

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

206619Orig1s000

Trade Name: VIEKIRA PAK

Generic Name: ombitasvir, paritaprevir, and ritonavir tablets;
dasabuvir tablets

Sponsor: AbbVie Inc.

Approval Date: December 19, 2014

Indications: VIEKIRA PAK with or without ribavirin is indicated for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
206619Orig1s000

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206619Orig1s000

APPROVAL LETTER



NDA 206619

NDA APPROVAL

AbbVie Inc.
Attention: Troy ZumBrunnen, PharmD
Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77/Bldg. AP30
North Chicago, IL 60064

Dear Dr. ZumBrunnen:

Please refer to your New Drug Application (NDA) dated April 21, 2014, received April 21, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Viekira Pak™ (ombitasvir, paritaprevir, and ritonavir tablets, 12.5 mg/75 mg/50 mg; dasabuvir tablets, 250 mg), co-packaged for oral use.

We acknowledge receipt of your amendments dated:

May 5, 2014	August 4, 2014	October 10, 2014
May 8, 2014	August 5, 2014	October 17, 2014 (2)
May 14, 2014	August 8, 2014	October 22, 2014 (2)
May 19, 2014	August 11, 2014	October 23, 2014
May 21, 2014	August 15, 2014	October 24, 2014
May 22, 2014	August 20, 2014	October 30, 2014
May 27, 2014	August 25, 2014	November 5, 2014
June 2, 2014	August 29, 2014	November 17, 2014
June 3, 2014	September 2, 2014	November 24, 2014
June 13, 2014	September 12, 2014	December 3, 2014
June 19, 2014 (2)	September 16, 2014	December 5, 2014
July 1, 2014	September 19, 2014	December 8, 2014
July 14, 2014	September 25, 2014	December 10, 2014
July 18, 2014	September 30, 2014	December 11, 2014
July 23, 2014	October 1, 2014 (2)	December 17, 2014
July 25, 2014	October 2, 2014	
July 30, 2014	October 3, 2014	

This new drug application provides for the use of Viekira Pak™ (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets) with or without ribavirin for the treatment of patients with

genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 206619.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Katherine Schumann, M.S.
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6360
10903 New Hampshire Avenue
Silver Spring, Maryland

*Use zip code **20903** if shipping via United States Postal Service (USPS).*

*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

ADVISORY COMMITTEE

Your application for Viekira Pak™ (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets) was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected and because outside expertise was not necessary as there were no significant issues identified that would benefit from an advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement from birth to less than 3 years because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group.

We are deferring submission of your pediatric studies for ages 3 to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. These required studies are listed below.

2830-1 Evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response as the primary endpoint) of ombitasvir, paritaprevir, ritonavir,

dasabuvir (Viekira Pak™) in pediatric subjects 3 to less than 18 years of age with chronic hepatitis C virus infection.

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

2830-2 Collect and analyze long-term safety data for subjects enrolled in the pediatric ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak™) pharmacokinetic, safety, and antiviral efficacy study(ies). Data collected should include at least 3 years of follow-up in order to characterize the durability of response to ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak™) and the long-term safety including growth assessment, sexual maturation, and characterization of resistance associated substitutions in viral isolates from subjects failing therapy.

Final Protocol Submission: 07/31/2015
Trial Completion: 04/30/2022
Final Report Submission: 08/31/2022

Submit the protocols to your IND 103,526, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of drug resistance- and cross-resistance-related risk of treatment failure with Viekira Pak™ (ombitasvir, paritaprevir, and ritonavir, with dasabuvir). In addition, drug resistance-associated substitutions emerged in subjects who experienced virologic failure in Viekira Pak™ (ombitasvir, paritaprevir, and ritonavir, with dasabuvir) clinical trials and the persistence of some of these substitutions is not completely understood. Therefore, a study of patients who participated in phase 2 and 3 trials will be required to assess a risk of drug resistance and cross-resistance due to the persistence of resistance-associated substitutions. A study will also be required to identify an unexpected serious risk of toxicity or of the emergence of resistance in Black/African American patients.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2830-3 Conduct the following site-directed mutant HCV replicon phenotype analyses:
- Sofosbuvir activity against HCV replicons carrying NS5B substitutions associated with dasabuvir resistance: C316Y (GT1a and GT1b) and S556G (GT1a).
 - Dasabuvir activity against HCV replicons carrying the following NS5B substitutions: L159F (GT1a and GT1b), V321A (GT1a and GT1b), M423I (GT1a), I482T (GT1a) and A486V (GT1b).
 - Paritaprevir activity against HCV replicons carrying substitutions in the NS3 helicase (e.g., P334S, S342P, V406A/I, T449I, P470S) that emerged in virologic failure subjects treated with the 3-DAA ± RBV regimen; evaluate the impact of these substitutions alone and in combination with other key resistance-associated substitutions (e.g., R155K or D168x) that were often detected in combination.

The timetable you submitted on November 6, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/28/2015

- 2830-4 Submit a final report for ongoing observational study M13-102, "A Follow-up Study to Assess Resistance and Durability of Response to AbbVie Direct-Acting Antiviral Agent (DAA) Therapy in Subjects Who Participated in Phase 2 or 3 Clinical Studies for the Treatment of Chronic Hepatitis C Virus (HCV) Infection."

The timetable you submitted on November 6, 2014, states that you will conduct this study according to the following schedule:

Study Completion: 10/31/2016
Final Report Submission: 10/31/2017

- 2830-5 Conduct an observational study to investigate the safety and efficacy of ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak™) in a sufficient number of Blacks/African Americans with and without cirrhosis compared to whites/Caucasians.

The timetable you submitted on December 10, 2014, states that you will conduct this study according to the following schedule:

Protocol Submission: 07/31/2015
Study Completion: 06/30/2019
Final Report Submission: 12/31/2020

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify the unexpected serious risks of toxicity in patients with severe renal impairment or end-stage renal disease and to identify an unexpected serious risk of the potential for increased toxicity based on expected higher paritaprevir exposure in patients with moderate to severe hepatic impairment.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 2830-6 Submit the final report and datasets for the ongoing clinical 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."

The timetable you submitted on November 6, 2014, states that you will conduct this trial according to the following schedule:

Trial Completion: 12/31/2016
Final Report Submission: 12/31/2017

- 2830-7 Submit the final report and datasets for the ongoing clinical 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."

The timetable you submitted on November 6, 2014, states that you will conduct this trial according to the following schedule:

Trial Completion: 05/31/2016
Final Report Submission: 05/31/2017

Submit the protocols to your IND 103,526, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to

report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 2830-8 Submit the final report and datasets for the ongoing Phase 3 clinical trial M11-646 entitled "A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-administered with Ribavirin (RBV) in Treatment-Naïve Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection."

The timetable you submitted on November 6, 2014, states that you will conduct this trial according to the following schedule:

Trial Completion: 12/31/2014
Final Report Submission: 10/31/2015

- 2830-9 Submit the final report and datasets for the Phase 3 clinical trial M13-098 entitled "A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-administered with Ribavirin (RBV) in Treatment-Experienced Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection."

The timetable you submitted on November 6, 2014, states that you will conduct this trial according to the following schedule:

Trial Completion: 12/31/2014
Final Report Submission: 10/31/2015

- 2830-10 Submit the final report and datasets for the Phase 3 clinical trial M13-099 entitled "A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered

with Ribavirin (RBV) in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis."

The timetable you submitted on November 6, 2014, states that you will conduct this trial according to the following schedule:

Trial Completion: 12/31/2014
Final Report Submission: 09/30/2015

- 2830-11 Submit the final report and datasets for the Phase 3 clinical trial M13-961 entitled "A Randomized, Double-Blind, Controlled Study to Evaluate the Efficacy and Safety of the Combination of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With and Without Ribavirin (RBV) in Treatment-Naïve Adults with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection."

The timetable you submitted on November 6, 2014, states that you will conduct this trial according to the following schedule:

Trial Completion: 12/31/2014
Final Report Submission: 09/30/2015

- 2830-12 Submit the final report and datasets for the Phase 3 clinical trial M13-389 entitled "A Randomized, Open-Label, Multicenter Study to Evaluate the Safety and Antiviral Activity of the Combination of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With and Without Ribavirin in Treatment-Experienced Subjects with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection."

The timetable you submitted on November 6, 2014, states that you will conduct this trial according to the following schedule:

Trial Completion: 12/31/2014
Final Report Submission: 10/31/2015

- 2830-13 Submit the final report and datasets for the Phase 3 clinical trial M14-002 entitled "A Randomized, Double-Blind, Controlled Study to Evaluate the Efficacy and Safety of the Combination of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With and Without Ribavirin (RBV) in Treatment-Naïve Adults with Genotype 1a Chronic Hepatitis C Virus (HCV) Infection."

The timetable you submitted on November 6, 2014, states that you will conduct this trial according to the following schedule:

Trial Completion: 12/31/2014
Final Report Submission: 09/30/2015

- 2830-14 Submit the final report and datasets for the ongoing clinical trial M12-999 entitled "Open-label, Phase 2 Study to Evaluate the Safety and Efficacy of the Combination of ABT-450/ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With or Without Ribavirin (RBV) in Adult Liver Transplant Recipients with Genotype 1 Hepatitis C Virus (HCV) Infection."

The timetable you submitted on December 3, 2014, states that you will conduct this trial according to the following schedule:

Trial Completion: 03/21/2017
Final Report Submission: 02/21/2018

- 2830-15 Submit the final report and datasets for the ongoing clinical trial M14-004 entitled "A Randomized, Open-label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered with Ribavirin (RBV) in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Human Immunodeficiency Virus, Type 1 (HIV-1) Coinfection."

The timetable you submitted on November 6, 2014, states that you will conduct this trial according to the following schedule:

Trial Completion: 06/30/2017
Final Report Submission: 06/30/2018

- 2830-16 Submit the final report and datasets for the ongoing clinical trial M14-490 entitled "An Open-Label, Single-Arm Study to Evaluate the Safety and Efficacy of Ombitasvir/ABT-450/Ritonavir and Dasabuvir in Adults with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis."

The timetable you submitted on November 6, 2014, states that you will conduct this trial according to the following schedule:

Trial Completion: 11/30/2015
Final Report Submission: 11/30/2016

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

- 2830-17 Develop a test for [REDACTED] ^{(b)(4)} with a sensitivity of [REDACTED] ^{(b)(4)} % in the ombitasvir, paritaprevir, ritonavir drug product tablet for the release and stability specification.

The timetable you submitted on November 6, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/31/2016

Submit clinical protocols to your IND 103,536 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Katherine Schumann, M.S., Regulatory Project Manager, at (301) 796-1182.

Sincerely,

{See appended electronic signature page}

John Farley, M.D., M.P.H.
Deputy Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures:

Content of Labeling
Carton and Container Labeling

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

/s/

JOHN J FARLEY
12/19/2014