

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207931Orig1s000**

**CHEMISTRY REVIEW(S)**



**Expedited Review**

**Recommendation:**

**NDA: Approval**

**NDA 207931  
Review #1**

<b>Drug Name/Dosage Form</b>	ombitasvir, paritaprevir and ritonavir/ Tablets, Film-coated
<b>Strength</b>	12.5 mg/ 75 mg/ 50 mg
<b>Route of Administration</b>	Oral
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	AbbVie Inc.
<b>US agent, if applicable</b>	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED

**Quality Review Team**

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Milton J. Sloan, Ph.D.	III/1
Drug Product	Milton J. Sloan, Ph.D.	
Process		
Microbiology		
Facility	Rose Xu, M. Sc	OPQ/OPF/DIA
Biopharmaceutics	Jing Li, Ph.D.	Division of Biopharmaceutics/ONDP/OPQ
Regulatory Business Process Manager	Olga Simakova, Ph.D. Giuseppe Randazzo, MS	
Application Technical Lead	Stephen P. Miller, Ph.D.	
Laboratory (OTR)		
ORA Lead		
Environmental Assessment (EA)		

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## Quality Review Data Sheet

**1. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type III	[REDACTED]	(b) (4)			See Information in review of NDA 206619
	Type III					"
	Type III					"
	Type III					"
	Type III					"

**B. Other Documents: IND, RLD, or sister applications**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-659	Ritonavir (Norvir®) Oral Solution
NDA	22-417	Ritonavir (Norvir®) Tablets:
NDA	206619	Ombitasvir/Paritaprevir/Ritonavir Tablets and Dasabuvir Tablets (Viekira® Pak)
IND	103526	Paritaprevir
IND	108434	Ombitasvir
IND	120467	2-DAA combination IND, ombitasvir/paritaprevir/ritonavir

**2. CONSULTS:**

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other				

## Executive Summary

### I. Recommendations

This NDA is recommended for Approval from the Product Quality perspective. CMC-related labeling recommendations have been provided to the OND PM, for consideration during final labeling.

#### A. Recommendation and Conclusion on Approvability

1. Summary of Complete Response issues – Not Applicable
2. Action letter language, related to critical issues such as expiration date  
An expiration dating period of 24 months is recommended.
3. Benefit/Risk Considerations  
None to note: solid oral product in reasonably straight-forward packaging.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

### II. Summary of Quality Assessments

#### A. Drug Substances [Ombitasvir, Paritaprevir and Ritonavir] Quality Summary

All information about the three drug substances is unchanged from original review of NDA 206619. See that CMC review for information on this section.

1. Chemical Name or IUPAC Name/Structure
2. Properties/CQAs Relevant to Drug Product Quality
3. List of starting materials
4. Suppliers of starting materials (site)
5. Summary of Synthesis
6. Process
  - a. Sterilization processes of the sterile bulk, as applicable
  - b. Critical equipment
7. Container Closure
8. Retest Period & Storage Conditions

#### B. Drug Product [Ombitasvir, Paritaprevir and Ritonavir Tablets] Quality Summary

1. Strength 12.5 mg/ 75 mg/ 50 mg
2. Description/Commercial Image pink-colored, film-coated, oblong, biconvex-shaped tablet debossed with “AV1” on one side
3. Summary of Product Design – see CMC Review of orig NDA 206619
4. List of Excipients – see CMC Review of orig NDA 206619
5. Process Selection (Unit Operations Summary) – see CMC Review of orig NDA 206619
  - a. Sterilization processes of the drug product, as applicable
  - b. Critical equipment

6. Container Closure Daily blister cards of 2 tablets; seven cards in a 1-week pack; four 1-week cartons per monthly carton
7. Expiration Date & Storage Conditions: 24 months when stored at or below 30°C (86°F).
8. List of co-packaged components None

**C. Summary of Drug Product Intended Use**

<b>Proprietary Name of the Drug Product</b>	Technivie
<b>Non Proprietary Name of the Drug Product</b>	Ombitasvir, Paritaprevir and Ritonavir Tablets
<b>Non Proprietary Name of the Drug Substance</b>	Ombitasvir, Paritaprevir and Ritonavir
<b>Proposed Indication(s) including Intended Patient Population</b>	Treatment of chronic infection with genotype 4 Hepatitis C virus, in combination with ribavirin
<b>Duration of Treatment</b>	12 weeks
<b>Maximum Daily Dose</b>	Two tablets
<b>Alternative Methods of Administration</b>	None

**D. Biopharmaceutics Considerations**

All Biopharmaceutics information is unchanged from the original review of NDA 206619. See that Biopharmaceutics review for information on this section.

1. BCS Classification:
  - Drug Substance:
  - Drug Product:
2. Biowaivers/Biostudies
  - Biowaiver Requests
  - PK studies
  - IVIVC

**E. Novel Approaches** None

**F. Any Special Product Quality Labeling Recommendations** None

**G. Life Cycle Knowledge Information (see Attachment A)**

All life cycle knowledge information is unchanged from original review of NDA 206619. See the final risk table from that CMC review.

## OVERALL ASSESSMENT AND SIGNATURE: EXECUTIVE SUMMARY

### Application Technical Lead Signature:

**This NDA is recommended for approval from the Product Quality perspective.**

Stephen  
Miller -S

Digitally signed by Stephen Miller -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Stephen Miller  
-S,  
0.9.2342.19200300.100.1.1=1300087013  
Date: 2015.06.30 22:55:40 -04'00'

**Stephen Miller, Ph.D.; CMC-Lead; Branch 3; Division of New Drug Products I**

## Primary Quality Review

### ASSESSMENT OF THE DRUG SUBSTANCE

#### 2.3.S DRUG SUBSTANCE

##### 2.3.S.1 General Information

**Applicant’s Information:**

Ombitasvir and Paritaprevir drug substances used in the manufacture of Ombitasvir/ Paritaprevir /Ritonavir Film Coated Tablets are described in the NDA 206619 Ombitasvir Drug Substance sections. The ritonavir drug substance used in the manufacture of Ombitasvir/Paritaprevir/Ritonavir Film Coated Tablets is described in the Norvir® Oral Solution NDA (20-659) Drug Substance sections. A cross reference table for the content of ritonavir drug substance is provided in the NDA 206619 Module 1.4.4.

**Reviewer’s Assessment:**

All of the CMC data relevant to the NDA 207931 are contained within NDA 206619. Per agreement with the FDA, any changes to the CMC information for this NDA will be submitted to NDA 206619.

##### 2.3.S.2 Manufacture

###### *S.2.2 Description of the Manufacturing Process and Controls*

1. Is the commercial manufacturing process adequately described and controlled to ensure consistent manufacturing of acceptable drug substance batches?
2. Is there any proposal for online/at line/in line monitoring technologies for routine commercial production that allows for real-time process monitoring and control? If so, is it acceptable?

**Applicant’s Information:**

The Ombitasvir drug substance is manufactured and tested at the following sites (Table 1).

**Table 1. Manufacturing and Testing Sites**

Site	Function(s)
(b) (4)	

(b) (4)

(b) (4)	
AbbVie Ireland NL B.V. Manorhamilton Road Sligo, Ireland  Establishment Registration Number: 3004364014	Drug Substance: Manufacturing, Testing and Stability Testing
AbbVie Inc. 1401 Sheridan Rd. North Chicago, IL 60064 USA  Establishment Registration Number: 1411365	Drug Substance: Stability Testing

The paritaprevir drug substance is manufactured and tested at the following sites (Table 2)

**Table 2 Manufacturing and Testing Sites**

Site	Function s
(b) (4)	
AbbVie Ireland NL B V Manorhamilton Road Sligo Ireland  Establishment Registration Number 3004364014	Drug Substance Manufacturing Testing and Stability Testing
AbbVie Inc 1401 Sheridan Rd North Chicago IL 60064 USA  Establishment Registration Number 1411365	Drug Substance Stability Testing

The Ritonavir drug substance is manufactured, packaged, and/or tested at the site(s) in Table 3.

**Table 3. Manufacturing, Packaging, and Testing Sites**

Site	Establishment Registration Number	Function(s)
AbbVie S.r.l, S.R. 148 Pontina km 52 SNC 04011 Campoverde di Aprilia (LT) Italy	3002806277	Manufacture, Packaging, and Analytical Testing (Release and Stability)

**Reviewer’s Assessment:**

The detailed information on each drug substance is cross-referenced in the NDA 206619. The commercial manufacturing process and controls are the same as previously approved.

*Control of Critical Steps and (b) (4)*

3. What are the critical steps which could significantly affect the structure of the drug substance and impurity profiles? If so, are the critical process parameters (CPPs) adequate to ensure the identity and purity of the drug substance?
4. Are (b) (4) controlled adequately to assure the structure and impurity profile of the final drug substance?

**Applicant’s Information:**

For detailed information on each drug substance please see the cross-referenced NDA 206619.

**Reviewer’s Assessment:**

The detailed information on each drug substance is cross-referenced in the NDA 206619. The critical steps and (b) (4) controls have been evaluated and are the same as previously approved.

*Process Validation and/or Evaluation*

5. Is the proposed process validated adequately?

*Manufacturing Process Development*

6. What process development and scale up information supports the commercial process and proposed control strategy?

**Applicant's Information:**

For detailed information on each drug substance please see the cross-referenced NDA 206619.

**Reviewer's Assessment:**

The detailed information on each drug substance is cross-referenced in the NDA 206619. The process validation and manufacturing process development have been evaluated and are the same as previously approved.

**2.3.S.3 Characterization**

7. Do all the characterization data unequivocally support the proposed structure?
8. Are the potential impurities (e.g. related substances, degradants, inorganic impurities, residual solvents, reagents, and genotoxic impurities) well characterized and controlled in the drug substance?

**Applicant's Response:**

For detailed information on each drug substance please see the cross-referenced NDA 206619.

**Reviewer's Assessment:**

The detailed information on each drug substance is cross-referenced in the NDA 206619. Each drug substance has been well characterized and data is the same as previously approved.

**2.3.S.4 Control of Drug Substance**

9. Is the proposed specification adequate to assure the identity, strength, purity, and quality of the drug substance?
10. Are all the analytical procedures appropriately described and validated for their intended use?

**Applicant's Information:**

For detailed information on each drug substance please see the cross-referenced NDA 206619.

**Reviewer's Assessment:**

The drug substance specifications that are included in NDA 207931 are (b) (4) approved under NDA 206619. The detailed information on each drug substance is cross-referenced in the NDA 206619. Control of each drug substance with adequate specifications and validated analytical procedures has been described.

11. Is the proposed control strategy for the drug substance manufactured at commercial stage acceptable? Is there any residual risk upon implementation of the control strategy at the commercial scale?

**Applicant's Information:**

For detailed information on each drug substance please see the cross-referenced NDA 206619.

**Reviewer's Assessment:**

The detailed information on each drug substance is cross-referenced in the NDA 206619. Control strategy has been found adequate specifications and is described in the previously approved referenced NDA.

**2.3.S.5 Reference Standards or Materials**

12. Are the drug substance reference standards satisfactory?

**Applicant's Information:**

For detailed information on each drug substance please see the cross-referenced NDA 206619.

**Reviewer's Assessment:**

The reference standards for each drug substance are satisfactory.

**2.3.S.6 Container Closure System**

13. Is the proposed container closure system(s) for commercial packaging of the drug substance adequate to protect the drug substance from the environment (oxygen, moisture, microorganism, etc.) during the storage?

**Applicant's Information:**

For detailed information on each drug substance please see the cross-referenced NDA 206619.

**Reviewer's Assessment:**

The container closure systems for the drug substances [redacted] (b) (4) [redacted] are satisfactory.

**2.3.S.7 Stability**

14. What is the proposed retest period for the drug substance? Do the drug substance stability data support the proposed retest period and storage conditions in the commercial container closure system? How does statistical evaluation of the stability data, if any and any observed trends support your proposed retest period?
15. Are the post-approval stability protocols and other stability commitments for the drug substance satisfactory?

**Applicant's Information:**

For detailed information on each drug substance please see the cross-referenced NDA 206619.

**Reviewer's Assessment:**

The post approval stability protocols and commitments were approved in the referenced NDAs. The drug substances were show to be very stable. No changes have been observed for: Ombitasvir up to 24 months long term (retest (b) (4) months; Paritaprevir up to 18 months long term (retest (b) (4) months) and Ritonavir data (original NDA 20-659, approved in 1995).

**OVERALL ASSESSMENT AND SIGNATURES: DRUG SUBSTANCE**

**Reviewer's Assessment and Signature:**

The manufacture and controls for the drug substances Ombitasvir, Paritaprevir, and Ritonavir remains adequate. The detailed information on each drug substance is cross-referenced in the approved NDA 206619.

Milton J. Sloan, PhD.  
June 25, 2015

**Secondary Review Comments and Concurrence:**

I concur. June 29, 2015  
Stephen Miller, Ph.D.; CMC-Lead; Branch 3; DNDP-1

## ASSESSMENT OF THE DRUG PRODUCT

### 2.3.P DRUG PRODUCT

The fixed-dose combination (FDC) ombitasvir/paritaprevir/ritonavir tablets are approved in NDA 206619 as one of two co-packaged drug products that are marketed in a blister copackaging configuration. The FDC tablets will be marketed alone, without co-packaging them with another drug product either in blisters (b)(4). All of the CMC data relevant to the NDA 207931, including the container closure systems and the stability data for both the blister and the (b)(4) configurations are contained within NDA 206619.

#### 2.3.P.1 Description and Composition of the Drug Product

**Table 1. Composition of Ombitasvir/ABT-450/Ritonavir Film-Coated Tablets, 12.5 mg/75 mg/ 50 mg**

Component	Quality Standard	Function	Amount (mg)/Tablet
(b)(4)			
Ombitasvir	In-house standard	Active	12.5
(b)(4)			
(b)(4)			
ABT-450	In-house standard	Active	75.0
(b)(4)			
(b)(4)			
Ritonavir	USP/Ph. Eur.	PK Enhancer	50.0
(b)(4)			

**Table 1. Composition of Ombitasvir/ABT-450/Ritonavir Film-Coated Tablets, 12.5 mg/75 mg/ 50 mg (continued)**

Component	Quality Standard	Function	Amount (mg)/Tablet
(b)(4)			

(b) (4)

(b) (4)

**Table 3. Blister Container Closure Systems for Ombitasvir/ABT-450/Ritonavir, Film-Coated Tablets, 12.5 mg/75 mg/50 mg**

Description	Container Materials
Clear Blister	(b) (4)
Foil Lidding	(b) (4)

16. Are there any scientific or regulatory concerns about the proposed composition of the drug product?

**Applicant's Information:**

(b) (4)

**ASSESSMENT OF BIOPHARMACUETICS INFORMATION**

38. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

**Reviewer's Assessment:**

Yes.

The proposed fixed-dose combination (FDC) Ombitasvir/Paritaprevir/Ritonavir Film-Coated Tablet (12.5mg/75mg/50mg) submitted under NDA 207931 (b) (4) the FDC tablet approved under NDA 206619. The FDC tablet was co-packaged with Dasabuvir Tablets and marketed in a blister co-packaging configuration under NDA 206619. For NDA 207931, the (b) (4) FDC tablets will be marketed alone, in (b) (4) (or blisters), without co-packaging with another drug product.

All of the in vitro dissolution data for the proposed FDC Tablet, including dissolution method, acceptance criteria, bridging studies among formulations, and stability data have been submitted and reviewed under NDA 206619.

There is no in vivo Bioequivalence study submitted in NDA 207931, as it is not needed due to (b) (4) the FDC tablet in NDA 206619. The Applicant has submitted a bioavailability study (M14-229) which will be reviewed by the Clinical Pharmacology Reviewer.

(b) (4)

Therefore there is no Biopharmaceutics information to review in this NDA.

39. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

**Reviewer's Assessment:**

Not applicable. See response to Question 38 above.

## OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACEUTICS

### Reviewer's Assessment and Signature:

There is no Biopharmaceutics information to review in this NDA.  
**Apr 15, 2015**

Jing Li, Ph.D.  
Biopharmaceutics Reviewer  
Division of Biopharmaceutics  
Office of New Drug Product  
Office of Pharmaceutical Quality

### Secondary Review Comments and Concurrence:

**I concur.**  
**Apr 15, 2015**

Elsbeth Chikhale, Ph.D.  
Acting Biopharmaceutics Lead  
Division of Biopharmaceutics  
Office of New Drug Product  
Office of Pharmaceutical Quality

## ASSESSMENT OF MICROBIOLOGY

There are no changes in manufacture or controls for the tablet, so a re-evaluation of the microbial controls is not necessary. See review of NDA 206-619.

40. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?
41. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?
42. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?
43. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

## ASSESSMENT OF ENVIRONMENTAL ANALYSIS

44. Is the applicant's claim for categorical exclusion acceptable?
45. Is the applicant's Environmental Assessment adequate for approval of the application?

### **Applicant's Information:**

#### **Claim for Categorical Exclusion According to 21 CFR Part 25.15 (d)**

The requested action, approval of NDA 207931, qualifies for a categorical exclusion from the requirement to prepare an environmental assessment (EA) under 21 CFR § 25.31(b) for each of the three active pharmaceutical ingredients (APIs), ombitasvir, paritaprevir, and ritonavir. To the applicant's knowledge, no extraordinary circumstances exist for any of these three APIs that would warrant the preparation of an EA.

**Reviewer's Assessment:**

The claim for categorical exclusion is acceptable.

**OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL****Reviewer's Assessment and Signature:**

The claim for categorical exclusion is acceptable.  
Milton J. Sloan, PhD.  
June 25, 2015

**Secondary Review Comments and Concurrence:**

I concur. June 26, 2015  
Stephen Miller, Ph.D.; CMC-Lead; Branch 3; DNDP-1

**I. Review of Common Technical Document-Quality (Ctd-Q) Module 1****Labeling & Package Insert****1. Package Insert****(a) "Highlights" Section (21CFR 201.57(a))**

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
<b>Product title, Drug name (201.57(a)(2))</b>		
Proprietary name and established name	TECHNIVIE	Acceptable
Dosage form, route of administration	Yes	Acceptable
Controlled drug substance symbol (if applicable)	N/A	N/A
<b>Dosage Forms and Strengths (201.57(a)(8))</b>		
A concise summary of dosage forms and strengths	Yes	Acceptable

**Conclusion:**

The PLR regulations require that the Package Insert Highlights, excluding the boxed warning, be limited in length to one-half page (21 CFR 201.57(d)(8)). AbbVie was unable to limit in length the Highlights section of the draft labeling to one-half page as required in 21 CFR 201.57(d)(8). AbbVie requests a waiver in accordance with 21 CFR 201.58 to allow the Highlights section to extend beyond the one-half page requirement because of the important product and safety information in the proposed draft Highlights section.

**There is no objection to this waiver request from the Product Quality perspective.**

**(b) “Full Prescribing Information” Section**

**# 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))**

**3 DOSAGE FORMS AND STRENGTHS**

TECHNIVIE is a pink-colored, film-coated, oblong, biconvex-shaped tablet debossed “AV1” on one side. Each tablet contains 12.5 mg ombitasvir, 75 mg paritaprevir and 50 mg ritonavir.

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Yes	Acceptable
Strengths: in metric system	Yes	Acceptable
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Yes	Acceptable

**Conclusion:**

The dosage form and strengths section adequately describes the dosage form and strength. The section is consistent with the OPR tablet labeling in the referenced

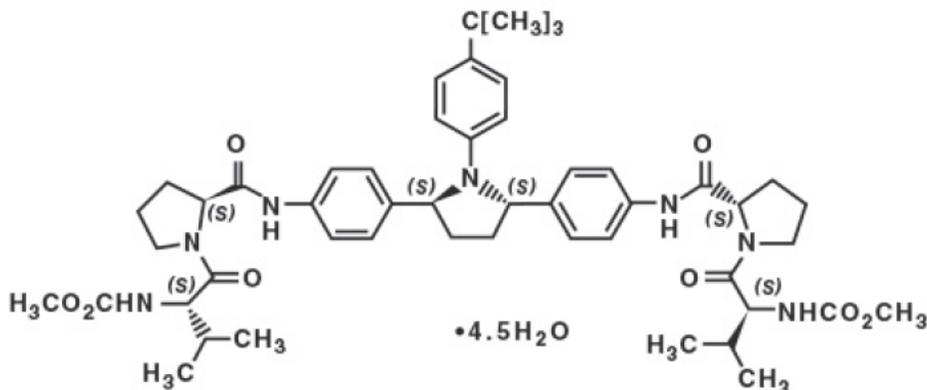
NDA 206619.

**#11: Description (21CFR 201.57(c)(12))****11 DESCRIPTION**

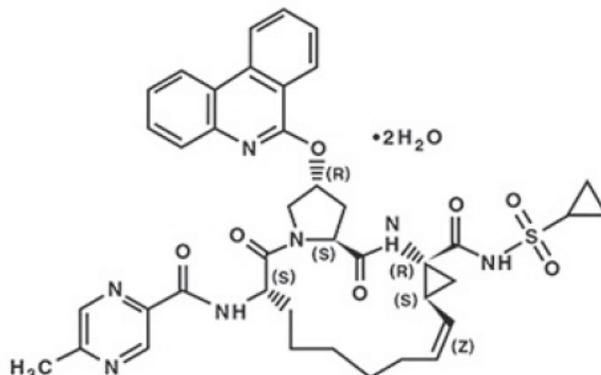
(b) (4)

Ombitasvir

The chemical name of ombitasvir is 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. The molecular formula is C<sub>50</sub>H<sub>67</sub>N<sub>7</sub>O<sub>8</sub>•4.5H<sub>2</sub>O (hydrate) and the molecular weight for the drug substance is 975.20 (hydrate). The drug substance is white to light yellow to light pink powder, and is practically insoluble in aqueous buffers but is soluble in ethanol. Ombitasvir has the following molecular structure:

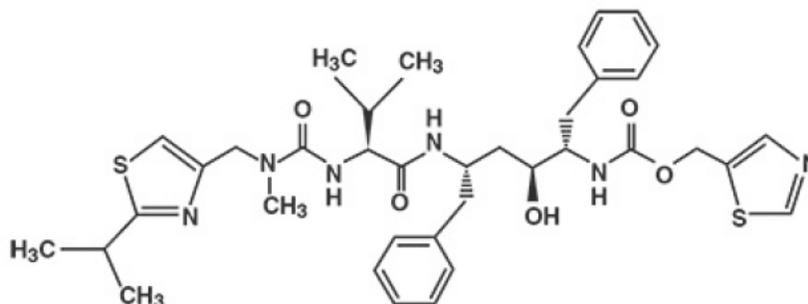
Paritaprevir

The chemical name of paritaprevir is (2*R*,6*S*,12*Z*,13*aS*,14*aR*,16*aS*)-*N*-(cyclopropylsulfonyl)-6-[[[(5-methylpyrazin-2-yl)carbonyl]amino]-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13*a*,14,15,16,16*a*-tetradecahydrocyclopropa[*e*]pyrrolo[1,2-*a*][1,4]diazacyclopentadecine-14*a*(5*H*)-carboxamide dihydrate. The molecular formula is C<sub>40</sub>H<sub>43</sub>N<sub>7</sub>O<sub>7</sub>S•2H<sub>2</sub>O (dihydrate) and the molecular weight for the drug substance is 801.91 (dihydrate). The drug substance is white to off-white powder with very low water solubility. Paritaprevir has the following molecular structure:



### Ritonavir

The chemical name of ritonavir is [5S-(5R\*,8R\*,10R\*,11R\*)]10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid,5-thiazolylmethyl ester. The molecular formula is  $C_{37}H_{48}N_6O_5S_2$  and the molecular weight for the drug substance is 720.95. The drug substance is white to off white to light tan powder practically insoluble in water and freely soluble in methanol and ethanol. Ritonavir has the following molecular structure:



### Ombitasvir, Paritaprevir, Ritonavir Fixed-Dose Combination Tablets

Ombitasvir, paritaprevir and ritonavir film-coated tablets are co-formulated immediate release tablets. The tablet contains copovidone, K value 28, vitamin E polyethylene glycol succinate, propylene glycol monolaurate Type I, sorbitan monolaurate, colloidal silicon dioxide/colloidal anhydrous silica, sodium stearyl fumarate, polyvinyl alcohol, polyethylene glycol 3350/macrogol 3350, talc, titanium dioxide, and iron oxide red. The strength for the tablet is 12.5 mg ombitasvir, 75 mg paritaprevir, 50 mg ritonavir.

<b>Item</b>	<b>Information Provided in NDA</b>	<b>Reviewer's Assessment</b>
Proprietary name and established name	Yes	Acceptable
Dosage form and route of administration	Yes	Acceptable
Active moiety expression of strength with equivalence statement for salt (if applicable)	N/A	N/A
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Yes	Acceptable
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	No	Recommend to add.
Chemical name, structural formula, molecular weight	Yes	Acceptable
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Yes	Acceptable

**Conclusion:**

The location of the structure of ritonavir should be moved to above the previous paragraph. PI has now been revised as recommended.

The pharmacological/therapeutic classes of the three active ingredients should be added to Section 11 (Description). This was conveyed to OND for consideration during labeling negotiations.

**Recommended statement:**

Ombitasvir, paritaprevir, ritonavir fixed dose combination tablet includes a hepatitis C virus NS5A inhibitor (ombitasvir), a hepatitis C virus NS3/4A protease inhibitor (paritaprevir), and a CYP3A inhibitor (ritonavir) that inhibits CYP3A mediated metabolism of paritaprevir, thereby providing increased plasma concentration of paritaprevir.

**#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))**

**16 HOW SUPPLIED/STORAGE AND HANDLING**

TECHNIVIE is dispensed in a monthly carton for a total of 28 days of therapy. Each monthly carton contains four weekly cartons. Each weekly carton contains seven daily dose packs.

Each child resistant daily dose pack contains two TECHNIVIE tablets. The NDC number is NDC-0074-3082-28.

TECHNIVIE is a pink-colored, film-coated, oblong, biconvex-shaped tablet debossed with “AV1” on one side. Each tablet contains 12.5 mg ombitasvir, 75 mg paritaprevir and 50 mg ritonavir.

Store at or below 30°C (86°F).

Item	Information Provided in NDA	Reviewer’s Assessment
Strength of dosage form	Yes	No change from approved- Acceptable
Available units (e.g., bottles of 100 tablets)	Yes	Provided in section- Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes	No change from approved- Acceptable
Special handling (e.g., protect from light, do not freeze)	Yes	No change from approved- Acceptable
Storage conditions	Yes	No change from approved- Acceptable

**Manufacturer/distributor name listed at the end of PI, following Section #17**

Manufactured by AbbVie Inc., North Chicago, IL 60064.

(b) (4)

TECHNIVIE and NORVIR are trademarks of AbbVie Inc. All other brands listed are trademarks of their respective owners and are not trademarks of AbbVie Inc. The makers of these brands are not affiliated with and do not endorse AbbVie Inc. or its products.

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Item	Information Provided in NDA	Reviewer’s Assessment
Manufacturer/distributor name (21 CFR 201.1)	Yes	Acceptable

**Conclusion:**

The (b) (4) presentation will not be marketed and an assessment has not been made as a result. Abbvie has revised Section #16 as indicated above to blister packaging.

**2. Container and Carton Labeling**

**1) Immediate Container Label**



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The proprietary name is provided along with the established name. The established name font size is half and is less prominent.	Acceptable
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	The strength of each active ingredient is provided.	Acceptable
Route of administration 21.CFR 201.100(b)(3))	See double asterisk(**) below	Acceptable
Net contents* (21 CFR 201.51(a))	Provided	Acceptable
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21CFR 201.100(b)(5)**	Information is provided in PI and not on Blister Carton.	Acceptable
Lot number per 21 CFR 201.18	Please see comments below from DEMPA labeling review.	Acceptable
Expiration date per 21 CFR 201.17	Please see comments below from DEMPA labeling review.	Acceptable
“Rx only” statement per 21 CFR 201.100(b)(1)	Provided	Acceptable
Storage (not required)	Provided	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Acceptable
Bar Code per 21 CFR 201.25(c)(2)***	Provided	Acceptable
Name of manufacturer/distributor (21 CFR 201.1)	Provided	Acceptable
Others		

\*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams.

\*\*For solid oral dosage forms, CDER policy provides for exclusion of “oral” from the container label

\*\*\*Not required for Physician’s samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

**Conclusion:**

Recommendations from DEMA:

Container Label (Daily dose wallet pack)

1. The lot number and expiration date are required on the immediate container per 21 CFR 201.18 and 21 CFR 201.17, respectively. Add both to the back of the packaging.

Container Label and Carton Labeling (Daily, Weekly, and Monthly dose packs)

1. Consider removing the red color block from the strength statement and using no color, as the colored background may reduce the readability of the strength.

**The container labels will be revised to delete the colored bar behind the strengths, as recommended by DMEPA. AbbVie agreed to make this change in the June 19, 2015 amendment.**

**2) Carton Labeling**

## QUALITY ASSESSMENT



(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	The proprietary name is provided along with the established name. The established name font size is half and is less prominent.	Acceptable
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	The strength of each active ingredient is provided.	Acceptable
Net contents (21 CFR 201.51(a))	Provided	Acceptable
Lot number per 21 CFR 201.18	Please see comments below from DEMPA labeling review.	Acceptable
Expiration date per 21 CFR 201.17	Please see comments below from DEMPA labeling review.	Acceptable
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[ 201.10(a), 21CFR201.100(d)(2)]	Information is provided in PI and not on Blister Carton.	Acceptable
Sterility Information (if applicable)	N/A	N/A
“Rx only” statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	Provided	Acceptable
Storage Conditions	Provided	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	Acceptable
Bar Code per 21 CFR 201.25(c)(2)**	Provided	Acceptable
Name of manufacturer/distributor	Provided	Acceptable
“See package insert for dosage information” (21 CFR 201.55)	Provided	Acceptable
“Keep out of reach of children” (optional for Rx, required for OTC)	N/A	Acceptable
Route of Administration (not required for oral, 21 CFR 201.100(d)(1) and (d)(2))	N/A	Acceptable

**Conclusion:**

Recommendations from DEMA:

Container Label (Daily dose wallet pack)

1. The lot number and expiration date are required on the immediate container per 21 CFR 201.18 and 21 CFR 201.17, respectively. Add both to the back of the packaging.

Container Label and Carton Labeling (Daily, Weekly, and Monthly dose packs)

1. Consider removing the red color block from the strength statement and using no color, as the colored background may reduce the readability of the strength.

**The container labels will be revised to delete the colored bar behind the strengths, as recommended by DMEPA. AbbVie agreed to make this change in the June 19, 2015 amendment.**

**OVERALL ASSESSMENT AND SIGNATURES: LABELING****Reviewer's Assessment and Signature:**

Labeling concerns have been conveyed to OND for consideration during labeling negotiations. For those already addressed, the revisions to the relevant sections are acceptable.

Milton J. Sloan, PhD.  
June 26, 2015

**Secondary Review Comments and Concurrence:**

I concur. June 29, 2015  
Stephen Miller, Ph.D.; CMC-Lead; Branch 3; DNDP-1

**II. List of Deficiencies To Be Communicated**

None

**III. Attachments**

A. Lifecycle Knowledge Management

All life cycle knowledge information is unchanged from original review of NDA 206619. See the final risk table from that CMC review.