CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208624Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

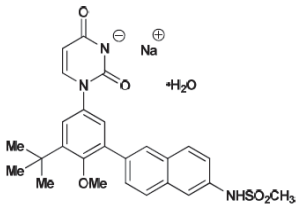
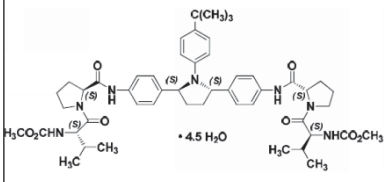
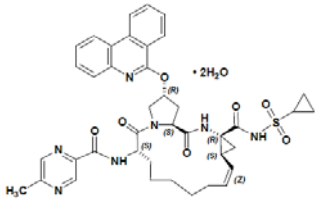
DIVISION OF ANTIVIRAL PRODUCTS
CLINICAL VIROLOGY REVIEW
NDA: 208624 **SDN**: 000 (001 in DARRTS) **eCTD:** 0000 **REVIEW COMPLETED:** 06/16/2016

NDA#: 208624 **SDN:** 000 (001 in DARRTS)
Reviewer's Name(s): Patrick R. Harrington, Ph.D.

Sponsor: AbbVie, Inc.
1 N. Waukegan Road, Dp. PA77/Bldg. AP30
North Chicago, IL 60064
Sherie VL Massé

Submission Dates:
Correspondence Date: 09/28/2015
CDER Receipt Date: 09/28/2015
Assigned Date: 09/28/2015

Review Complete Date: 06/16/2016

Proprietary Name	**Viekira XR™ (fixed-dose combination product: dasabuvir/ombitasvir/paritaprevir/ritonavir)**		
Individual Drug Names [class]	dasabuvir (DSV, ABT-333) [non-nucleoside NS5B-palm polymerase inhibitor]	ombitasvir (OBV, ABT-267) [NS5A inhibitor]	paritaprevir (PTV, ABT-450) [NS3/4A protease inhibitor]
Individual IND #s	101636	108434	103526
Chemical Names	Sodium 3-(3-tert-butyl-4-methoxy-5-{6-[(methylsulfonyl)amino] naphthalen-2-yl}phenyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ide hydrate (1:1:1)	Dimethyl ([(2S,5S)-1-(4-tert-butylphenyl)pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]}) biscarbamate hydrate	(2R,6S,12Z,13aS,14aR,16aS)-N-(Cyclopropylsulfonyl)-6-{[(5-methylpyrazin-2-yl)carbonyl] amino}-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a tetradecahydrocyclopropa[e]pyrrolo[1,2-a][1,4] diazacyclopentadecine-14a(5H)-carboxamide dihydrate
Structures	 **dasabuvir**	 **ombitasvir**	 **paritaprevir**
Molecular Formulas	$C_{26}H_{26}N_3O_5S•Na•H_2O$ (salt); (b)(4)	$C_{50}H_{67}N_7O_8 • 4.5H_2O$	$C_{40}H_{43}N_7O_7S • 2H_2O$
Molecular Weights	533.57 (salt); (b)(4)	(b)(4) 975.20 (hydrate)	(b)(4) 801.91 (hydrate)

Related/Supporting Documents: Clinical Virology review of Original NDA 206619; Label updates in SDNs 005, 009, and 012 (received 2/17/16, 5/2/16, and 6/14/16, respectively)
Dosage Form and Route of Administration: 200/8.33/50/33.33 mg tablet (dasabuvir/ombitasvir/paritaprevir/ritonavir); 3 tablets QD, Oral
Dispensed: Rx **x** OTC__
Indication: Treatment of chronic HCV GT1 infection

BACKGROUND AND SUMMARY

Introduction

This is a new NDA submission for a fixed-dose combination tablet product (Viekira XR™) consisting of the following HCV direct-acting antivirals DAAs: dasabuvir (DSV, ABT-333; non-nucleoside NS5B-palm polymerase inhibitor), paritaprevir (PTV, ABT-450; NS3/4A protease inhibitor, boosted with ritonavir [rtv]) and ombitasvir (OBV, ABT-267; NS5A inhibitor). This fixed-dose combination tablet is essentially a reformulation of the FDA-approved Viekira Pak™ 3-DAA combination product (OBV/PTV/rtv tablets plus DSV tablets) into a single dosage form to be administered as 3 tablets once-daily, with or without ribavirin (RBV). Viekira Pak™ was approved December 19, 2014.

Data Supporting NDA 208624

Clinical data and analyses to support NDA 208624 are primarily from bioavailability/bioequivalence studies conducted in healthy volunteers, as well as from exposure-response analyses and simulations to show the similarity of the safety and efficacy profiles between the Viekira XR™ and Viekira Pak™ formulations. The primary efficacy, safety, virology and drug resistance characteristics of Viekira XR™ are supported by data included in NDA 206619 for Viekira Pak™. No new Clinical Virology data were included in NDA 208624. Please see the Clinical Virology reviews of NDA 206619 and relevant efficacy supplements for the Clinical Virology analyses and review of the 3-DAAs in Viekira XR™.

Prescribing Information

Section 12.4 of the proposed label for Viekira XR™ is identical to that of Viekira Pak™ with the exception of formatting changes. Specifically, the sponsor re-arranged the order of presentation of virology information to be based on alphabetical order of the individual DAAs (DSV, OBV, PTV), which is a standard convention for fixed-dose combinations. These changes are acceptable.

In addition, the sponsor re-arranged the presentation of Table 10 (treatment-emergent amino acid substitutions in subjects who failed regimens that include the DAAs in Viekira XR™) to display substitutions by drug target in the following order: NS5B, NS3, NS5A. Presumably the sponsor intended to display these data by the drug targets corresponding to the alphabetical order of the DAAs (i.e., NS5B, NS5A, NS3). Nevertheless, we disagree with the proposed changes to the format of Table 10. We prefer the treatment-emergent substitution data are presented in a manner that corresponds to the organization of the HCV genome (NS3, NS5A, NS5B), consistent with the current Viekira Pak™ label. As further justification for retaining this order of presentation, resistance-associated substitutions in NS3 or NS5A are more likely to be clinically meaningful relative to those in NS5B, as there are currently no other FDA-approved non-nucleoside NS5B palm polymerase inhibitors, and thus cross-resistance between DSV and other DAAs is not a concern at this time.

CONCLUSIONS

NDA 208624 is approvable with respect to Clinical Virology. The label recommendation noted above was forwarded to the sponsor on 6/8/2016. In revised labeling submitted in SDN 12 (eCTD 0011), Table 10 reports the substitution data in the original order corresponding to the organization of the HCV genome (NS3, NS5A, NS5B), as recommended. No further action is indicated at this time with respect to Clinical Virology.

Patrick R. Harrington, Ph.D.
Clinical Virology Reviewer

CONCURRENCES

_____Date: _____
DAVP/Clin Virol TL/J O'Rear

cc:
DAVP/newNDA
DAVP/RPM/Strayhorn

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

/s/

PATRICK R HARRINGTON
06/21/2016

JULIAN J O REAR
06/21/2016