CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207931Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	July 1, 2015
From	Jeffrey S. Murray MD, MPH, Deputy Director
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	207931 Original
Applicant Name	AbbVie, Inc.
Date of Submission	February 25, 2015
PDUFA Goal Date	August 25, 2015
Proprietary Name / **Established (USAN) Name**	Technivie™ (ombitasvir, paritaprevir and ritonavir tablets)
Dosage Forms / Strength	Co-formulated Tablets Ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg
Proposed Indication(s)	Treatment of genotype (GT) 4 chronic hepatitis C virus infection
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Joint Clinical, Statistical, and Virology Review	Russell Fleischer Karen Qi Pat Harrington
CMC Review	Milton Sloan
Clinical Pharmacology Review	Vikram Arya

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

1. Introduction

This memorandum serves as both the Summary Review of Regulatory Action for the Division of Antiviral Products and the Cross-Discipline Team Leader memo. Note that the clinical, statistical and virology reviews are written under one joint review. Memos were combined for this application because: 1) the NDA includes molecular entities that have previously been approved, 2) there is only one trial supporting the indication for the treatment of genotype 4 (GT4) HCV, 3) the product appears to be highly efficacious (no virologic failures when administered with ribavirin in GT4 patients in the submitted trial), and 4) there are no significant review issues.

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 without interferon (IFN) to treat all genotypes. Presently, several all oral IFN-free regimens

are approved for GT1 and one oral regimen is approved for GTs 2 and 3; however there are no approved IFN-free regimens for GT4. Only IFN-based regimens with or without ribavirin and the NS5B polymerase sofosbuvir (Sovaldi®) are approved for the treatment of GT4 infection in the United States. This new drug application (NDA) is for a co-formulated product called Technivie intended to treat noncirrhotic patients with chronic GT4 HCV infection. Technivie[1] contains two direct-acting HCV antivirals (DAAs), ombitasvir and paritaprevir, and a CYP3A inhibitor, ritonavir, to increase exposures of paritaprevir. Technivie will generally be used with ribavirin (strongly recommended for patients able to take ribavirin) for a treatment duration of 12 weeks. The components and strengths of the fixed dose combination tablets are:

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)

Paritaprevir was the fourth HCV protease inhibitor and ombitasvir was the second NS5A inhibitor to be approved for the treatment of GT1 HCV infection and are components of a product with the trade name Viekira Pak™. Viekira Pak™ also includes a non-nucleoside HCV RNA polymerase inhibitor, dasabuvir, but this drug is not included in Technivie because it has no activity against GT4.

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 Technivie). 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) or, in this case the HCV NS3/4A inhibitor paritaprevir, by inhibiting CYP3A metabolism. Any drug combination containing ritonavir can be expected to have a significant amount of drug-drug interactions.

2. Background

A Pre-NDA meeting for the 2-DAA combination took place on October 9, 2014. This NDA was reviewed as a Breakthrough therapy (designation granted on 6/30/14) under a priority review time clock.

HCV GT4 is uncommon in the U.S. but is prevalent in other parts of the world particularly the Middle East and certain regions of Africa. In the U.S. approximately 1-2% of HCV infected patients are infected with GT4. HCV GT4 is extremely diverse, with at least 17 confirmed subtypes. The prevalence of specific HCV GT4 subtypes in the U.S. had not been established.

[1] The trade name Technivie for this FDC of three drugs is used throughout the review for efficiency

1) CMC (Chemistry, Manufacturing, Controls)

Technivie™ (ombitasvir, paritaprevir, ritonavir) tablets are pink-colored, film-coated, oblong biconvex shaped tablets containing 12.5 mg ombitasvir, 75 mg paritaprevir and 50 mg of ritonavir debossed with "AV1" on one side. The full daily regimen is co-packaged and dispensed in a monthly carton for a total of 28 days of therapy. Each monthly carton contains four weekly cartons, and each weekly carton contains seven daily dose packs.

Refer to the review prepared by Milton Sloan Ph.D. who concurs with approval of the product. The drug substances, product and biopharmaceutics information have not changed since the review of this fixed dose tablet for Viekira Pak™ (NDA 206619). In addition, no inspections of manufacturing and testing sites were conducted because these sites were inspected during review of the Viekira Pak™ NDA.

2) Nonclinical Pharmacology/Toxicology

Refer to the review prepared by Dr. Mark Seaton recommending approval of Technivie.

All nonclinical information for the current NDA is cross-referenced to the Viekira Pak™ NDA (206619) and to the INDs or NDAs for the individual drugs: IND 103,526 (paritaprevir), IND 108,434 (ombitasvir), NDA 206-619 (Viekira Pak™) and NDA 22-417 (ritonavir). No additional nonclinical toxicology information is included in this NDA submission. The referenced nonclinical package was complete and consists of studies in mice, rats, rabbits, monkeys and dogs.

As stated in the Viekira Pak™ review, the nonclinical studies were conducted with the individual drug components of Technivie and 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[2], 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.

As a brief summary, animal studies identified the gallbladder, and to a lesser extent the liver, as potential toxicities to be monitored for in clinical trials. Repeat dose toxicology studies of the two HCV DAAs 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. 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 in patients administered Technivie.

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

Ritonavir has been shown to have liver toxicity in humans particularly at the doses initially used for the treatment of HIV.

Carcinogenicity and reproductive toxicology are discussed in the reviews of Viekira Pak™.

3) Clinical Pharmacology/Biopharmaceutics

For a complete discussion of the clinical pharmacology issues, please refer to the Clinical Pharmacology Review prepared by Dr. Vikram Arya. Dr. Arya's review concludes that the information in the application supports the approval of Technivie.

Dr. Ayra notes that the clinical trial supporting this NDA was conducted using individual drug formulations of paritaprevir, ombitasvir, and ritonavir and not with the to-be-marketed fixed dose combination (FDC). The bioavailability of the FDC formulation is greater than that of the individual formulations used in the clinical trial. As stated in Dr. Arya's review, higher exposures with the FDC should not have a negative effect on efficacy and safety of the FDC formulation was evaluated in the phase 3 trials supporting approval of Viekira Pak™.

AbbVie anticipated many clinically relevant drug interactions, primarily because paritaprevir is extensively metabolized by CYP3A4, and ritonavir is a potent inhibitor of CYP3A4. Dr. Arya reviewed drug-drug interaction data obtained using the 2-DAA regimen (8 trials) from drug-drug interaction trials submitted to the Viekira Pak™ NDA in which multiple arms evaluated both the two and three drug DAA regimens with co-administered drugs. Dr. Ayra's review describes in detail the basis for drug-interaction labeling recommendations for the two DAA regimen compared to the three DAA regimen. For some co-administered drugs labeling recommendations are the same for the two regimens, for other co-administered drugs labeling recommendations differ for Viekira Pak™ and Technivie.

In addition to the clinical trial submitted to support the efficacy and safety of Technivie for the treatment of GT4 HCV infection in noncirrhotic patients, the applicant also submitted the results of an absolute bioavailability study (M14-229). Following single dose administration of paritaprevir as an oral co-formulated product with ombitasvir and ritonavir under non-fasting conditions, the geometric mean absolute bioavailability of paritaprevir and ombitasvir was 52.6% and 48.1 %, respectively.

4) Clinical Virology

Refer to the relevant virology sections in the joint review mentioned above for detailed information regarding prevalence of GT4 by subtype and resistance analyses in trial M13-393. The joint review includes the following table of GT4 subtypes overall for the trial and in the U.S. It is noteworthy that 89% of U.S. patients in the trial were GT4a, only one subject of 18 was GT4d.

HCV GT4 subtypes in M13-393 based on phylogenetic analysis (consensus results from NS3/4A, NS5A and NS5B)

GT 4 Subtypes	Number of Subjects
4 (i.e., analyzed, but not determined)	1 (1%)
4a	50 (38%)
4b	3 (2%)
4c	1 (1%)
4d	68 (52%)
4f	7 (5%)
4g/4k	1 (1%)
4o	1 (1%)
Not Reported	3
GT 4 Subtypes (U.S.)	**Number of Subjects**
4a	16 (89%)
4c	1 (6%)
4d	1 (6%)

The three subjects who experienced virologic failure in M13-393 were infected with HCV GT4d, which appears to be an infrequent subtype in the U.S based on the GT4 patients enrolled in this trial. In HCV GT4d infected subjects, no baseline polymorphisms were observed at NS3 positions previously associated with resistance to NS3/4A protease inhibitors, and therefore the impact of baseline NS3 polymorphisms on treatment efficacy cannot be assessed. All three patients with virologic failure had treatment-emergent NS3 D168V, which was a substitution associated with treatment failure in HCV GT1 infected subjects observed in the Viekira Pak™ NDA. A Y56H substitution, which is also associated with paritaprevir resistance in GT1, emerged in a patient who experienced virologic breakthrough. The D168V substitution alone confers a 313-fold reduction anti-HCV activity of paritaprevir and the Y56H + D168V combination a >12,000-fold reduction in activity.

5) Clinical/Statistical-Efficacy

This NDA is supported by a single clinical trial (M13-393) entitled "A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Co-administration of ABT-450 (paritaprevir) with Ritonavir (ABT-450/r) and ABT-267 (ombitasvir) in Adults with Chronic Hepatitis C Virus Infection (PEARL-I)." A single trial is considered appropriate to serve as basis for approval because of the extensive amount of safety and efficacy data available for ombitasvir and paritaprevir (as components of Viekira Pak™) in the treatment of GT1a and GT1b infections. Efficacy of these drugs in the treatment of other HCV genotype/subtypes is considered to be supportive evidence for the efficacy of these drugs in GT4.

The study was conducted in 181 HCV GT1b-infected adults with and without compensated cirrhosis and 135 non-cirrhotic HCV GT4-infected subjects. The applicant is only asking for approval of Technivie for GT4 infection. For more detailed descriptions of the trial design supporting efficacy, please refer to the joint Clinical-Statistical and Virology Review prepared by Senior Clinical Analyst Russell Fleischer, Patrick Harrington Ph.D. (virologist) and Karen Qi Ph.D. (statistician).

Study M13-393 is a trial that was designed to evaluate open-label paritaprevir/ritonavir + ombitasvir with and without RBV for 12 weeks in treatment-naïve and pegIFN/RBV-experienced HCV GT1b-infected cirrhotic and non-cirrhotic subjects and GT4-infected non-cirrhotic subjects. The primary endpoint was the percentage of subjects achieving SVR12, defined as HCV RNA less than the lower limit of quantification (<LLOQ) 12 weeks after the last dose of study drug. The study was conducted at 46 sites in the United States (US), Puerto Rico, France, Hungary, Italy, Poland, Romania, Spain and Turkey.

This memo will only summarize efficacy for patients with GT4. Three GT4 groups were studied:

- Group 1: Treatment naïve subjects treated with Technivie for 12 weeks
- Group 4: Treatment naïve subjects treated with Technivie plus ribavirin for 12 weeks
- Group 6: Prior pegIFN/RBV non-responders treated with Technivie plus ribavirin for 12 weeks

Eligible GT4 treatment naïve subjects were randomized in a 1:1 ratio into Group 1 or Group 4. A total of 135 HCV GT4-infected subjects were enrolled: 42 into Group 1, 44 into Group 4 and 49 in Group 6. Demographic and disease characteristics were similar across the three treatment groups with most subjects being male (65%) and Caucasian (90%); all subjects had a Childs-Pugh score <6; 77% had F0-F1 fibrosis, 16% had F2 fibrosis, 7% F3 fibrosis and <1% F4 fibrosis. The inclusion criteria specified that patients should not be known to have cirrhosis by biopsy or noninvasive tests.

Efficacy results are shown in the table below. There were no virologic failures among the 91 patients, naïve and treatment experienced, who received Technivie with ribavirin. The ribavirin –free regimen (Group 1) produced a lower SVR12 rate, which was statistically significant in some analyses (refer to the joint review), compared to that of Groups in which ribavirin was administered with Technivie; however, Group 1 SVR12 rates were still greater than 90%. Three of the four patients classified as nonresponders had virologic failure (relapse or breakthrough).

SVR12 rates and reasons for non-response in GT4-infected subjects

	Group 1 (Naïve) Technivie n=44	**Group 4 (Naïve) Technivie + RBV n=42**	**Group 6 (PR exp.) Technivie + RBV n=49**
SVR12	40/44 (91%)	42/42 (100)	49/49 (100)
[95% CI]	[78.3%, 97.5%]	[91.6%, 100.0%]	[92.7%, 100.0%]
Reasons for non-response			
-On-treatment failure	1 (2%)	0	0
-Relapse	2 (5%)	0	0
-Premature discontinuation	1 (2%)	0	0

6) Safety

Data from patients who received Technivie in trial M13-393, 181 with GT1b and 135 with GT4 infection, formed the basis for the safety review. In addition, the fixed dose combination of paritaprevir, ombitasvir, and ritonavir (in addition to a third HCV DAA) was administered to >2300 subjects with GT1 infection and safety data was reviewed under NDA 206619 for Viekira Pak™.

There were no on-treatment deaths in M13-393. One GT1b subject died due to gastrointestinal complications post-treatment which appeared to be related to complications of cirrhosis in a patient with a history of esophageal varices.

No GT4-infected subjects discontinued dosing or the trial due to adverse events. Three GT1b-infected patients with cirrhosis discontinued study drug due to an adverse event, only one event, peripheral edema was considered treatment related.

Headache, asthenia, fatigue, nausea, and insomnia were the most common treatment-emergent adverse events among the GT4 subjects treated with Technivie Tablets + RBV. A similar adverse event profile was observed for GT1b patients and is also consistent with that of Viekira Pak™ + RBV. The following table shows the number (percentage) of adverse events occurring in at greater than 10% of subjects at least one of the GT4 treatment groups.

Number (%) Treatment-emergent adverse events in >10% of GT4 subjects

	Technivie Treatment-naïve N=44	**Technivie + RBV Treatment-naïve N=42**	**Technivie + RBV Treatment-experienced N=49**
Diarrhea	2 (4.5)	6 (14)	3 (6)
Nausea	4 (9)	7 (17)	6 (12)
Asthenia	11 (25)	10 (24)	16 (33)
Fatigue	3 (7)	5 (12)	9 (18)
Irritability	3 (7)	6 (14)	2 (4)
Myalgia	0	0	5 (10)
Headache	13 (29.5)	14 (33)	14 (29)
Insomnia	2 (4.5)	4 (9.5)	8 (16)
Pruritus	2 (4.5)	1 (2)	5 (10)

Liver-related Adverse Reactions

The interpretation of liver related toxicity is confounded by the fact that both paritaprevir and ribavirin increase bilirubin levels (predominantly indirect bilirubin) by mechanisms other than direct hepatobiliary toxicity. Paritaprevir increases bilirubin levels by inhibiting the organic anion transporting polypeptide transporter OATP1B1 and ribavirin causes a hemolytic anemia leading to indirect hyperbilirubinemina.

Transaminitis occurred in approximately 1% of subjects treated with Viekira Pak™; this risk increased to 27% among females taking a concomitant estradiol or ethylene estradiol

medication. The current Viekira Pak™ labeling carries a Warning that all subjects be monitored for ALT elevations during treatment, and co-administration of estradiol and ethylene estradiol containing medications are contraindicated. The frequency of grade 3 or greater (> 5 -10 times the upper limit of normal) AST and ALT elevations among patients receiving Technivie in trial M13-393 was 2%, and were primarily observed in GT1b subjects with cirrhosis. No grade 3 or greater ALT elevations occurred in GT4 patients.

As was done for the Viekira Pak™ NDA, AbbVie assembled an independent expert panel to review cases of patients who had elevations of both transaminases and bilirubin in trial M13-393. There were 5 patients with elevations in both transaminases and bilirubin levels: three in the Hy's law quadrant (ALT >3 x ULN and total bilirubin >2 x ULN) and two in the subset of Temple's corollary quadrant (ALT >5 x ULN and total bilirubin <2 x ULN). The panel concluded that none of the five cases were a potential Hy's law case. However, two cases were considered highly likely related, one possibly related and one probably related to study drugs. Of note, all five subjects achieved SVR12. In summary, some of these cases were considered to be drug-induced liver injury (DILI) that was "adaptive" and without evidence of global hepatic synthetic dysfunction. The review of cases from the Viekira Pak™ review led to the same conclusions.

7) 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 with lower 95% confidence bounds exceeding 90% when Technivie is administered with ribavirin. FDA and the applicant were able to reach consensus on labeling.

8) Pediatrics

No children were studied in the trial submitted in this NDA. This application triggers PREA. Given Technivie is ready for approval in adults the PREA requirement will be deferred. See section 11 for a list of PMRs and PMCs to which the applicant has agreed.

9) Other Relevant Regulatory Issues

There are no unresolved regulatory issues.

As stated in the joint review, "No inspections were conducted as most U.S. investigators for Study M13-393 were recently inspected for GCP and found to be NAI (no actions indicated) or enrolled too few subjects to be in a position to influence the study results. Most ex-U.S. investigators were in Europe, Eastern Europe and Russia, and, again, enrolled too few subjects, that would have influenced the study data, to warrant inspection." Clinical inspections for some of the same clinical sites had already been conducted for the Viekira Pak™ NDA.

10) Labeling

The Warnings and Precautions and many of the drug interactions recommendations for Technivie are the same as that for Viekira Pak™. As for Viekira Pak™ the Technivie labeling will include a medication guide. The original decision to include a medication guide was based, in part, on the contraindication of EE containing medications to reduce the risk of transaminase elevations (presumably associated with the paritaprevir component) and to make patients familiar with prescribing information warnings with respect to potential liver toxicity.

The indication specifies that Technivie is approved for patients without cirrhosis. Technivie with ribavirin administered for 12 weeks is the recommended dosing regimen. However, the label includes a a footnote to the dosing table, which states that use of Technivie without ribavirin may be considered for treatment naïve patients who are unable to take ribavirin.

11) Decision/Action/Risk Benefit Assessment

- Regulatory Action
  I recommend that Technivie with ribavirin for the treatment of chronic hepatitis C virus infection with genotype 4 in patients without cirrhosis be granted approval.

- Benefit-Risk Assessment

  The Benefit-Risk of Technivie is highly favorable and improved over the previously approved interferon-based regimens. Specifically, based on a sample size of 11 patients, a 48 week course of Peg-IFN plus ribavirin yielded SVR24 rates of 82% in GT4 patients(Pegasys Package insert). The SVR12 rate for a 12 week course of Peg-IFN plus ribavirin and sofosbuvir for GT4 HCV infection was 96% (based on a sample size of 28 patients). Therefore the 100% virologic success rate in trial M13-393 is better than that of Peg-IFN plus ribavirin and at least as good as Peg-IFN/ribavirin/sofosbuvir without the poor tolerability and serious safety concerns of IFN injections for 12 to 48 weeks. Although trial M13-393 was relatively small (n=135 GT4 patients), it was many times larger than previous databases used to support indications for GT4 and the confidence intervals around the treatment effect provides substantial reassurance that efficacy of this regimen is at least as good as the currently approved sofosbuvir regimen and substantially better than interferon-based regimens without sofosbuvir.

  Limitations to the trial are lack of data in patients with cirrhosis. For certain genotypes SVR12 rates are lower for patients with cirrhosis and sometimes regimen intensification in terms of duration or additional drugs is needed. For this reason additional data will be needed to extend the GT4 indication to include patients with cirrhosis. [redacted] (b) (4)

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 data from trial M13-393 support the contribution of ribavirin towards overall efficacy in terms of increasing SVR12 rate and reducing the risk of resistance. However, some individuals may not be able to take or tolerate ribavirin. Such individuals could still benefit from Technivie with an expected response of 90% or more; however a small percentage are at risk for developing resistance. For this reason ribavirin is recommended but Technivie alone may be considered in treatment naïve patients who absolutely cannot take ribavirin. It is possible that patients in the U.S. may be at less risk for virologic failure when taking Technivie alone if subtype 4d is a risk factor for virologic failure and if subtype 4d is infrequent in the U.S. Limited data from this trial suggest that this might be the case, but there are too few patients to draw firm conclusions.

The strong efficacy of Technivie is balanced with a favorable tolerability profile; in this trial population (n=135) no GT4 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 as was observed with the use of paritaprevir/ritonavir in Viekira Pak™ and in GT1b patients in trial M13-393. The transaminase elevations signify some degree of liver injury; however, most patients who experienced this were asymptomatic and increases in transaminases resolved while continuing on treatment in some patients.

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

PREA PMR
Evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response as the primary endpoint) of ombitasvir, paritaprevir, and ritonavir (TECHNIVIE) in a cohort of pediatric subjects 3 to less than 18 years of age with chronic genotype 4 hepatitis C virus infection.

Final Protocol Submission:	07/31/2015
Study Completion:	04/30/2019
Final Report Submission:	08/31/2019

The applicant agreed to the following additional PMR:

Submit a final report on the persistence of treatment-emergent, ombitasvir or paritaprevir resistance-associated substitutions through Post-Treatment Week 48 in ongoing trials of HCV genotype 4 infected subjects.

Final Report Submission: 01/31/2018

The applicant agreed to the following in vitro study as a Postmarketing Commitment:

Conduct a cell culture study to characterize the antiviral activity of ombitasvir against representative HCV subtype 4b isolates, including those with amino acid variability (relative to subtypes 4a and 4d) at NS5A positions 30 and 93.

Final Report Submission: 03/31/2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEFFREY S MURRAY
07/22/2015