CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	207-931
Supporting document/s:	001
Applicant's letter date:	February 25, 2015
CDER stamp date:	February 25, 2015
Product:	Technivie, consisting of: 12.5 mg/75 mg/50 mg of ombitasvir, paritaprevir, and ritonavir, respectively per tablet
Indication:	Treatment of genotype 4 chronic hepatitis C virus infection.
Applicant:	AbbVie, Inc.
Review Division:	DAVP
Reviewer:	Mark Seaton, Ph.D., DABT
Supervisor/Team Leader:	Hanan Ghantous, Ph.D., DABT
Division Director:	Debra Birnkrant, M.D.
Project Manager:	Katherine Schumann, PharmD

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TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

The applicant is seeking marketing approval for Technivie, consisting of:
A nonstructural protein 3 (NS3) inhibitor (Paritaprevir) combined with Ritonavir to enhance systemic exposures, and a nonstructural protein 5A (NS5A) inhibitor (Ombitasvir). Technivie would be marketed as a treatment of chronic HCV genotype 4 infection in adults, (b) (4) who are either treatment-naïve or previously treated with pegylated interferon (pegIFN) and ribavirin. The proposed daily dosages for the components of Technivie are Paritaprevir (150 mg)/ Ritonavir (100 mg), and Ombitasvir (25 mg). The applicant has referenced the complete nonclinical package for NDA 206-619 (Viekira Pak) consisting of studies in mice, rats, rabbits, monkeys and dogs.

1.2 Brief Discussion of Nonclinical Findings

Paritaprevir
The gallbladder was identified as a target organ of Paritaprevir toxicity in repeat dose studies in mice and dogs. Findings include edema, mononuclear and mixed cell infiltration and epithelial cell necrosis with increased serum alkaline phosphatase, suggesting biliary effects.

In clinical trials, the safety profile of ombitasvir, paritaprevir and ritonavir (Technivie; 2 DAAs) with or without ribavirin for 12 weeks is consistent with the safety profile of ombitasvir, paritaprevir and ritonavir plus dasabuvir (Viekira Pak; 3 DAAs) with or without ribavirin for 12 or 24 weeks. Transient elevations in total bilirubin that peaked at Week 1 and declined thereafter were observed in subjects who received three DAAs and Ribavirin (RBV). The increase was driven by an elevation in the indirect bilirubin fraction. Paritaprevir is a known inhibitor of the organic anion transporting polypeptide 1B1 (OATP1B1) bilirubin transporter. In addition, RBV-induced hemolysis may have contributed to hyperbilirubinemia. There were no clinically significant increases in alkaline phosphatase.

Paritaprevir was neither genotoxic nor carcinogenic in nonclinical studies. Likewise, oral administration of Paritaprevir to pregnant rats and mice did not result in teratogenicity at systemic exposures up to 8x (rats) and 98x (mice) the expected human exposure. Paritaprevir did not affect male or female fertility in rats at systemic exposures 5x the expected human exposure.

Ritonavir
In nonclinical toxicology studies with ritonavir, the main target organs of toxicity were the liver and the eyes. As stated on the Norvir label, hepatic transaminase elevations exceeding 5 times the upper limit of normal, clinical hepatitis, and jaundice have occurred in patients receiving NORVIR alone or in combination with other antiretroviral

drugs. Retinal toxicity was observed in animals but this has not been seen in patients. Also, pancreatitis has been observed in patients receiving NORVIR therapy, including those who developed hypertriglyceridemia. In some cases fatalities have been observed.

Ombitasvir

Ombitasvir (ABT-267) has minimal solubility in aqueous solutions (<0.1 µg/mL). In toxicology studies, optimized lipid/surfactant solution formulations provided maximum feasible exposures at steady state in mice, rats and dogs. At maximum feasible doses and at exposure levels that reflect saturation of absorption, no toxicologically significant effects of ombitasvir were noted in nonclinical studies. In those studies, systemic exposures were approximately 20-40-fold higher than clinical exposures. Therefore, although no target organs of toxicity were identified, the nonclinical toxicology program is considered to be adequate to predict toxicity in the clinical setting.

Two metabolites of ombitasvir, M29 and M36 (A-1538855 and A-1548255, respectively), were identified as unique human metabolites (i.e., metabolites that were not present in significant amounts in nonclinical species). The toxicological profile of each metabolite was assessed in genetic toxicology assays, repeat dose studies and reproductive toxicology studies. No significant toxicological effects were identified.

As noted above, no target organs were identified in nonclinical toxicology studies. Ombitasvir was not genotoxic, and was not carcinogenic in transgenic mice at exposures up to 26x exposures at the recommended clinical dose.
Ombitasvir did not affect male or female fertility in mice up to 29x exposures at the recommended clinical dose. Ombitasvir-related changes in male reproductive organ weights that were not considered to be toxicologically significant included increases weights of the prostate and seminal vesicles (without fluid) and decreases in the absolute and relative weights of the testes.

In mice, ombitasvir was not maternally toxic or teratogenic up to 29x exposures at the recommended clinical dose. In rabbits, ombitasvir was not maternally toxic or teratogenic at doses up to 4x exposures at the recommended clinical dose, with plasma drug levels measured in fetuses between 1% and 2% of those measured in females at the time of Caesarean-section.

1.3 Recommendations

1.3.1 Approvability

It is recommended that Technivie be approved.

1.3.2 Additional Non Clinical Recommendations

No additional nonclinical studies are recommended.

1.3.3 Labeling

8.1 Pregnancy

Pregnancy Category B

(b) (4)

Risk Summary

Adequate and well controlled studies with TRADENAME have not been conducted in pregnant women. In animal reproduction studies, no evidence of teratogenicity was observed with the administration of ombitasvir (mice and rabbits), paritaprevir or ritonavir (mice and rats) at exposures higher than the recommended clinical dose [see Data]. Because animal reproduction studies are not always predictive of human response, TRADENAME should be used during pregnancy only if clearly needed.

Since TRADENAME is administered with ribavirin, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the ribavirin prescribing information for more information on use in (b) (4)

Data

Animal data

In animal reproduction studies, there was no evidence of teratogenicity in offspring born to animals treated throughout pregnancy with ombitasvir and its major inactive human metabolites (M29, M36), paritaprevir or ritonavir. For ombitasvir, the highest dose tested produced exposures approximately 29-fold (mouse) or 4-fold (rabbit) the exposures in humans at the recommended clinical dose. The highest doses of the major, inactive human metabolites similarly tested produced exposures approximately 26-fold the exposures in humans at the recommended clinical dose. For paritaprevir, ritonavir, the highest doses tested produced exposures approximately 143-fold (mouse) or 12-fold (rat) the exposures of paritaprevir in humans at the recommended clinical dose.

8.3 Nursing Mothers

It is not known whether any of the components of TRADENAME or their metabolites are present in human milk. Unchanged ombitasvir, and paritaprevir and its hydrolysis product M13 were the predominant components observed in the milk of lactating rats, without effect on nursing pups.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed child from TRADENAME or from the underlying maternal condition.

When TRADENAME is administered with ribavirin, the nursing mothers information for ribavirin also applies to this combination regimen (see prescribing information for ribavirin).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Ombitasvir

Ombitasvir was not carcinogenic in a 6-month transgenic mouse study up to the highest dose tested (150 mg per kg per day).

The carcinogenicity study of ombitasvir in rats is ongoing.

Ombitasvir and its major inactive human metabolites (M29, M36) were not genotoxic in a battery of in vitro or in vivo assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes and in vivo mouse micronucleus assays.

Paritaprevir, ritonavir

Paritaprevir, ritonavir was not carcinogenic in a 6-month transgenic mouse study up to the highest dose tested (300/30 mg per kg per day). Similarly, paritaprevir, ritonavir was not carcinogenic in a 2-year rat study up to the highest dose tested (300/30 mg per kg per day), resulting in paritaprevir exposures approximately 11-fold higher than those in humans at 150 mg.

Paritaprevir was positive in an in vitro chromosome aberration test using human lymphocytes. Paritaprevir was negative in a bacterial mutation assay, and in two in vivo genetic toxicology assays (rat bone marrow micronucleus and rat liver Comet tests).

TRADENAME is administered with ribavirin. Refer to the prescribing information for ribavirin for information on carcinogenesis and mutagenesis.

Impairment of Fertility

Ombitasvir

Ombitasvir had no effects on embryo-fetal viability or on fertility when evaluated in mice up to the highest dose of 200 mg per kg per day. Ombitasvir exposures at this dose were approximately 26-fold the exposure in humans at the recommended clinical dose.

Paritaprevir, ritonavir

Paritaprevir, ritonavir had no effects on embryo-fetal viability or on fertility when evaluated in rats up to the highest dose of 300/30 mg per kg per day. Paritaprevir exposures at this dose were approximately 3- to 8-fold the exposure in humans at the recommended clinical dose.

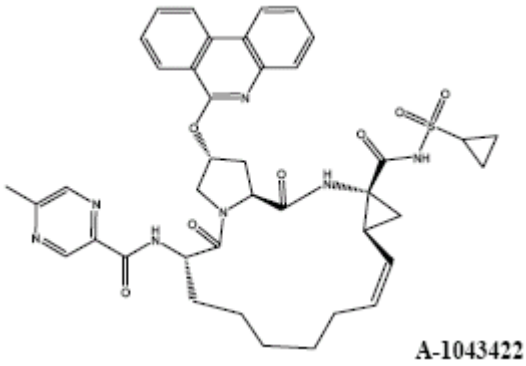
TRADENAME is administered with ribavirin. Refer to the prescribing information for ribavirin for information on Impairment of Fertility.

2 Drug Information

2.1 Drug

Generic Name	Paritaprevir
Code Name	ABT-450; A-1043422
Chemical Name	(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 hydrate
Molecular Formula/Molecular Weight	(b) (4) C40H43N7O7S•H2O (hydrate) (b) (4)

Structure or Biochemical Description



A-1043422

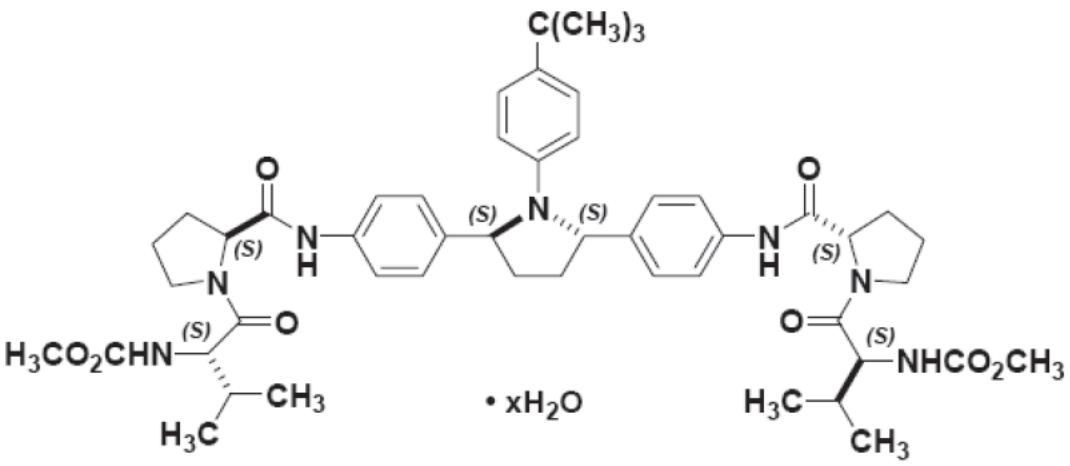
Pharmacologic Class	Nonstructural protein 3 (NS3) inhibitor
Generic Name	Ombitasvir
Code Name	ABT-267; A-1233617

Chemical Name

Dimethyl ([(2*S*,5*S*)-1-(4-*tert*-butylphenyl) pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2*S*)pyrrolidine-2,1-diyl[(2*S*)-3- methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate

Molecular Formula/Molecular Weight	C50H67N7O8 •4.5H20 (hydrate)/ (b) (4) 975.20 (hydrate)

Structure or Biochemical Description



Pharmacologic Class Nonstructural protein 5A (NS5A) inhibitor.

2.2 Relevant INDs, NDAs, BLAs and DMFs

AbbVie evaluated direct acting agents (DAAs) for chronic hepatitis C under the following INDs: IND 103,526 (Paritaprevir), IND 108,434 (Ombitasvir)

Cross references are made to the Viekira Pak NDA, 206-619 and Norvir (Ritonavir) NDA 22-417.

2.3 Drug Formulation

The Ombitasvir/Paritaprevir/Ritonavir tablet comprises (b) (4) to form the final tablet. (b) (4)

2.4 Comments on Novel Excipients

None.

2.5 Comments on Impurities/Degradants of Concern

The sponsor's proposed specifications for impurities/degradants likely to be present in the drug product are considered acceptable from a pharmacology/toxicology

perspective based on the results of general toxicology studies, empirical Ames assays, in vitro chromosomal aberration assays, and/or (quantitative) structure-activity relationship [(Q)SAR] predictions of mutagenicity. See complete review by Dr. Mark Powley in the Pharmacology/Toxicology NDA Review and Evaluation for NDA 206-619 (Appendix 5).

2.6 Proposed Clinical Population and Dosing Regimen

Paritaprevir /r/Ombitasvir are indicated for the treatment of GT4 hepatitis C infection. The recommended adult oral dose of Paritaprevir/r/Ombitasvir is two 75/50/12.5 mg tablets QD (in the morning) with food without regard to fat or calorie content.

2.7 Regulatory Background

This NDA will be reviewed under the PDUFA V program under Priority Review. These drugs were previously reviewed under INDs 103,526 and 108,434, and NDA 206-619.

3 Studies Submitted

3.1 Studies Reviewed

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. Refer to applicable sections of IND 103,526 (Paritaprevir), IND 108,434 (Ombitasvir), NDA 206-619 (Viekira Pak) and NDA 22-417 (Norvir).

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/s/

MARK J SEATON
06/22/2015

HANAN N GHANTOUS
06/22/2015

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 207-931 **Applicant:** AbbVie, Inc. **Stamp Date:** April 21, 2014

Drug Name: ombitasvir/ paritaprevir/ ritonavir **NDA/BLA Type:** FDC

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?	X		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

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

/s/

MARK J SEATON
04/20/2015

HANAN N GHANTOUS
04/20/2015