section 12.3 Pharmacokinetics was updated to reflect changes in bioavailability with the new formulation of the drugs in the healthy volunteer studies. At the time of this review, it states at [REDACTED] (b) (4)

[REDACTED] respectively. Evaluations of labelling modifications are continuing at the time of this review. Final labelling recommendations will follow from the review team.

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/s/

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